World Journal of

Psychiatry

Contents

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Psychiatry*, Massimo Pasquini, MD, PhD, Associate Professor, Doctor, Department of Human Neurosciences, Sapienza University, Rome 00185, Italy. massimo.pasquini@uniroma1.it

AIMS AND SCOPE

The primary aim of *World Journal of Psychiatry* (*WJP*, *World J Psychiatry*) is to provide scholars and readers from various fields of psychiatry with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJP mainly publishes articles reporting research results and findings obtained in the field of psychiatry and covering a wide range of topics including adolescent psychiatry, biological psychiatry, child psychiatry, community psychiatry, ethnopsychology, psychoanalysis, psychosomatic medicine, *etc*.

INDEXING/ABSTRACTING

The *WJP* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJP* as 4.571; IF without journal self cites: 4.429; 5-year IF: 7.697; Journal Citation Indicator: 0.73; Ranking: 46 among 156 journals in psychiatry; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Jia-Hui Li*; **Production Department Director:** *Xu Guo*; **Editorial Office Director:** *Jia-Ping Yan.*

Prevalence and correlates of aggressive behavior in psychiatric inpatient populations

Hunor Girasek, Vanda Adél Nagy, Szabolcs Fekete, Gabor S Ungvari, Gábor Gazdag

ORCID number: Hunor Girasek 0000-0002-8140-2065; Vanda Adél Nagy 0000-0002-4390-796X; Szabolcs Fekete 0000-0003-1517-5121; Gabor S Ungvari 0000-0003-4821-4764; Gábor Gazdag 0000-0002-6914-8041.

Hunor Girasek, Vanda Adél Nagy, Gábor Gazdag, Department of Psychiatry and Psychiatric Rehabilitation, Jahn Ferenc South Pest Hospital, Budapest 1204, Hungary

Szabolcs Fekete, Department of Psychiatry, National Institute of Forensic Psychiatry, Budapest 1108, Hungary

Szabolcs Fekete, School of PhD Studies, Semmelweis University, Budapest 1085, Hungary

Gabor S Ungvari, Division of Psychiatry, School of Medicine, University of Western Australia, Crawley 6009, Australia

Gabor S Ungvari, Section of Psychiatry, University of Notre Dame, Fremantle 6160, Australia

Gábor Gazdag, Department of Psychiatry and Psychotherapy, Faculty of Medicine, Semmelweis University, Budapest 1083, Hungary

Corresponding author: Gábor Gazdag, MD, PhD, Professor, Department of Psychiatry and Psychiatric Rehabilitation, Jahn Ferenc South Pest Hospital, Köves út 1, Budapest 1204, Hungary. gazdag@lamb.hu

Abstract

Aggressive behavior in patients with psychiatric disorders is attracting increasing research interest. One reason for this is that psychiatric patients are generally considered more likely to be aggressive, which raises a related question of whether diagnoses of psychiatric disorders predict the prevalence of aggressive behavior. Predicting aggression in psychiatric wards is crucial, because aggressive behavior not only endangers the safety of both patients and staff, but it also extends the hospitalization times. Predictions of aggressive behavior also need careful attention to ensure effective treatment planning. This literature review explores the relationship between aggressive behavior and psychiatric disorders and syndromes (dementia, psychoactive substance use, acute psychotic disorder, schizophrenia, bipolar affective disorder, major depressive disorder, obsessive-compulsive disorder, personality disorders and intellectual disability). The prevalence of aggressive behavior and its underlying risk factors, such as sex, age, comorbid psychiatric disorders, socioeconomic status, and history of aggressive behavior are discussed as these are the components that mostly contribute to the increased risk of aggressive behavior. Measurement tools commonly used to predict and detect aggressive behavior and to differentiate between different forms of aggressive behavior in both research and clinical practice are also

reviewed. Successful aggression prevention programs can be developed based on the current findings of the correlates of aggressive behavior in psychiatric patients.

Key Words: Aggression; Mental disorders; Inpatients; Prevalence; Risk factors; Risk assessment

Core Tip: The aim of this paper is to provide an overview of the prevalence of aggressive behavior of patients with various psychiatric disorders focusing mainly on inpatient populations. It also discusses the most commonly used measurement tools for aggressive behavior. As aggressive behavior endangers the safety of both patients and staff, predicting aggression is a key to its prevention. This review also highlights the importance of risk assessment and prevention of aggression in psychiatric patients.

INTRODUCTION

The relationship between psychiatric disorders and aggressive behavior has always been a contentious issue, as it is difficult to determine whether psychiatric patients are more likely to be aggressive and whether psychiatric disorders predict aggressive behavior[1].

The authors of most recently published studies agree that there is an increased risk of aggressive behavior in certain psychiatric disorders[2-5]. In a meta-analysis, the proportion of patients classified as aggressive during their acute psychiatric treatment ranged from 8% to 44%[2]. Aggressive behavior and violence pose a serious challenge to psychiatric care providers as they threaten the safety of both the patients and staff[1, 2,6]. They also result in longer hospitalization times and the increased stigmatization of psychiatric patients[3]. To predict and prevent violent events in inpatient units, it is crucial to recognize the relationships of the sociodemographic and clinical characteristics of inpatients with the risk of aggression[2].

The aims of this paper are to review the risks of aggressive behavior associated with different psychiatric disorders and assess the commonly used measurement tools to measure various aspects of aggressive behavior.

DEFINITION OF AGGRESSION

There are several definitions of aggression, a rather broad term used with different emphases in criminology, political and social science, and psychiatry. For the purpose of this review, aggression is defined as a human behavior manifesting as verbal or physical acts that target other human beings, animals, or objects with the aim of causing harm. The aggressors are not always aware of the implications of their actions and the damage caused. If the harm is coincidental or a secondary consequence, the act is not considered as aggressive[7,8].

Instrumental or proactive aggression involves intentionally harming an individual to achieve a desired goal. In contrast, impulsive aggression is often referred to as hostile or reactive aggression that has no identifiable goal. In impulsive aggression, the perpetrator is driven by anger, and the act is an inconsiderate and unplanned response to perceived provocation[7,9,10]. In line with most definitions, in this paper, violence is referred to as an extreme form of aggressive behavior with the purpose of physically harming others, irrespective of the consequences[7].

METHODS OF THE REVIEW

This narrative review began with a search of the PubMed, PsychINFO, Google Scholar databases using the key words such as (psychiat* or mental*) and (aggress* or violen* or hostil*) and measure*. The publication was chosen if it included any of the following categories of psychiatric disorders and syndromes: dementia, psychoactive substance use, acute psychotic disorder, schizophrenia, bipolar affective disorder, major depressive disorder, obsessive-compulsive disorder, personality disorders (PDs) and intellectual disability. The papers included were peer-reviewed journal articles and books that were published mainly in English. Further articles were reached by following up references. We tried to review the most recent research data to present the current findings of the prevalence and correlates of aggressive behavior in psychiatric inpatient populations.

AGGRESSION IN DIFFERENT PSYCHIATRIC DISORDERS

Dementia

Alzheimer's disease (AD) and mild cognitive impairment (MCI) increase the risk of agitation and aggressive behavior[11-14]. Aggressive behavior is one of the most common and disturbing complications of cognitive impairment, such as dementia; it contributes to early hospital admission and increases the burdens of caregivers and hospital staff[11], as patients with dementia can harm themselves and other patients [12,13]. The extent of functional deficits and cognitive impairment in dementia is correlated with behavioral and psychiatric symptoms, including apathy, irritability, agitation, aggression, delusions, depressive mood, and anxiety[12].

The main neuropathological finding related to progressive changes in behavior and aggression[15-17] is prefrontal cortical atrophy, which is also associated with dementia [18]. In frontotemporal dementia, anger and other confrontational/critical and emotionally charged ideas and behaviors underpin the development of interpersonal aggression and social isolation[19]. Further brain areas significantly associated with aggression in dementia include the dorsomedial prefrontal and orbitofrontal cortices and the amygdala[20-22].

In a meta-analysis, the prevalence of aggressive behavior in patients with AD and MCI was reported to be 27.8% and 7.4%, respectively[11]. However in another study aggression was found to be the major cause of hospitalization - in 34.2% of all cases - particularly in patients with moderate/severe dementia[23]. Place of residence was also correlated with aggression. For example, agitation and aggressive behavior were observed in 20% of outpatients living in the community, but in 40%–60% of patients living in nursing homes[24]. In a meta-analysis, no significant difference was observed in the risk of physical aggression between patients with different types of dementia with the exception of patients with frontotemporal dementia, among whom the prevalence of criminal behavior was 37%, as opposed to only 8% in patients with AD [11]. In contrast, studies of verbal aggression in AD showed significantly higher rates ranging from 28% to 67%[14]. However, no significant correlation was reported between verbal aggression and the severity of dementia measured by the Mini Mental State Examination, although verbal aggression was found to be related to the presence of delusions[14].

Aggressive behavior in AD is associated with depression, loss of family contact, a poor caregiver–patient relationship, and chronic pain[11,25-27]. Objectively assessing the level of pain in dementia patients can be challenging, although reducing pain could decrease agitation and aggressive behavior[13].

A systematic review confirmed the clinical impression that compared with women, men have higher rates of aggression and other behavioral problems, such as wandering, abuse of others, and social incompetence[28].

Psychoactive substance use

Substance use disorders are among the most prevalent psychiatric disorders, but only a minority of such patients seeks treatment. The relationship between drug use and aggressive behavior is a constantly growing concern[29,30]. It is universally accepted that alcohol and certain drugs significantly increase the incidence of aggressive behavior[2,29-33]. In a forensic psychiatric sample, 28% of patients with previous offences committed crime under the influence of a psychoactive substance[34]. Aggressive behavior occurs at any stage of drug use: in acute intoxication, in connection with drug-seeking behavior, in withdrawal, or in episodes of drug-induced psychosis[31].

Drugs and violence are related directly when the drug pharmacologically induces violence or indirectly when the violence serves as a method of obtaining the drug[32]. Overall, the relationship between drugs and aggression is complex and is driven by a combination of factors related to both transient and permanent physiological, psychological, environmental, and individual differences[30].

Alcohol: Alcohol is the substance most commonly associated with aggressive and violent behavior[31]. The link between acute alcohol consumption and aggressive behavior is well-known[35]. Even moderate amounts of alcohol increase the likelihood of aggressive behavior[32]. Alcohol consumption has been associated with increased frequency and severity of physical aggression toward acquaintances and strangers[36, 37], increased verbal aggression[38], domestic and marital violence[39,40], sexual harassment[41-43], and suicide[44]. There is preliminary evidence that alcohol is more closely associated with murder, rape, and abuse than any other substance[31].

Alcohol increases aggression in both men and women, but this effect is stronger in men[35]; men intoxicated with alcohol are prone to physical aggression, whereas women are prone to verbal aggression[45]. However, a recent study[46] found no intersex difference in the effect of alcohol on aggressive behavior. Alcohol consumed by women at home increases their physical aggression toward their male partners, and the amount of alcohol consumed is positively correlated with physical aggression[47-49].

Chronic alcohol dependence can lead to changes in personality structure; the person increasingly blames others for his/her condition, and frequent interpersonal conflicts develop, often leading to physical or verbal aggression. Furthermore, irritability and agitation increase during periods of withdrawal, triggering the onset of aggression[31].

Because of the high individual variability in the effects of alcohol on aggressive behavior, most authors emphasize the interplay between several factors[32]. Alcohol impairs frontal lobe functions, affecting the handling of threatening situations[50-53], reduces inhibitions[51], and influences neurochemical systems that mediate aggressive behavior[54-56]. It is well-established that heavy alcohol consumption affects prefrontal cortex thereby contributing to the development of aggressive behavior[57-59]. Even a small amount of alcohol can reduce the activity of the medial prefrontal cortex[60] resulting in the impairment of prefrontal executive functions, which may lead to careless, inappropriate, or aggressive behavior[61,62]. Alcohol consumption frequently provides false justification for the variety of antisocial behaviors displayed by the intoxicated person[63].

Heroin: There is compelling evidence that heroin increases aggressive behavior, including physical aggression against others, impulsivity, and suicidality[30,64-66]. An analysis of the history of 527 heroin users found that almost 43% of them had attempted suicide[67]. The symptoms of opioid withdrawal can be so severe and painful that opioid users may unintentionally become violent when trying to obtain opioid drugs to seek relief from the withdrawal symptoms[31]. Research data support the view that the elevated level of aggression among heroin users is driven by individual differences in aggressive behavior and other risk factors, such as childhood abuse, family history of aggression and psychiatric illness, and living in a poor neighborhood, rather than the direct effect of heroin itself[30,68].

Cannabis: Cannabis is commonly regarded as a relatively harmless substance, but there is strong evidence that cannabis withdrawal can cause anger and lead to hostile behavior[30,69,70]. Compared with non-users, regular cannabis users were almost twice as likely to show aggressive behavior towards their partner, were 1.2 times more likely to be victims of aggression by their partners and were 2.4 times more likely to be both perpetrators and victims of aggressive behavior[71]. These findings remained true even after controlling for the effects of alcohol and other drugs[71].

Stimulants: Both cocaine[22,59] and methamphetamine use can trigger hostile behavior[31,72-74]. 3,4-methylenedioxy-N-methamphetamine has been found to reduce aggression during its acute use[30,75,76], followed by a flare-up of aggression in the following days and a return to baseline after approximately one week[77]. A meta-analysis found that among illicit drugs, cocaine has the strongest link to physical, sexual, and psychological aggression[78]. Tomlinson *et al*[30] highlighted that the relationship between cocaine use and aggressive behavior may be enhanced by personality traits, such as poor impulse control and antisocial traits.

Hallucinogens: The use of most hallucinogens has been negatively correlated with aggression, *i.e.*, positively associated with a lowered risk of aggressive behavior and

elevated mood[30,79]. Both psilocybin[80] and lysergic acid diethylamide[30,31] decrease interpersonal conflicts and subsequent aggressive behavior[81].

Acute psychotic disorder

More than 50% of all violent incidents in the context of psychiatric illness occur during psychiatric care[82-85]. Psychotic symptoms have traditionally been considered as a major contributing factor to aggression[83,86-88].

Several studies have shown that first-episode psychoses carry a high risk of aggressive behavior[89-91]: approximately one-third of patients with first-episode psychosis exhibit hostility and verbal and/or physical aggression during hospitalization, and the severity of their violence frequently poses risk to others[92]. In one study, 16% of patients with first-episode psychosis were reported to be aggressive in the week before admission, 7% were aggressive in the week after admission, and 10% were aggressive in both periods[92]. In another study, aggressive behavior was observed in more than half of the patients with first-episode psychosis, with verbal aggression being the most common aggressive behavior in inpatient wards[88,93]. In a similar study, nearly 70% of participants with first-episode psychosis were reported to have committed at least one act of physical and/or verbal abuse in the year prior to admission, and 43% and 61.5% showed physical and verbal aggression, respectively [85].

A study reported that most of the violent acts by patients with first-episode psychosis targeted themselves or property, whereas only 7% of the violent acts were committed against another person, and only 2.5% of these caused actual injuries, such as bruises and scratches[92]. Furthermore, 46% of patients had conflicts with the law, of whom 42.9% were arrested and 35.1% spent at least one night in prison[85]. Approximately one-fifth of patients reported some form of suicidal ideation and behavior, including suicide attempts, during the first episode of psychosis[88]. A recent meta-analysis found that 18.4% of patients attempted suicide during their first episode of psychosis prior to seeking treatment[94].

Several sociodemographic and illness-related factors can contribute to the development of aggressive behavior[95,96]. Risk factors for aggression during first-episode psychosis include younger age, male sex, lower socioeconomic status, a longer duration of untreated psychosis, a manic state, drug use, antisocial personality traits, childhood emotional/physical/sexual abuse, and impulsivity[85,88,90,97-99].

Schizophrenia

Patients with schizophrenia tend to exhibit hostile behavior, particularly during an acute psychotic episode. These patients face an almost four times greater risk of aggressive behavior than people with no psychiatric problems[82,100,101]. The degree of aggression is significantly related to psychopathology[101-103]. Violent behavior is more commonly displayed by patients who have psychotic symptoms, such as command hallucinations that encourage them to act violently[104]. Impulsivity in schizophrenia is also closely related to aggression and suicidal behavior[3,105-107]; in a study of risk factors for suicide in schizophrenia, 11.6% of the patients attempted suicide right after the violent behavior[108]. Patients with schizophrenia, particularly those in the acute phase, frequently exhibit hostility, anger, and agitation that can lead to verbal or even physical aggression[109-111]. Both hostility and aggressive behavior are associated with longer and more frequent hospitalization[100,112-115]. Aggression also occurs frequently after discharge from hospital: a meta-analysis revealed that 10% of patients with schizophrenia, compared with only 2% of the general population, exhibited aggressive behavior in the community[116].

The prevalence of threatening and aggressive behavior is common in hospitalized schizophrenia patients, ranging from 10% to 45%[1,110,117-121], but a recent meta-analysis found higher rates of 15.3%–53.2%[122]. Although different forms of aggression are common, with verbal aggression occurring in up to 75% of the cases, serious physical injury is rare[1,93,123-125].

The prevalence of auto- and hetero-aggression in schizophrenia has been reported to show considerable intersex differences. For example, in a previous study, 75% of the male patients and 53% of the female patients demonstrated some form of aggressive behavior during their first hospitalization and in the following two years, while 17% of the male patients and 26% of the female patients attempted suicide[100]. Demographic factors that predict aggression include younger age, male sex, and single marital status [1,3].

Co-morbid psychiatric disorders, primarily substance use disorders, significantly contribute to aggressive and violent behavior in patients with schizophrenia[100,116,

126,127]. It is estimated that 20%–65% of patients with schizophrenia use illicit drugs, compared with 16.7% of the general population[101]. In addition to substance use disorders, other common comorbidities, such as antisocial personality disorder, can also increase the risk of aggressive behavior in patients with schizophrenia[2,3].

Bipolar affective disorder

Bipolar disorder is associated with an increased risk of aggressive behavior[128-131]. A high risk of aggressive behavior has also been demonstrated in bipolar patients in remission[110,132-134]. The lifetime prevalence of aggression was 12.2% in a mixed group of bipolar patients[135] and 25.3% in patients with bipolar I disorder[136].

Aggressive or violent behavior in bipolar patients usually appears during acute manic episodes[137-139] and is a common cause of hospitalization in this population [130,140-142]. Involuntary hospitalization for acute mania is significantly associated with higher rates of aggression/violence and lower rates of insight[109,143]. A clear association was found between the presence and severity of aggression during a manic episode and psychotic symptoms[130,144]. Patients with mood-incongruent psychotic symptoms are more prone to agitation or aggression[145-149]. Agitation — a common symptom in acute bipolar mania — is characterized by motor restlessness and increased responsiveness that can lead to physical aggression[110,150]. No association has been found between aggressive and suicidal behaviors in bipolar illness[130] or between male sex and aggressive behavior[141,151].

Serotonergic hypoactivation has been hypothesized to play a role in the neurobiological basis of aggression in bipolar illness[131]. The association between prefrontal cortical dysfunction and aggressive behavior in bipolar patients has been repeatedly confirmed[152-154]. Damage to the prefrontal cortex results in disruption of executive functions, leading to dysfunctional patterns of behavior in the social realms including emotional outbursts, increased risk-taking and aggression as well as disorganized behavior[61,155]. Executive dysfunction is common in bipolar disorder, schizophrenia and acute psychoses[156,157], where impaired impulse control and dysregulated behavior manifest in aggression[158].

A further possible explanatory factor for aggression in mania may be a lack of insight. Aggressiveness during acute manic episodes depends on the severity of the episode and the degree of insight[130,159]. Possible predictors of aggressive or violent behavior in mania include past aggressive or violent behavior, criminal history, childhood sexual abuse, being a victim of previous violence, comorbid PDs, and alcohol and/or drug abuse[110].

Major depressive disorder

Depression is a risk factor for aggressive behavior, mostly in the form of auto-aggression[160]. Factors associated with aggressive behavior in depression include impulsivity[160-163], alcohol use[160,164-168], and the risk of suicidal behavior[169-173]. High impulsivity scores were found in a sample of patients diagnosed with major depressive disorder who had previously attempted suicide[163]. Suicide attempters are more aggressive than non-attempters[174-177].

Associations have also been found between attachment anxiety and suicide attempts[178,179] and between the expression, proneness, and attributions of anger and adult attachment styles[179]. Adults with a preoccupied attachment style, which is characterized by the person having a negative image of him/herself and a positive image of others, are more likely to display high-risk behaviors and even suicidal gestures due to their dysregulated emotional and behavioral control[178]. Insecurity is associated with signs of dysfunctional anger, such as hostility. An anxious-ambivalent attachment style is characterized by inward-directed anger and displaced aggression, whereas a secure attachment style is characterized by the appropriate, functional expression of anger[173,178,179].

Symptoms of depression and anger have been associated with attachment style and auto-aggression in depressed inpatients[173]. It was hypothesized that the aggressive behavior of patients with elevated attachment anxiety is self-directed, resulting in non-suicidal self-harm or suicide attempts. This theory is supported by the fact that depressive symptoms are strongly associated with suicide attempts, suggesting that depression is a partial mediator to the relationship between attachment anxiety and self-directed aggression[173].

Increased alcohol consumption is also a mediator to the relationship between depression and aggression. In one study, the prevalence of alcohol use disorder was estimated at 32.3% in a sample of people who reported a depressive episode in the previous year, as opposed to only 9.5% in the non-depressed sample[180].

It was hypothesized that in the anxiety/aggression-driven subtype of depression, depressive episodes are triggered by increased anxiety and/or unregulated, outwardly directed aggression, such as irritability or outbursts of anger. Consequently, in this subtype of depression, the symptoms of dysregulated aggression and/or anxiety mask the depressive mood[181]. Assessment of depression should include a search for evidence of comorbidity with alcoholism and personality traits such as aggression and impulsivity to better understand the link between depression and suicidal behavior and to identify patients at a higher risk of suicidal behavior[166].

Obsessive–compulsive disorder

The relationship between obsessive–compulsive disorder (OCD) and aggression has been explored in relatively few studies. Increased aggression and hostility in OCD are positively correlated with symptoms of hoarding[182,183], the inhibition of avoidant behavior or rituals[184], and the severity of OCD symptoms[183,185,186].

In OCD, indirect aggression is more common and direct aggression is relatively infrequent[187]. The relationship between latent aggression (hostility/aggression toward other individuals, which is not openly expressed but manifested in fantasies or disguised forms that are not always conscious to the individual) and OCD has been explored[188-190] but not extensively studied. Explanations offered for this association include the psychodynamic theory of OCD[189,190] and the role of anxiety, which may prevent OCD patients from expressing their anger because they are worried about how others will react to an openly aggressive behavior[183,191].

Increased anger[192,193], hostile behavior[183,194], and frequent interpersonal conflicts have been reported in studies on OCD[183,189,190,195]. In one study, more than half of the OCD patients reported interpersonal conflicts, with one in two patients admitting that they were aggressive with their partner[195]. Family members who refuse to participate in the rituals of an OCD patient may be targets of aggressive behavior[190,195]. Another source of interpersonal conflict in OCD is when patients take excessive precautions to maintain the safety of others (*e.g.*, forced control of locks) who do not take these precautions as seriously[196], which induces anger and hostile behavior in OCD patients[197]. Patients find it harder to alleviate their anxiety when experiencing high levels of hostility, which predicts poor treatment outcomes[183,191, 198]. Hostility and high levels of anxiety are linked to suicide in OCD patients; in a recent study, 27% of the OCD patients had suicidal ideation during their lifetime and 33% had attempted suicide[198].

Personality disorders

PDs are associated with an increased risk of developing aggressive and violent behavior[199-201]. The relationship between PDs and aggression is complex, because PDs differ in terms of the type, severity of frequency of aggressive behavior[202,203]. Among the 10 PDs described in the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, aggression is typically associated with Cluster B PDs (antisocial, borderline, histrionic, and narcissistic PDs) and paranoid PD among Cluster A PDs[204-208]. Patients with Cluster B PDs are 10 times more likely to have a criminal conviction and eight times more likely to be in prison than patients with other PDs[209]. Violent crime is most frequently exhibited by individuals with antisocial PD but is also common among criminals with borderline, narcissistic, and paranoid PDs [210].

Patients with antisocial and borderline PDs have the greatest risk of hostile behavior [208], being four times more likely to be hostile in a psychiatric ward than patients with other PDs[121]. Patients with antisocial PD are 12.8 times more likely to commit a violent act, compared with the general population[211]. Up to 73% of patients with borderline PD have been found to behave aggressively during a one-year period[212], 58% participated in "occasional or frequent" fights, and 25% used a gun against others at some point in their lives[213]. Crimes committed by patients with borderline PD are impulsive, explosive episodes of physical violence, whereas those committed by patients with antisocial PD are driven by instrumental aggression[214,215].

Borderline personality disorder: The hostile behavior of patients with borderline PD is predicted by several possible factors, including interpersonal dysfunction, negative interpersonal events[216,217], hypersensitivity to social rejection[218], and increased sensitivity to threat[208,219]. One study reported that patients with borderline PD experienced significantly more fear than did healthy controls when presented with neutral faces[220,221]. These results suggest that patients with borderline PD do not properly recognize facial emotional expressions, which increases their feelings of threat or provocation and may ultimately lead to reactive aggression[219]. Factors

underlying hostility in borderline PD include comorbid psychiatric disorders and/or substance use, affective lability, and childhood abuse[222,223]. Affective dysregulation and impulsive aggression in these patients require special attention, as they are risk factors for suicidal behavior, self-harm, and interpersonal aggression and influence the choice of psycho- and pharmacotherapy[223]. Most studies have found no significant intersex difference in the aggressive behavior of patients with borderline PD, but one study reported more self-aggressive behavior among female patients than among their male counterparts[224].

Antisocial personality disorder: While the aggressive behavior of patients with borderline PD is generated primarily from intense anger and instability[225], patients with antisocial PD usually perceive their environment as hostile, and therefore, their aggressive behavior stems from their perceived need to fight for their own safety and survival[226]. These patients use hostility to gain personal benefits[227-229]. They are scarcely able to delay gratification and thus use aggressive behavior when their demands are not met[226].

Narcissistic personality disorder: Narcissism has been reported to be a significant predictor of violent behavior in clinical and forensic psychiatric samples, with odds ratios ranging from 1.21 to 11.46[230]. A systematic review found that both low self-esteem[231] and unstable self-esteem[230] in patients with narcissistic PD are associated with violent behavior and hostility. Individuals with high but unstable self-esteem are most likely to report anger and hostility, whereas high but stable self-esteem prevents anger and aggression[225].

Intellectual disability
Aggressive behavior by people with intellectual disability is the main reason for their referral to healthcare services[232-235]. A hostile attitude can have serious negative consequences for people with intellectual disabilities, as it can damage their personal development and social relationships and their quality of life[236-238]. In addition, the aggressive behavior of patients with intellectual disabilities often imposes a heavy burden on their relatives and caregivers and thereby negatively impacts their quality of life[235,237].

Patients with intellectual disabilities exhibit different forms of aggression, including physical and verbal aggression, destructive behavior toward the physical environment, self-harm behavior, and sexually aggressive behavior[232,235], and the prevalence of these different forms also differs significantly among patients[239]. The prevalence of physical aggression ranges from 2.1%[240] to 24.4%[232], while that of verbal aggression ranges from 5.9%[241] to 37.6%[232]. Verbal aggression is the most common form of aggressive behavior in this population[232,234,242]. A study reported that the incidence of any form of aggressive behavior in these patients assessed in a one-year period was 51%, whereas that of all forms of hostile behavior was less than 6%[232].

The extent of hostility and its behavioral manifestations are linked with psychosocial and sociodemographic factors, the severity of intellectual disability, and the presence of comorbid psychiatric disorders. For example, aggressive behavior is more common in men with intellectual disability than in women[243]. Sexually aggressive behavior is associated with the severity of intellectual disability[235] and with the frequency of rage and objectionable personal habits[244]. Physical aggression is associated with more severe intellectual disability and younger age[234]. Hostile behavior is more common in cases wherein intellectual disability is associated with autism, psychotic disorder, paranoia, depression, and/or a PD[245]. Self-harm behavior is more common in cases with comorbid autism[232,246].

The incidence of auto-aggression, destructive behavior, and hostility against others is higher in health care facilities than at home[247]. van den Akker *et al*[235] emphasized that hostility is also determined by factors such as the quality of care and the quality and frequency of interpersonal interactions with caregivers. Among patients with intellectual disability, aggressive behavior is frequently used to attract the attention of caregivers thereby increasing the frequency of social interactions[235, 248]. Therefore, understanding the background of hostile behavior for each individual is essential to find an effective treatment[235].

MEASUREMENT TOOLS FOR AGGRESSION

Predicting and preventing aggression and violence are key issues faced by psychiatrists and forensic physicians[249]. Several methods are used to measure aggression, namely interviews, observation, laboratory tests, and projective and self-reported questionnaires[250]. However, all of these methods have limitations, such as social desirability, the effect of cognitive functioning on an individual's self-perception, or the observer's effect on observational methods[250,251]. Interpretation of risk factors should involve the patients and their family members to better understand the triggering factors, such as impulsive behavior and substance use[5]. Self-administered questionnaires correctly predict aggressive acts only if the patients admit to committing violent acts[252]. Patients who deny their symptoms and aggressive behavior, particularly physical aggression, have lower scores in self-administered questionnaires (*e.g.*, in AQ)[252]. Structured, systematic assessment tools for predicting direct aggression are a relatively new addition to clinicians' armamentarium to report, predict, and assess the risk of violence in psychiatric populations[249,253]. In a study by Ogloff *et al*[254], the accuracy of predicting impending aggression was significantly increased by using a dynamic, structured risk assessment tool for nurses in an acute psychiatric hospital. The main limitations of structured risk assessment tools are the time and resources required to administer them and the difficulties in translating the results into clinical practice[255] (Table 1).

Measurement tools based on observation

Dynamic Appraisal of Situational Aggression–Inpatient Version (DASA-IV[254]): The DASA-IV is a 7-item (negative attitudes, impulsivity, irritability, verbal threats, sensitive to perceived provocation, easily angered when requests are denied, and unwillingness to follow directions) structured risk assessment tool used to evaluate inpatient aggression. Each of the seven items is evaluated dichotomically, based on its presence or absence in the last 24 h. It takes less than 5 min to complete the scale. Scores of 0, 1 to 3, and 4 or higher indicate very low, medium, and high risks of aggression, respectively, while a score of 6 or 7 indicates a risk of immediate aggression warranting preventive measures[254]. The DASA-IV has moderate or good power for predicting aggressive events[249,253,255].

Historical, clinical, risk management: 20 factors (HCR-20$^{V3[256]}$): The HCR-20^{V3} is a 20-item assessment tool that predicts the risk of interpersonal violence. The historical (H) scale consists of 10 items related to violence, and their presence is not expected to decrease with time or treatment even if the relevance of these factors may change over time. The clinical (C) scale consists of five items that are dynamic in nature and can change over time or during treatment. The risk management (R) scale also consists of five items that are dynamic and appraise concerns about the future. The items of the HCR-20^{V3} are similar to those in the second version of the HCR-20, although some have been revised or classified under other items in the third version[257]. Although relatively few validation studies have been performed on the third version[258], good inter-rater reliability was found for both the whole scale and its sub-scales (between 0.90 and 0.93) when scores were based on interviews and clinical documentation. The HCR-20^{V3} has good predictive value for violence occurring over a 6- to 12-mo follow-up period[259].

Brøset Violence Checklist (BVC[260]): The BVC is a 6-item violence risk assessment checklist that evaluates six behavioral changes (confusion, irritability, boisterousness, physical threats, verbal threats, and attacks on objects) that often trigger aggression among inpatients[260]. The BVC can be assessed quickly and easily ("1" denotes the presence of the behavior and "0" its absence) and is intended to predict the risk of inpatient violence occurring within 24 h. The total score is derived from the sum of the scores for each item. A score of 1 or 2 indicates a moderate risk of violence that requires preventive action, whereas a score of 3 or higher indicates a high risk of violence that requires immediate preventive action and activation of attack management plans[253,260,261].

Staff Observation Aggression Scale-Revised (SOAS-R[262]): The SOAS-R consists of five items measuring different aspects of aggression: observed provocation, means used by patient, aim of aggression, consequences, and immediate measures taken by nurses. The total score is calculated by summing the scores for each item; scores range from 0 (no aggression) to 22 (most severe form of aggression). A score of 9 or higher indicates severe aggression[262]. The good psychometric properties of this scale have been confirmed by validation studies[249,262,263].

Name of the questionnaire	Year of development	Method of rating	Items	Scoring
Table 1 Measurement tools for agression				
Dynamic Appraisal of Situational Aggression–Inpatient Version[254]	2006	Observation	7 (negative attitudes, impulsivity, irritability, verbal threats, sensitive to perceived provocation, easily angered when requests are denied, and unwillingness to follow directions)	0-7
Historical, clinical, risk management: 20 factors[256]	2013	Observation	20 (historical (H) scale consists of 10 items; clinical (C) scale consists of 5 items; risk management (R) scale consists of 5 items)	0-40
Brøset Violence Checklist[260]	2000	Observation	6 (confusion, irritability, boisterousness, physical threats, verbal threats, and attacks on objects)	0-6
Staff Observation Aggression Scale-Revised[262]	1999	Observation	5 (observed provocation, means used by patient, aim of aggression, consequences, and immediate measures taken by nurses)	0-22
Modified Overt Aggression Scale[264]	1989	Observation	4 (verbal aggression and aggression against property, self, and others)	0-40
Buss–Durkee Hostility Inventory[269]	1957	Self-rating	75 (7 subscales: assault or direct physical violence against others; indirect hostility; irritability or explosiveness; negativism; resentment, anger, jealousy; mistrust; and verbal aggression)	0-66 total hostility score; 0-9 guilt score
Aggression Questionnaire[272]	2000	Self-rating	34 (5 subscales: physical aggression; verbal aggression; anger; and hostility; indirect aggression)	34-170 (5-point Likert scale)
State–Trait Anger Expression Inventory 2[274]	1999	Self-rating	57 (contains 6 scales: state anger; trait anger; anger expression-out; anger expression-in; anger control-out; anger control-in and 5 subscales: state anger/feeling, state anger/verbal, state anger/physical, trait anger/temperament, and trait anger/reaction, and an anger expression index)	57-228 (4-point Likert scale)

Modified Overt Aggression Scale (MOAS[264]): Adapted from the Overt Aggression Scale[265], the MOAS is used to measure aggression. Although the scale was developed to evaluate the hostile behavior of adult psychiatric inpatients, it has also been used in older patients with dementia[250]. The MOAS consists of four subscales (verbal aggression and aggression against property, self, and others). The items are rated on a 5-point Likert scale, and each category is weighted: the severity of verbal aggression is given the lowest weight, whereas that of physical aggression is given the highest weight. The sum of the scores for the four subscales indicates the severity of overall aggressive behavior. The total weighted score ranges from 0 to 40. Psychometric studies of the MOAS have demonstrated good reliability and validity[266-268].

Self-report measurement scales
Buss–Durkee Hostility Inventory (BDHI[269]): The BDHI consists of 75 dichotomous (true or false) items and is divided into seven subscales: assault or direct physical violence against others; indirect hostility through gossiping, joking, slamming doors, or breaking things; irritability or explosiveness and annoyance at the smallest stimulus; negativism as either active rebellion or passive obedience to rules and authority; resentment, anger, jealousy, and/or hate of others due to real or supposed maltreatment; mistrust and the belief that others are damaging and diminishing the

patient; and verbal aggression in style or content. Scores are added up to obtain a total hostility score based on 66 of the 75 items, after omitting the guilt items, which form a separate guilt scale to examine the influence of guilt on aggressive behavior. In a meta-analysis, the subscale score reliability for the BDHI was found to be less than desirable, as the Cronbach's alpha coefficients were generally between 0.50 and 0.69[270]. Nevertheless, the BDHI is one of the most widely used aggression measurement questionnaires both in clinical practice and research[271].

Aggression Questionnaire (AQ[272]): The AQ was developed to measure aggression [272], following the widespread and most commonly used BDHI[248]. The AQ contains 29 items rated on a 5-point Likert scale and has four subscales: physical aggression (9 items), verbal aggression (5 items), anger (7 items), and hostility (8 items). Buss and Warren[273] revised the AQ and developed a 34-item version in which a fifth subscale—indirect aggression—was added. A higher score indicates an elevated predisposition to aggression. For the 29-item AQ, the Cronbach's alpha scores for the subscales ranged from 0.72 (verbal aggression) to 0.85 (physical aggression), and with a score of 0.89 for the overall scale. The internal consistency of the 34-item AQ is acceptable, with Cronbach's alpha scores for the subscales ranging from 0.71 (indirect aggression) to 0.88 (physical aggression) and an overall reliability score of 0.94[271,273].

State–Trait Anger Expression Inventory 2 (STAXI-2[274]): The 57-item STAXI-2 consists of six scales that evaluate the experience, expression, and control of anger [274]. The State Anger subscale assesses the intensity of anger at a particular time, whereas the Trait Anger scale measures the intensity of anger over time. The Anger Expression and Anger Control scales assess four mostly independent traits: expression of anger toward objects or others (Anger Expression-Out), holding in or suppressing angry feelings (Anger Expression-In), controlling angry feelings by preventing their expression toward objects or others (Anger Control-Out), and controlling suppressed anger by calming down or cooling off (Anger Control-In). The psychometric indicators of the STAXI-2 suggest adequate reliability and factorial, criterion, and construct validity[275-278].

CONCLUSION

The aim of this review was to provide an overview of the aggressive behavior exhibited by patients with various psychiatric disorders. It discussed the manifestations and frequencies of aggression and the most commonly used measurement tools for aggression. Our review reveals that certain psychiatric disorders may carry an increased risk of aggressive behavior, which may be influenced by several other factors in addition to the presence of the psychiatric disorder. Examples of such factors include sex, age, socioeconomic status, comorbid disorders, and pre-existing aggressive behavior. Quantitative measurement tools, of which we have presented the most frequently used options, can help with the appropriate assessment of aggression. Successful aggression prevention programs can be developed based on the results of aggression risk evaluation. Note that the present review does not intend to increase the degree of stigmatization of psychiatric patients. Rather, it aims to draw attention to the risk factors for aggressive behavior, the importance of risk assessment and prevention of aggression, and the different possible interventions to manage aggression.

REFERENCES

1   **Cornaggia CM**, Beghi M, Pavone F, Barale F. Aggression in psychiatry wards: a systematic review. *Psychiatry Res* 2011; **189**: 10-20 [PMID: 21236497 DOI: 10.1016/j.psychres.2010.12.024]
2   **Dack C**, Ross J, Papadopoulos C, Stewart D, Bowers L. A review and meta-analysis of the patient factors associated with psychiatric in-patient aggression. *Acta Psychiatr Scand* 2013; **127**: 255-268 [PMID: 23289890 DOI: 10.1111/acps.12053]
3   **Pompili E**, Carlone C, Silvestrini C, Nicolò G. Focus on aggressive behaviour in mental illness. *Riv Psichiatr* 2017; **52**: 175-179 [PMID: 29105699 DOI: 10.1708/2801.28344]
4   **Li Q**, Zhong S, Zhou J, Wang X. Delusion, excitement, violence, and suicide history are risk factors for aggressive behavior in general inpatients with serious mental illnesses: A multicenter study in China. *Psychiatry Res* 2019; **272**: 130-134 [PMID: 30580136 DOI: 10.1016/j.psychres.2018.12.071]
5   **Faay MDM**, Sommer IE. Risk and Prevention of Aggression in Patients With Psychotic Disorders.

Am J Psychiatry 2021; **178**: 218-220 [PMID: 33641377 DOI: 10.1176/appi.ajp.2020.21010035]

6   **Woods P**, Ashley C. Violence and aggression: a literature review. *J Psychiatr Ment Health Nurs* 2007; **14**: 652-660 [PMID: 17880659 DOI: 10.1111/j.1365-2850.2007.01149.x]

7   **Anderson CA**, Bushman BJ. Human aggression. *Annu Rev Psychol* 2002; **53**: 27-51 [PMID: 11752478 DOI: 10.1146/annurev.psych.53.100901.135231]

8   **Tuente SK**, Bogaerts S, Veling W.   Hostile attribution bias and aggression in adults-a systematic review. Aggress Violent Behav 2019; 46: 66-81 [DOI: 10.1016/j.avb.2019.01.009]

9   **Coccaro EF**.   Aggression: Psychiatric assessment and treatment. New York: Marcel Dekker, 2003 [DOI: 10.1201/b14206]

10   **Wrangham RW**. Two types of aggression in human evolution. *Proc Natl Acad Sci U S A* 2018; **115**: 245-253 [PMID: 29279379 DOI: 10.1073/pnas.1713611115]

11   **Yu R**, Topiwala A, Jacoby R, Fazel S. Aggressive Behaviors in Alzheimer Disease and Mild Cognitive Impairment: Systematic Review and Meta-Analysis. *Am J Geriatr Psychiatry* 2019; **27**: 290-300 [PMID: 30527275 DOI: 10.1016/j.jagp.2018.10.008]

12   **Khan SS**, Ye B, Taati B, Mihailidis A. Detecting agitation and aggression in people with dementia using sensors-A systematic review. *Alzheimers Dement* 2018; **14**: 824-832 [PMID: 29571749 DOI: 10.1016/j.jalz.2018.02.004]

13   **Ballard C**, Corbett A. Agitation and aggression in people with Alzheimer's disease. *Curr Opin Psychiatry* 2013; **26**: 252-259 [PMID: 23528917 DOI: 10.1097/YCO.0b013e32835f414b]

14   **Eustace A**, Kidd N, Greene E, Fallon C, Bhrain SN, Cunningham C, Coen R, Walsh JB, Coakley D, Lawlor BA. Verbal aggression in Alzheimer's disease. Clinical, functional and neuropsychological correlates. *Int J Geriatr Psychiatry* 2001; **16**: 858-861 [PMID: 11571764 DOI: 10.1002/gps.410]

15   **Bear D**. Neurological perspectives on aggressive behavior. *J Neuropsychiatry Clin Neurosci* 1991; **3**: S3-S8 [PMID: 1821218]

16   **Hirono N**, Mega MS, Dinov ID, Mishkin F, Cummings JL. Left frontotemporal hypoperfusion is associated with aggression in patients with dementia. *Arch Neurol* 2000; **57**: 861-866 [PMID: 10867784 DOI: 10.1001/archneur.57.6.861]

17   **Wittenberg D**, Possin KL, Rascovsky K, Rankin KP, Miller BL, Kramer JH. The early neuropsychological and behavioral characteristics of frontotemporal dementia. *Neuropsychol Rev* 2008; **18**: 91-102 [PMID: 18311522 DOI: 10.1007/s11065-008-9056-z]

18   **Burgmans S**, van Boxtel MP, Smeets F, Vuurman EF, Gronenschild EH, Verhey FR, Uylings HB, Jolles J. Prefrontal cortex atrophy predicts dementia over a six-year period. *Neurobiol Aging* 2009; **30**: 1413-1419 [PMID: 18258339 DOI: 10.1016/j.neurobiolaging.2007.11.028]

19   **Moll J**, Schulkin J. Social attachment and aversion in human moral cognition. *Neurosci Biobehav Rev* 2009; **33**: 456-465 [PMID: 19126412 DOI: 10.1016/j.neubiorev.2008.12.001]

20   **Decety J**, Jackson PL, Sommerville JA, Chaminade T, Meltzoff AN. The neural bases of cooperation and competition: an fMRI investigation. *Neuroimage* 2004; **23**: 744-751 [PMID: 15488424 DOI: 10.1016/j.neuroimage.2004.05.025]

21   **Buckholtz JW**, Asplund CL, Dux PE, Zald DH, Gore JC, Jones OD, Marois R. The neural correlates of third-party punishment. *Neuron* 2008; **60**: 930-940 [PMID: 19081385 DOI: 10.1016/j.neuron.2008.10.016]

22   **Moll J**, Zahn R, de Oliveira-Souza R, Bramati IE, Krueger F, Tura B, Cavanagh AL, Grafman J. Impairment of prosocial sentiments is associated with frontopolar and septal damage in frontotemporal dementia. *Neuroimage* 2011; **54**: 1735-1742 [PMID: 20728544 DOI: 10.1016/j.neuroimage.2010.08.026]

23   **Takacs R**, Ungvari GS, Gazdag G. Reasons for acute psychiatric admission of patients with dementia. *Neuropsychopharmacol Hung* 2015; **17**: 141-145 [PMID: 26485744]

24   **Margallo-Lana M**, Swann A, O'Brien J, Fairbairn A, Reichelt K, Potkins D, Mynt P, Ballard C. Prevalence and pharmacological management of behavioural and psychological symptoms amongst dementia sufferers living in care environments. *Int J Geriatr Psychiatry* 2001; **16**: 39-44 [PMID: 11180484 DOI: 10.1002/1099-1166(200101)16:1<39::aid-gps269>3.0.co;2-f]

25   **Kim JM**, Chu K, Jung KH, Lee ST, Choi SS, Lee SK. Criminal manifestations of dementia patients: report from the national forensic hospital. *Dement Geriatr Cogn Dis Extra* 2011; **1**: 433-438 [PMID: 22279449 DOI: 10.1159/000330929]

26   **Nguyen VT**, Love AR, Kunik ME. Preventing aggression in persons with dementia. *Geriatrics* 2008; **63**: 21-26 [PMID: 18998764]

27   **Whall AL**, Colling KB, Kolanowski A, Kim H, Son Hong GR, DeCicco B, Ronis DL, Richards KC, Algase D, Beck C. Factors associated with aggressive behavior among nursing home residents with dementia. *Gerontologist* 2008; **48**: 721-731 [PMID: 19139246 DOI: 10.1093/geront/48.6.721]

28   **Ott BR**, Lapane KL, Gambassi G. Gender differences in the treatment of behavior problems in Alzheimer's disease. SAGE Study Group. Systemic Assessment of Geriatric drug use *via* Epidemiology. *Neurology* 2000; **54**: 427-432 [PMID: 10668707 DOI: 10.1212/wnl.54.2.427]

29   **Hoaken PN**, Hamill VL, Ross EH, Hancock M, Lau MJ, Tapscott JL.   Drug use and abuse and human aggressive behavior. In: Verster JC, Brady K, Galanter M, Conrod P. Drug Abuse and Addiction in Medical Illness. New York: Springer, 2012: 467-477 [DOI: 10.1007/978-1-4614-3375-0_38]

30   **Tomlinson MF**, Brown M, Hoaken PN.   Recreational drug use and human aggressive behavior: A comprehensive review since 2003. Aggress Violent Behav 2016; 27: 9-29 [DOI: 10.1016/j.avb.2016.02.004]

31   **Boles SM**, Miotto K.   Substance abuse and violence: A review of the literature. Aggress Violent Behav 2003; 8: 155-174 [DOI: 10.1016/S1359-1789(01)00057-X]

32   **Hoaken PN**, Stewart SH. Drugs of abuse and the elicitation of human aggressive behavior. *Addict Behav* 2003; **28**: 1533-1554 [PMID: 14656544 DOI: 10.1016/j.addbeh.2003.08.033]

33   **Pihl RO**, Sutton R. Drugs and aggression readily mix; so what now? *Subst Use Misuse* 2009; **44**: 1188-1203 [PMID: 19938914 DOI: 10.1080/10826080902959884]

34   **Baran B**, Szabó FÁ, Kara B, Kovács M, Uzonyi A, Antal A, Ungvári GS, Gazdag G. DO PREVIOUS OFFENCES PREDICT VIOLENT ACTS IN PSYCHIATRIC PATIENTS? *Ideggyogy Sz* 2015; **68**: 99-104 [PMID: 26434197]

35   **Giancola PR**, Levinson CA, Corman MD, Godlaski AJ, Morris DH, Phillips JP, Holt JC. Men and women, alcohol and aggression. *Exp Clin Psychopharmacol* 2009; **17**: 154-164 [PMID: 19586230 DOI: 10.1037/a0016385]

36   **Pridemore WA**. Weekend effects on binge drinking and homicide: the social connection between alcohol and violence in Russia. *Addiction* 2004; **99**: 1034-1041 [PMID: 15265100 DOI: 10.1111/j.1360-0443.2004.00762.x]

37   **Maldonado-Molina MM**, Jennings WG, Komro KA. Effects of alcohol on trajectories of physical aggression among urban youth: an application of latent trajectory modeling. *J Youth Adolesc* 2010; **39**: 1012-1026 [PMID: 20012555 DOI: 10.1007/s10964-009-9484-y]

38   **Sharma MK**, Marimuthu P. Prevalence and psychosocial factors of aggression among youth. *Indian J Psychol Med* 2014; **36**: 48-53 [PMID: 24701010 DOI: 10.4103/0253-7176.127249]

39   **Caetano R**, Schafer J, Fals-Stewart W, O'Farrell T, Miller B. Intimate partner violence and drinking: new research on methodological issues, stability and change, and treatment. *Alcohol Clin Exp Res* 2003; **27**: 292-300 [PMID: 12605079 DOI: 10.1097/01.ALC.0000057124.36127.45]

40   **Foran HM**, O'Leary KD. Alcohol and intimate partner violence: a meta-analytic review. *Clin Psychol Rev* 2008; **28**: 1222-1234 [PMID: 18550239 DOI: 10.1016/j.cpr.2008.05.001]

41   **Testa M**. The impact of men's alcohol consumption on perpetration of sexual aggression. *Clin Psychol Rev* 2002; **22**: 1239-1263 [PMID: 12436812 DOI: 10.1016/s0272-7358(02)00204-0]

42   **Abbey A**, Wegner R, Woerner J, Pegram SE, Pierce J. Review of survey and experimental research that examines the relationship between alcohol consumption and men's sexual aggression perpetration. *Trauma Violence Abuse* 2014; **15**: 265-282 [PMID: 24776459 DOI: 10.1177/1524838014521031]

43   **Zinzow HM**, Thompson M. Factors associated with use of verbally coercive, incapacitated, and forcible sexual assault tactics in a longitudinal study of college men. *Aggress Behav* 2015; **41**: 34-43 [PMID: 27539872 DOI: 10.1002/ab.21567]

44   **Chachamovich E**, Ding Y, Turecki G. Levels of aggressiveness are higher among alcohol-related suicides: results from a psychological autopsy study. *Alcohol* 2012; **46**: 529-536 [PMID: 22579734 DOI: 10.1016/j.alcohol.2012.03.007]

45   **Rolfe A**, Dalton S, Krishnan M, Orford J, Mehdikhani M, Cawley J, Ferrins-Brown M.   Alcohol, gender, aggression and violence: findings from the Birmingham untreated heavy drinkers project. J Subst Use 2006; 11: 343-358 [DOI: 10.1080/14659890600677487]

46   **Testa M**, Derrick JL. A daily process examination of the temporal association between alcohol use and verbal and physical aggression in community couples. *Psychol Addict Behav* 2014; **28**: 127-138 [PMID: 24341618 DOI: 10.1037/a0032988]

47   **Chase KA**, O'Farrell TJ, Murphy CM, Fals-Stewart W, Murphy M. Factors associated with partner violence among female alcoholic patients and their male partners. *J Stud Alcohol* 2003; **64**: 137-149 [PMID: 12608494 DOI: 10.15288/jsa.2003.64.137]

48   **Drapkin ML**, McCrady BS, Swingle JM, Epstein EE. Exploring bidirectional couple violence in a clinical sample of female alcoholics. *J Stud Alcohol* 2005; **66**: 213-219 [PMID: 15957672 DOI: 10.15288/jsa.2005.66.213]

49   **Mair C**, Cunradi CB, Gruenewald PJ, Todd M, Remer L. Drinking context-specific associations between intimate partner violence and frequency and volume of alcohol consumption. *Addiction* 2013; **108**: 2102-2111 [PMID: 24112796 DOI: 10.1111/add.12322]

50   **Pihl RO**, Peterson JB.   Alcohol and aggression: three potential mechanisms of drug effect. In: Martin SE. Alcohol and interpersonal violence: fostering multidisciplinary perspectives. Rockville, MD: US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism, 1993: 1-36

51   **Pihl RO**, Peterson JB.   Alcohol/drug use and aggressive behavior. In: Hodgins S. Mental disorder and crime. Newbury Park, CA: Sage, 1993: 263-283

52   **Khanna P**, Bhat PS, Jacob J. Frontal lobe executive dysfunction and cerebral perfusion study in alcohol dependence syndrome. *Ind Psychiatry J* 2017; **26**: 134-139 [PMID: 30089959 DOI: 10.4103/ipj.ipj_26_18]

53   **Marinkovic K**, Beaton LE, Rosen BQ, Happer JP, Wagner LC. Disruption of Frontal Lobe Neural Synchrony During Cognitive Control by Alcohol Intoxication. *J Vis Exp* 2019 [PMID: 30799848 DOI: 10.3791/58839]

54   **Miczek KA**, Weerts EM, DeBold JF.   Alcohol, aggression, and violence: biobehavioral determinants. In: Martin SE. Alcohol and interpersonal violence: fostering multidisciplinary perspectives. Rockville, MD: US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism, 1993: 83-119

55   **Volkow ND**, Wiers CE, Shokri-Kojori E, Tomasi D, Wang GJ, Baler R. Neurochemical and

metabolic effects of acute and chronic alcohol in the human brain: Studies with positron emission tomography. *Neuropharmacology* 2017; **122**: 175-188 [PMID: 28108358 DOI: 10.1016/j.neuropharm.2017.01.012]

56 **Waszkiewicz N**, Galińska-Skok B, Nestsiarovich A, Kułak-Bejda A, Wilczyńska K, Simonienko K, Kwiatkowski M, Konarzewska B. Neurobiological Effects of Binge Drinking Help in Its Detection and Differential Diagnosis from Alcohol Dependence. *Dis Markers* 2018; **2018**: 5623683 [PMID: 30069273 DOI: 10.1155/2018/5623683]

57 **Chermack ST**, Giancola PR. The relation between alcohol and aggression: an integrated biopsychosocial conceptualization. *Clin Psychol Rev* 1997; **17**: 621-649 [PMID: 9336688 DOI: 10.1016/s0272-7358(97)00038-x]

58 **Kringelbach ML**. The human orbitofrontal cortex: linking reward to hedonic experience. *Nat Rev Neurosci* 2005; **6**: 691-702 [PMID: 16136173 DOI: 10.1038/nrn1747]

59 **Heinz AJ**, Beck A, Meyer-Lindenberg A, Sterzer P, Heinz A. Cognitive and neurobiological mechanisms of alcohol-related aggression. *Nat Rev Neurosci* 2011; **12**: 400-413 [PMID: 21633380 DOI: 10.1038/nrn3042]

60 **Ridderinkhof KR**, de Vlugt Y, Bramlage A, Spaan M, Elton M, Snel J, Band GP. Alcohol consumption impairs detection of performance errors in mediofrontal cortex. *Science* 2002; **298**: 2209-2211 [PMID: 12424384 DOI: 10.1126/science.1076929]

61 **Hawkins KA**, Trobst KK. (2000). Frontal lobe dysfunction and aggression: Conceptual issues and research findings. Aggress Violent Behav 2000; 5: 147-157 [DOI: 10.1016/S1359-1789(98)00033-0]

62 **Adolphs R**. The social brain: neural basis of social knowledge. *Annu Rev Psychol* 2009; **60**: 693-716 [PMID: 18771388 DOI: 10.1146/annurev.psych.60.110707.163514]

63 **Jewkes R**. Intimate partner violence: causes and prevention. *Lancet* 2002; **359**: 1423-1429 [PMID: 11978358 DOI: 10.1016/S0140-6736(02)08357-5]

64 **Gerra G**, Zaimovic A, Raggi MA, Giusti F, Delsignore R, Bertacca S, Brambilla F. Aggressive responding of male heroin addicts under methadone treatment: psychometric and neuroendocrine correlates. *Drug Alcohol Depend* 2001; **65**: 85-95 [PMID: 11714593 DOI: 10.1016/s0376-8716(01)00152-1]

65 **Bozkurt M**, Evren C, Yllmaz A, Can Y, Cetingok S.   Aggression and impulsivity in different groups of alcohol and heroin dependent inpatient men. Klinik Psikofarmakol Bülteni 2013; 23: 335-344 [DOI: 10.5455/bcp.20130127021314]

66 **Maremmani I**, Avella MT, Novi M, Bacciardi S, Maremmani AG.   Aggressive Behavior and Substance Use Disorder: The Heroin Use Disorder as a Case Study. Addict Disord Their Treat 2020; 19: 161-173 [DOI: 10.1097/ADT.0000000000000199]

67 **Roy A**. Risk factors for attempting suicide in heroin addicts. *Suicide Life Threat Behav* 2010; **40**: 416-420 [PMID: 20822368 DOI: 10.1521/suli.2010.40.4.416]

68 **Maremmani I**, Pani PP, Pacini M, Bizzarri JV, Trogu E, Maremmani AG, Gerra G, Perugi G, Dell'Osso L. Subtyping patients with heroin addiction at treatment entry: factor derived from the Self-Report Symptom Inventory (SCL-90). *Ann Gen Psychiatry* 2010; **9**: 15 [PMID: 20388223 DOI: 10.1186/1744-859X-9-15]

69 **Chung T**, Martin CS, Cornelius JR, Clark DB. Cannabis withdrawal predicts severity of cannabis involvement at 1-year follow-up among treated adolescents. *Addiction* 2008; **103**: 787-799 [PMID: 18412757 DOI: 10.1111/j.1360-0443.2008.02158.x]

70 **Lee D**, Schroeder JR, Karschner EL, Goodwin RS, Hirvonen J, Gorelick DA, Huestis MA. Cannabis withdrawal in chronic, frequent cannabis smokers during sustained abstinence within a closed residential environment. *Am J Addict* 2014; **23**: 234-242 [PMID: 24724880 DOI: 10.1111/j.1521-0391.2014.12088.x]

71 **Reingle JM**, Staras SA, Jennings WG, Branchini J, Maldonado-Molina MM. The relationship between marijuana use and intimate partner violence in a nationally representative, longitudinal sample. *J Interpers Violence* 2012; **27**: 1562-1578 [PMID: 22080574 DOI: 10.1177/0886260511425787]

72 **Darke S**, Kaye S, McKetin R, Duflou J. Major physical and psychological harms of methamphetamine use. *Drug Alcohol Rev* 2008; **27**: 253-262 [PMID: 18368606 DOI: 10.1080/09595230801923702]

73 **Plüddemann A**, Flisher AJ, McKetin R, Parry C, Lombard C. Methamphetamine use, aggressive behavior and other mental health issues among high-school students in Cape Town, South Africa. *Drug Alcohol Depend* 2010; **109**: 14-19 [PMID: 20064699 DOI: 10.1016/j.drugalcdep.2009.11.021]

74 **Payer DE**, Lieberman MD, London ED. Neural correlates of affect processing and aggression in methamphetamine dependence. *Arch Gen Psychiatry* 2011; **68**: 271-282 [PMID: 21041607 DOI: 10.1001/archgenpsychiatry.2010.154]

75 **Machalova A**, Slais K, Vrskova D, Sulcova A. Differential effects of modafinil, methamphetamine, and MDMA on agonistic behavior in male mice. *Pharmacol Biochem Behav* 2012; **102**: 215-223 [PMID: 22579913 DOI: 10.1016/j.pbb.2012.04.013]

76 **Baggott MJ**, Kirkpatrick MG, Bedi G, de Wit H. Intimate insight: MDMA changes how people talk about significant others. *J Psychopharmacol* 2015; **29**: 669-677 [PMID: 25922420 DOI: 10.1177/0269881115581962]

77 **Curran HV**, Rees H, Hoare T, Hoshi R, Bond A. Empathy and aggression: two faces of ecstasy? *Psychopharmacology (Berl)* 2004; **173**: 425-433 [PMID: 14735288 DOI: 10.1007/s00213-003-1713-6]

78   **Moore TM**, Stuart GL, Meehan JC, Rhatigan DL, Hellmuth JC, Keen SM. Drug abuse and aggression between intimate partners: a meta-analytic review. *Clin Psychol Rev* 2008; **28**: 247-274 [PMID: 17604891 DOI: 10.1016/j.cpr.2007.05.003]

79   **Carhart-Harris RL**, Brugger S, Nutt DJ, Stone JM. Psychiatry's next top model: cause for a re-think on drug models of psychosis and other psychiatric disorders. *J Psychopharmacol* 2013; **27**: 771-778 [PMID: 23784738 DOI: 10.1177/0269881113494107]

80   **Griffiths RR**, Richards WA, McCann U, Jesse R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology (Berl)* 2006; **187**: 268-83; discussion 284 [PMID: 16826400 DOI: 10.1007/s00213-006-0457-5]

81   **Walsh Z**, Hendricks PS, Smith S, Kosson DS, Thiessen MS, Lucas P, Swogger MT. Hallucinogen use and intimate partner violence: Prospective evidence consistent with protective effects among men with histories of problematic substance use. *J Psychopharmacol* 2016; **30**: 601-607 [PMID: 27097733 DOI: 10.1177/0269881116642538]

82   **Swanson JW**, Holzer CE 3rd, Ganju VK, Jono RT. Violence and psychiatric disorder in the community: evidence from the Epidemiologic Catchment Area surveys. *Hosp Community Psychiatry* 1990; **41**: 761-770 [PMID: 2142118 DOI: 10.1176/ps.41.7.761]

83   **Link BG**, Andrews H, Cullen FT.   The violent and illegal behavior of mental patients reconsidered. American Sociological Review 1992; 57: 275-292 [DOI: 10.2307/2096235]

84   **Torrey EF**. Violent behavior by individuals with serious mental illness. *Hosp Community Psychiatry* 1994; **45**: 653-662 [PMID: 7927289 DOI: 10.1176/ps.45.7.653]

85   **Spidel A**, Lecomte T, Greaves C, Sahlstrom K, Yuille JC. Early psychosis and aggression: predictors and prevalence of violent behaviour amongst individuals with early onset psychosis. *Int J Law Psychiatry* 2010; **33**: 171-176 [PMID: 20546896 DOI: 10.1016/j.ijlp.2010.03.007]

86   **Khalid FN**, Ford T, Maughan B. Aggressive behaviour and psychosis in a clinically referred child and adolescent sample. *Soc Psychiatry Psychiatr Epidemiol* 2012; **47**: 1795-1806 [PMID: 22349207 DOI: 10.1007/s00127-012-0480-2]

87   **Taylor PJ**, Leese M, Williams D, Butwell M, Daly R, Larkin E. Mental disorder and violence. A special (high security) hospital study. *Br J Psychiatry* 1998; **172**: 218-226 [PMID: 9614470 DOI: 10.1192/bjp.172.3.218]

88   **Lopez-Garcia P**, Ashby S, Patel P, Pierce KM, Meyer M, Rosenthal A, Titone M, Carter C, Niendam T. Clinical and neurodevelopmental correlates of aggression in early psychosis. *Schizophr Res* 2019; **212**: 171-176 [PMID: 31387826 DOI: 10.1016/j.schres.2019.07.045]

89   **Humphreys MS**, Johnstone EC, MacMillan JF, Taylor PJ. Dangerous behaviour preceding first admissions for schizophrenia. *Br J Psychiatry* 1992; **161**: 501-505 [PMID: 1393336 DOI: 10.1192/bjp.161.4.501]

90   **Large MM**, Nielssen O. Violence in first-episode psychosis: a systematic review and meta-analysis. *Schizophr Res* 2011; **125**: 209-220 [PMID: 21208783 DOI: 10.1016/j.schres.2010.11.026]

91   **Winsper C**, Ganapathy R, Marwaha S, Large M, Birchwood M, Singh SP. A systematic review and meta-regression analysis of aggression during the first episode of psychosis. *Acta Psychiatr Scand* 2013; **128**: 413-421 [PMID: 23521361 DOI: 10.1111/acps.12113]

92   **Foley SR**, Kelly BD, Clarke M, McTigue O, Gervin M, Kamali M, Larkin C, O'Callaghan E, Browne S. Incidence and clinical correlates of aggression and violence at presentation in patients with first episode psychosis. *Schizophr Res* 2005; **72**: 161-168 [PMID: 15560961 DOI: 10.1016/j.schres.2004.03.010]

93   **Foster C**, Bowers L, Nijman H. Aggressive behaviour on acute psychiatric wards: prevalence, severity and management. *J Adv Nurs* 2007; **58**: 140-149 [PMID: 17445017 DOI: 10.1111/j.1365-2648.2007.04169.x]

94   **Challis S**, Nielssen O, Harris A, Large M. Systematic meta-analysis of the risk factors for deliberate self-harm before and after treatment for first-episode psychosis. *Acta Psychiatr Scand* 2013; **127**: 442-454 [PMID: 23298325 DOI: 10.1111/acps.12074]

95   **Krakowski M**, Volavka J, Brizer D. Psychopathology and violence: a review of literature. *Compr Psychiatry* 1986; **27**: 131-148 [PMID: 3514114 DOI: 10.1016/0010-440x(86)90022-2]

96   **Mulvey EP**, Lidz CW.   Clinical considerations in the prediction of dangerousness in mental patients. Clin Psychol Rev 1984; 4: 379-401 [DOI: 10.1016/0272-7358(84)90018-7]

97   **Arseneault L**, Moffitt TE, Caspi A, Taylor PJ, Silva PA. Mental disorders and violence in a total birth cohort: results from the Dunedin Study. *Arch Gen Psychiatry* 2000; **57**: 979-986 [PMID: 11015816 DOI: 10.1001/archpsyc.57.10.979]

98   **Witt K**, van Dorn R, Fazel S. Risk factors for violence in psychosis: systematic review and meta-regression analysis of 110 studies. *PLoS One* 2013; **8**: e55942 [PMID: 23418482 DOI: 10.1371/journal.pone.0055942]

99   **Faay MDM**, van Os J; Genetic Risk and Outcome of Psychosis (GROUP) Investigators. Aggressive Behavior, Hostility, and Associated Care Needs in Patients With Psychotic Disorders: A 6-Year Follow-Up Study. *Front Psychiatry* 2019; **10**: 934 [PMID: 31998154 DOI: 10.3389/fpsyt.2019.00934]

100   **Steinert T**, Wiebe C, Gebhardt RP. Aggressive behavior against self and others among first-admission patients with schizophrenia. *Psychiatr Serv* 1999; **50**: 85-90 [PMID: 9890585 DOI: 10.1176/ps.50.1.85]

101   **Markiewicz I**, Pilszyk A, Kudlak G. Psychological factors of aggressive behaviour in patients of

forensic psychiatry wards with the diagnosis of schizophrenia. *Int J Law Psychiatry* 2020; **72**: 101612 [PMID: 32889422 DOI: 10.1016/j.ijlp.2020.101612]

102 **Bobes J**, Fillat O, Arango C. Violence among schizophrenia out-patients compliant with medication: prevalence and associated factors. *Acta Psychiatr Scand* 2009; **119**: 218-225 [PMID: 19178395 DOI: 10.1111/j.1600-0447.2008.01302.x]

103 **Lahera G**, Herrera S, Reinares M, Benito A, Rullas M, González-Cases J, Vieta E. Hostile attributions in bipolar disorder and schizophrenia contribute to poor social functioning. *Acta Psychiatr Scand* 2015; **131**: 472-482 [PMID: 25645449 DOI: 10.1111/acps.12399]

104 **Junginger J**, McGuire L. The paradox of command hallucinations. *Psychiatr Serv* 2001; **52**: 385-386 [PMID: 11239112 DOI: 10.1176/appi.ps.52.3.385]

105 **Jakubczyk A**, Wojnar M.   Neurobiologia impulsywności i jej implikacje kliniczne [Neurobiology of impulsivity and its clinical implications]. Postep Neurol Neurochir Psychiatr 2009; 18: 357-365

106 **Grzesiak M**, Beszłej JA, Szechiński M.   Skala impulsywności Barratta. Postep Neurol Neurochir Psychiatr 2008; 17: 61-64

107 **Ouzir M**. Impulsivity in schizophrenia: a comprehensive update. *Aggress Violent Behav* 2013; **18**: 247-254 [DOI: 10.1016/j.avb.2012.11.014]

108 **Gazdag G**, Belán E, Szabó FA, Ungvari GS, Czobor P, Baran B. Predictors of suicide attempts after violent offences in schizophrenia spectrum disorders. *Psychiatry Res* 2015; **230**: 728-731 [PMID: 26522825 DOI: 10.1016/j.psychres.2015.10.027]

109 **Raja M**, Azzoni A. Hostility and violence of acute psychiatric inpatients. *Clin Pract Epidemiol Ment Health* 2005; **1**: 11 [PMID: 16053528 DOI: 10.1186/1745-0179-1-11]

110 **Yu X**, Correll CU, Xiang YT, Xu Y, Huang J, Yang F, Wang G, Si T, Kane JM, Masand P. Efficacy of Atypical Antipsychotics in the Management of Acute Agitation and Aggression in Hospitalized Patients with Schizophrenia or Bipolar Disorder: Results from a Systematic Review. *Shanghai Arch Psychiatry* 2016; **28**: 241-252 [PMID: 28638198 DOI: 10.11919/j.issn.1002-0829.216072]

111 **Perlini C**, Bellani M, Besteher B, Nenadić I, Brambilla P. The neural basis of hostility-related dimensions in schizophrenia. *Epidemiol Psychiatr Sci* 2018; **27**: 546-551 [PMID: 30208981 DOI: 10.1017/S2045796018000525]

112 **Greenfield TK**, McNiel DE, Binder RL. Violent behavior and length of psychiatric hospitalization. *Hosp Community Psychiatry* 1989; **40**: 809-814 [PMID: 2759570 DOI: 10.1176/ps.40.8.809]

113 **Steinert T**, Hermer K, Faust V.   Comparison of aggressive and non-aggressive schizophrenic inpatients matched for age and sex. Eur J Psychiatry 1996; 10: 100-107

114 **Wehring HJ**, Carpenter WT. Violence and schizophrenia. *Schizophr Bull* 2011; **37**: 877-878 [PMID: 21860032 DOI: 10.1093/schbul/sbr094]

115 **Ochoa S**, Suarez D, Novick D, Arranz B, Roca M, Baño V, Haro JM. Factors predicting hostility in outpatients with schizophrenia: 36-month results from the SOHO study. *J Nerv Ment Dis* 2013; **201**: 464-470 [PMID: 23686157 DOI: 10.1097/NMD.0b013e31829480b0]

116 **Fazel S**, Gulati G, Linsell L, Geddes JR, Grann M. Schizophrenia and violence: systematic review and meta-analysis. *PLoS Med* 2009; **6**: e1000120 [PMID: 19668362 DOI: 10.1371/journal.pmed.1000120]

117 **Craig TJ**. An epidemiologic study of problems associated with violence among psychiatric inpatients. *Am J Psychiatry* 1982; **139**: 1262-1266 [PMID: 7124976 DOI: 10.1176/ajp.139.10.1262]

118 **Rossi AM**, Jacobs M, Monteleone M, Olsen R, Surber RW, Winkler EL, Wommack A. Violent or fear-inducing behavior associated with hospital admission. *Hosp Community Psychiatry* 1985; **36**: 643-647 [PMID: 4007817 DOI: 10.1176/ps.36.6.643]

119 **James DV**, Fineberg NA, Shah AK, Priest RG. An increase in violence on an acute psychiatric ward. A study of associated factors. *Br J Psychiatry* 1990; **156**: 846-852 [PMID: 2207515 DOI: 10.1192/bjp.156.6.846]

120 **Miller RJ**, Zadolinnyj K, Hafner RJ. Profiles and predictors of assaultiveness for different psychiatric ward populations. *Am J Psychiatry* 1993; **150**: 1368-1373 [PMID: 8352348 DOI: 10.1176/ajp.150.9.1368]

121 **Tardiff K**, Marzuk PM, Leon AC, Portera L. A prospective study of violence by psychiatric patients after hospital discharge. *Psychiatr Serv* 1997; **48**: 678-681 [PMID: 9144823 DOI: 10.1176/ps.48.5.678]

122 **Zhou JS**, Zhong BL, Xiang YT, Chen Q, Cao XL, Correll CU, Ungvari GS, Chiu HF, Lai KY, Wang XP. Prevalence of aggression in hospitalized patients with schizophrenia in China: A meta-analysis. *Asia Pac Psychiatry* 2016; **8**: 60-69 [PMID: 26346165 DOI: 10.1111/appy.12209]

123 **Cooper AJ**, Mendonca JD. A prospective study of patient assaults on nurses in a provincial psychiatric hospital in Canada. *Acta Psychiatr Scand* 1991; **84**: 163-166 [PMID: 1950611 DOI: 10.1111/j.1600-0447.1991.tb03122.x]

124 **Bjørkly S**. A ten-year prospective study of aggression in a special secure unit for dangerous patients. *Scand J Psychol* 1999; **40**: 57-63 [PMID: 10216464 DOI: 10.1111/1467-9450.00098]

125 **Jonker EJ**, Goossens PJ, Steenhuis IH, Oud NE. Patient aggression in clinical psychiatry: perceptions of mental health nurses. *J Psychiatr Ment Health Nurs* 2008; **15**: 492-499 [PMID: 18638210 DOI: 10.1111/j.1365-2850.2008.01261.x]

126 **Krakowski MI**, Convit A, Jaeger J, Lin S, Volavka J. Neurological impairment in violent schizophrenic inpatients. *Am J Psychiatry* 1989; **146**: 849-853 [PMID: 2631695 DOI: 10.1176/ajp.146.7.849]

127 **Schiffer B**, Müller BW, Scherbaum N, Forsting M, Wiltfang J, Leygraf N, Gizewski ER.

Impulsivity-related brain volume deficits in schizophrenia-addiction comorbidity. *Brain* 2010; **133**: 3093-3103 [PMID: 20647266 DOI: 10.1093/brain/awq153]

128   **Yesavage JA**. Bipolar illness: correlates of dangerous inpatient behaviour. *Br J Psychiatry* 1983; **143**: 554-557 [PMID: 6661598 DOI: 10.1192/bjp.143.6.554]

129   **Ghaemi SN**, Stoll AL, Pope HG Jr. Lack of insight in bipolar disorder. The acute manic episode. *J Nerv Ment Dis* 1995; **183**: 464-467 [PMID: 7623019 DOI: 10.1097/00005053-199507000-00007]

130   **González-Ortega I**, Mosquera F, Echeburúa E, González-Pinto A. Insight, psychosis and aggressive behaviour in mania. Eur J Psychiatry 2010; 24: 70-77 [DOI: 10.4321/S0213-61632010000200002]

131   **Fico G**, Anmella G, Pacchiarotti I, Verdolini N, Sagué-Vilavella M, Corponi F, Manchia M, Vieta E, Murru A. The biology of aggressive behavior in bipolar disorder: A systematic review. *Neurosci Biobehav Rev* 2020; **119**: 9-20 [PMID: 32980400 DOI: 10.1016/j.neubiorev.2020.09.015]

132   **Volavka J**. Violence in schizophrenia and bipolar disorder. *Psychiatr Danub* 2013; **25**: 24-33 [PMID: 23470603]

133   **Ballester J**, Goldstein B, Goldstein TR, Yu H, Axelson D, Monk K, Hickey MB, Diler RS, Sakolsky DJ, Sparks G, Iyengar S, Kupfer DJ, Brent DA, Birmaher B. Prospective longitudinal course of aggression among adults with bipolar disorder. *Bipolar Disord* 2014; **16**: 262-269 [PMID: 24372913 DOI: 10.1111/bdi.12168]

134   **Johnson SL**, Carver CS. Emotion-relevant impulsivity predicts sustained anger and aggression after remission in bipolar I disorder. *J Affect Disord* 2016; **189**: 169-175 [PMID: 26437231 DOI: 10.1016/j.jad.2015.07.050]

135   **Corrigan PW**, Watson AC. Findings from the National Comorbidity Survey on the frequency of violent behavior in individuals with psychiatric disorders. *Psychiatry Res* 2005; **136**: 153-162 [PMID: 16125786 DOI: 10.1016/j.psychres.2005.06.005]

136   **Látalová K**. Bipolar disorder and aggression. *Int J Clin Pract* 2009; **63**: 889-899 [PMID: 19490199 DOI: 10.1111/j.1742-1241.2009.02001.x]

137   **Quirk A**, Lelliott P. What do we know about life on acute psychiatric wards in the UK? *Soc Sci Med* 2001; **53**: 1565-1574 [PMID: 11762883 DOI: 10.1016/s0277-9536(00)00457-3]

138   **Cassidy F**, Ahearn EP, Carroll BJ. Symptom profile consistency in recurrent manic episodes. *Compr Psychiatry* 2002; **43**: 179-181 [PMID: 11994834 DOI: 10.1053/comp.2002.32357]

139   **Sato T**, Bottlender R, Sievas M, Schröter A, Hecht S, Möller HJ. Long-term inter-episode stability of syndromes underlying mania. *Acta Psychiatr Scand* 2003; **108**: 310-313 [PMID: 12956833 DOI: 10.1034/j.1600-0447.2003.00194.x]

140   **McNiel DE**, Binder RL, Greenfield TK. Predictors of violence in civilly committed acute psychiatric patients. *Am J Psychiatry* 1988; **145**: 965-970 [PMID: 3394881 DOI: 10.1176/ajp.145.8.965]

141   **Barlow K**, Grenyer B, Ilkiw-Lavalle O. Prevalence and precipitants of aggression in psychiatric inpatient units. *Aust N Z J Psychiatry* 2000; **34**: 967-974 [PMID: 11127627 DOI: 10.1080/000486700271]

142   **El-Badri S**, Mellsop G. Aggressive behaviour in an acute general adult psychiatric unit. Psychiatr Bull R Coll Psychiatr 2006; 30: 166-168 [DOI: 10.1192/pb.30.5.166]

143   **Schuepbach D**, Goetz I, Boeker H, Hell D. Voluntary vs. involuntary hospital admission in acute mania of bipolar disorder: results from the Swiss sample of the EMBLEM study. *J Affect Disord* 2006; **90**: 57-61 [PMID: 16324749 DOI: 10.1016/j.jad.2005.09.012]

144   **Soyka M**, Schmidt P. Prevalence of delusional jealousy in psychiatric disorders. *J Forensic Sci* 2011; **56**: 450-452 [PMID: 21265838 DOI: 10.1111/j.1556-4029.2010.01664.x]

145   **Tohen M**, Tsuang MT, Goodwin DC. Prediction of outcome in mania by mood-congruent or mood-incongruent psychotic features. *Am J Psychiatry* 1992; **149**: 1580-1584 [PMID: 1415828 DOI: 10.1176/ajp.149.11.1580]

146   **Fennig S**, Bromet EJ, Karant MT, Ram R, Jandorf L. Mood-congruent versus mood-incongruent psychotic symptoms in first-admission patients with affective disorder. *J Affect Disord* 1996; **37**: 23-29 [PMID: 8682975 DOI: 10.1016/0165-0327(95)00073-9]

147   **Toni C**, Perugi G, Mata B, Madaro D, Maremmani I, Akiskal HS. Is mood-incongruent manic psychosis a distinct subtype? *Eur Arch Psychiatry Clin Neurosci* 2001; **251**: 12-17 [PMID: 11315512 DOI: 10.1007/s004060170061]

148   **Coryell W**, Leon AC, Turvey C, Akiskal HS, Mueller T, Endicott J. The significance of psychotic features in manic episodes: a report from the NIMH collaborative study. *J Affect Disord* 2001; **67**: 79-88 [PMID: 11869754 DOI: 10.1016/s0165-0327(99)00024-5]

149   **Azorin JM**, Akiskal H, Hantouche E. The mood-instability hypothesis in the origin of mood-congruent versus mood-incongruent psychotic distinction in mania: validation in a French National Study of 1090 patients. *J Affect Disord* 2006; **96**: 215-223 [PMID: 16427134 DOI: 10.1016/j.jad.2004.08.012]

150   **Mohr P**, Pecenák J, Svestka J, Swingler D, Treuer T. Treatment of acute agitation in psychotic disorders. *Neuro Endocrinol Lett* 2005; **26**: 327-335 [PMID: 16136016]

151   **Mellesdal L**. Aggression on a psychiatric acute ward: a three-year prospective study. *Psychol Rep* 2003; **92**: 1229-1248 [PMID: 12931943 DOI: 10.2466/pr0.2003.92.3c.1229]

152   **Critchley HD**, Simmons A, Daly EM, Russell A, van Amelsvoort T, Robertson DM, Glover A, Murphy DG. Prefrontal and medial temporal correlates of repetitive violence to self and others. *Biol Psychiatry* 2000; **47**: 928-934 [PMID: 10807966 DOI: 10.1016/s0006-3223(00)00231-6]

153   **Pietrini P**, Guazzelli M, Basso G, Jaffe K, Grafman J. Neural correlates of imaginal aggressive

behavior assessed by positron emission tomography in healthy subjects. *Am J Psychiatry* 2000; **157**: 1772-1781 [PMID: 11058474 DOI: 10.1176/appi.ajp.157.11.1772]

154   **Serper M**, Beech DR, Harvey PD, Dill C. Neuropsychological and symptom predictors of aggression on the psychiatric inpatient service. *J Clin Exp Neuropsychol* 2008; **30**: 700-709 [PMID: 18608673 DOI: 10.1080/13803390701684554]

155   **Fogel BS**. The significance of frontal system disorders for medical practice and health policy. *J Neuropsychiatry Clin Neurosci* 1994; **6**: 343-347 [PMID: 7841805 DOI: 10.1176/jnp.6.4.343]

156   **Rasmussen K**, Levander S, Sletvold H.   Aggressive and non-aggressive schizophrenics: symptom profile and neuropsychological differences. Psychol Crime Law 1995; 2: 119-129 [DOI: 10.1080/10683169508409770]

157   **Barkataki I**, Kumari V, Das M, Hill M, Morris R, O'Connell P, Taylor P, Sharma T. A neuropsychological investigation into violence and mental illness. *Schizophr Res* 2005; **74**: 1-13 [PMID: 15694749 DOI: 10.1016/j.schres.2004.08.001]

158   **Krakowski M**, Czobor P. Violence in psychiatric patients: the role of psychosis, frontal lobe impairment, and ward turmoil. *Compr Psychiatry* 1997; **38**: 230-236 [PMID: 9202880 DOI: 10.1016/s0010-440x(97)90031-6]

159   **González-Pinto A**, Ballesteros J, Aldama A, Pérez de Heredia JL, Gutierrez M, Mosquera F, González-Pinto A. Principal components of mania. *J Affect Disord* 2003; **76**: 95-102 [PMID: 12943938 DOI: 10.1016/s0165-0327(02)00070-8]

160   **Dutton DG**, Karakanta C.   Depression as a risk marker for aggression: A critical review. Aggress Violent Behav 2013; 18: 310-319 [DOI: 10.1016/j.avb.2012.12.002]

161   **Peluso MA**, Hatch JP, Glahn DC, Monkul ES, Sanches M, Najt P, Bowden CL, Barratt ES, Soares JC. Trait impulsivity in patients with mood disorders. *J Affect Disord* 2007; **100**: 227-231 [PMID: 17097740 DOI: 10.1016/j.jad.2006.09.037]

162   **Semple SJ**, Zians J, Strathdee SA, Patterson TL. Psychosocial and behavioral correlates of depressed mood among female methamphetamine users. *J Psychoactive Drugs* 2007; **Suppl** 4: 353-366 [PMID: 18284102 DOI: 10.1080/02791072.2007.10399897]

163   **Perroud N**, Baud P, Mouthon D, Courtet P, Malafosse A. Impulsivity, aggression and suicidal behavior in unipolar and bipolar disorders. *J Affect Disord* 2011; **134**: 112-118 [PMID: 21723616 DOI: 10.1016/j.jad.2011.05.048]

164   **Gilman SE**, Abraham HD. A longitudinal study of the order of onset of alcohol dependence and major depression. *Drug Alcohol Depend* 2001; **63**: 277-286 [PMID: 11418232 DOI: 10.1016/s0376-8716(00)00216-7]

165   **Thase ME**, Salloum IM, Cornelius JD. Comorbid alcoholism and depression: treatment issues. *J Clin Psychiatry* 2001; **62** Suppl 20: 32-41 [PMID: 11584873]

166   **Sher L**, Oquendo MA, Galfalvy HC, Grunebaum MF, Burke AK, Zalsman G, Mann JJ. The relationship of aggression to suicidal behavior in depressed patients with a history of alcoholism. *Addict Behav* 2005; **30**: 1144-1153 [PMID: 15925124 DOI: 10.1016/j.addbeh.2004.12.001]

167   **Conner KR**, Pinquart M, Gamble SA. Meta-analysis of depression and substance use among individuals with alcohol use disorders. *J Subst Abuse Treat* 2009; **37**: 127-137 [PMID: 19150207 DOI: 10.1016/j.jsat.2008.11.007]

168   **Boden JM**, Fergusson DM. Alcohol and depression. *Addiction* 2011; **106**: 906-914 [PMID: 21382111 DOI: 10.1111/j.1360-0443.2010.03351.x]

169   **Hintikka J**, Viinamäki H, Koivumaa-Honkanen HT, Saarinen P, Tanskanen A, Lehtonen J. Risk factors for suicidal ideation in psychiatric patients. *Soc Psychiatry Psychiatr Epidemiol* 1998; **33**: 235-240 [PMID: 9604674 DOI: 10.1007/s001270050049]

170   **Blair-West GW**, Cantor CH, Mellsop GW, Eyeson-Annan ML. Lifetime suicide risk in major depression: sex and age determinants. *J Affect Disord* 1999; **55**: 171-178 [PMID: 10628886 DOI: 10.1016/s0165-0327(99)00004-x]

171   **O'Connor RC**, Connery H, Cheyne WM. Hopelessness: The role of depression, future directed thinking and cognitive vulnerability. *Psychol Health Med* 2000; **5**: 155-161 [PMID: 29156959 DOI: 10.1080/713690188]

172   **Muehlenkamp JJ**, Swanson JD, Brausch AM.   Self-objectification, risk taking, and self-harm in college women. Psychol Women Q 2005; 29: 24-32 [DOI: 10.1111/j.1471-6402.2005.00164.x]

173   **Gormley B**, McNiel DE.   Adult attachment orientations, depressive symptoms, anger, and self-directed aggression by psychiatric patients. Cognit Ther Res 2010; 34: 272-281 [DOI: 10.1007/s10608-009-9267-5]

174   **Linnoila M**, Virkkunen M, Scheinin M, Nuutila A, Rimon R, Goodwin FK. Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from nonimpulsive violent behavior. *Life Sci* 1983; **33**: 2609-2614 [PMID: 6198573 DOI: 10.1016/0024-3205(83)90344-2]

175   **Mann JJ**, Waternaux C, Haas GL, Malone KM. Toward a clinical model of suicidal behavior in psychiatric patients. *Am J Psychiatry* 1999; **156**: 181-189 [PMID: 9989552 DOI: 10.1176/ajp.156.2.181]

176   **Placidi GP**, Oquendo MA, Malone KM, Huang YY, Ellis SP, Mann JJ. Aggressivity, suicide attempts, and depression: relationship to cerebrospinal fluid monoamine metabolite levels. *Biol Psychiatry* 2001; **50**: 783-791 [PMID: 11720697 DOI: 10.1016/s0006-3223(01)01170-2]

177   **van Heeringen K**. The neurobiology of suicide and suicidality. *Can J Psychiatry* 2003; **48**: 292-300 [PMID: 12866334 DOI: 10.1177/070674370304800504]

178   **Alexander**, PC, Anderson CL.   An attachment approach to psychotherapy with the incest survivor.

Psychotherapy (Chic) 1994; 31: 665-675 [DOI: 10.1037/0033-3204.31.4.665]

179   **Mikulincer M**. Adult attachment style and individual differences in functional versus dysfunctional experiences of anger. *J Pers Soc Psychol* 1998; **74**: 513-524 [PMID: 9491590 DOI: 10.1037//0022-3514.74.2.513]

180   **Lukassen J**, Beaudet MP. Alcohol dependence and depression among heavy drinkers in Canada. *Soc Sci Med* 2005; **61**: 1658-1667 [PMID: 15869834 DOI: 10.1016/j.socscimed.2005.03.019]

181   **van Praag HM**. Anxiety and increased aggression as pacemakers of depression. *Acta Psychiatr Scand Suppl* 1998; **393**: 81-88 [PMID: 9777052 DOI: 10.1111/j.1600-0447.1998.tb05971.x]

182   **Storch EA**, Lack CW, Merlo LJ, Geffken GR, Jacob ML, Murphy TK, Goodman WK. Clinical features of children and adolescents with obsessive-compulsive disorder and hoarding symptoms. *Compr Psychiatry* 2007; **48**: 313-318 [PMID: 17560950 DOI: 10.1016/j.comppsych.2007.03.001]

183   **Koeck B**, Sander G. [Elastic deformation of the mandibular arch]. *Dtsch Zahnarztl Z* 1978; **33**: 254-261 [PMID: 274280]

184   **Ivarsson T**, Melin K, Wallin L. Categorical and dimensional aspects of co-morbidity in obsessive-compulsive disorder (OCD). *Eur Child Adolesc Psychiatry* 2008; **17**: 20-31 [PMID: 18004647 DOI: 10.1007/s00787-007-0626-z]

185   **Watson D**, Clark LA, Stasik SM. Emotions and the emotional disorders: a quantitative hierarchical perspective. Int J Clin Health Psycho 2011; 11: 429-442

186   **Wetterneck CT**, Singh S, Hart J. Shame proneness in symptom dimensions of obsessive-compulsive disorder. *Bull Menninger Clin* 2014; **78**: 177-190 [PMID: 24870849 DOI: 10.1521/bumc.2014.78.2.177]

187   **Bejerot S**, Ekselius L, von Knorring L. Comorbidity between obsessive-compulsive disorder (OCD) and personality disorders. *Acta Psychiatr Scand* 1998; **97**: 398-402 [PMID: 9669509 DOI: 10.1111/j.1600-0447.1998.tb10021.x]

188   **Stein DJ**, Hollander E. Impulsive Aggression and Obsessive-Compulsive Disorder. Psychiatr Ann 1993; 23: 389-395 [DOI: 10.3928/0048-5713-19930701-10]

189   **Cogan R**, Ashford D, Chaney B, Embry S, Emory L, Goebel H, Holstrom N, Keithley D 3rd, Lawson M, Mcpherson J, Scott B, Tebbets J Jr. Obsessiveness and a thematic apperception test-based measure of aggression. *Psychol Rep* 2004; **95**: 828-830 [PMID: 15666912 DOI: 10.2466/pr0.95.3.828-830]

190   **Moritz S**, Kempke S, Luyten P, Randjbar S, Jelinek L. Was Freud partly right on obsessive-compulsive disorder (OCD)? *Psychiatry Res* 2011; **187**: 180-184 [PMID: 20950865 DOI: 10.1016/j.psychres.2010.09.007]

191   Angelopoulos NV. Relation of Anxiety to Hostility in the Course of Inpatient Treatment. Aggress Behav 2006; 32: 1-6 [DOI: 10.1002/ab.20100]

192   **Rubenstein CS**, Altemus M, Pigott TA, Hess A, Murphy DL. Symptom overlap between OCD and bulimia nervosa. J Anxiety Disord 1995; 9: 1-9 [DOI: 10.1016/0887-6185(95)91551-R]

193   **Whiteside SP**, Abramowitz JS. Obsessive-compulsive symptoms and the expression of anger. Cognit Ther Res 2004; 28: 259-268 [DOI: 10.1023/B:COTR.0000021544.64104.29]

194   **Whiteside SP**, Abramowitz JS. The expression of anger and its relationship to symptoms and cognitions in obsessive-compulsive disorder. *Depress Anxiety* 2005; **21**: 106-111 [PMID: 15965995 DOI: 10.1002/da.20066]

195   **Hauschildt M**, Jelinek L, Randjbar S, Hottenrott B, Moritz S. Generic and illness-specific quality of life in obsessive-compulsive disorder. *Behav Cogn Psychother* 2010; **38**: 417-436 [PMID: 20529398 DOI: 10.1017/S1352465810000275]

196   **Asbaugh AR**, Gelfand LA, Radomsky AS. Interpersonal aspects of responsiblity and obsessive compulsive symptoms. Behav Cogn Psychother 2006; 151-163 [DOI: 10.1017/S1352465805002699]

197   **Radomsky AS**, Ashbaugh AR, Gelfand LA. Relationships between anger, symptoms, and cognitive factors in OCD checkers. *Behav Res Ther* 2007; **45**: 2712-2725 [PMID: 17723225 DOI: 10.1016/j.brat.2007.07.009]

198   **Nagy NE**, El-Serafi DM, Elrassas HH, Abdeen MS, Mohamed DA. Impulsivity, hostility and suicidality in patients diagnosed with obsessive compulsive disorder. *Int J Psychiatry Clin Pract* 2020; **24**: 284-292 [PMID: 32628055 DOI: 10.1080/13651501.2020.1773503]

199   **Fountoulakis KN**, Leucht S, Kaprinis GS. Personality disorders and violence. *Curr Opin Psychiatry* 2008; **21**: 84-92 [PMID: 18281846 DOI: 10.1097/YCO.0b013e3282f31137]

200   **Duggan C**, Howard R. The 'functional link' between personality disorder and violence: A critical appraisal. In: McMurran M, Howard R. Personality, personality disorder and violence: An evidence based approach. Chichester, UK: Wiley-Blackwell, 2009: 19-37

201   **Dunne AL**, Gilbert F, Daffern M. Elucidating the relationship between personality disorder traits and aggression using the new DSM-5 dimensional-categorical model for personality disorder. Psychol Violence 2018; 8: 615-629 [DOI: 10.1037/vio0000144]

202   **Johnson JG**, Cohen P, Smailes E, Kasen S, Oldham JM, Skodol AE, Brook JS. Adolescent personality disorders associated with violence and criminal behavior during adolescence and early adulthood. *Am J Psychiatry* 2000; **157**: 1406-1412 [PMID: 10964855 DOI: 10.1176/appi.ajp.157.9.1406]

203   **Gilbert F**, Daffern M, Talevski D, Ogloff JR. Understanding the personality disorder and aggression relationship: an investigation using contemporary aggression theory. *J Pers Disord* 2015; **29**: 100-114 [PMID: 23398093 DOI: 10.1521/pedi_2013_27_077]

204   **Westen D**, Shedler J, Durrett C, Glass S, Martens A. Personality diagnoses in adolescence: DSM-IV axis II diagnoses and an empirically derived alternative. *Am J Psychiatry* 2003; **160**: 952-966 [PMID: 12727701 DOI: 10.1176/appi.ajp.160.5.952]

205   **Gilbert F**, Daffern M.   Illuminating the relationship between personality disorder and violence: Contributions of the General Aggression Model. Psychol Violence 2011; 1: 230-244 [DOI: 10.1037/a0024089]

206   **Lobbestael J**, Cima M, Lemmens A. The relationship between personality disorder traits and reactive versus proactive motivation for aggression. *Psychiatry Res* 2015; **229**: 155-160 [PMID: 26213380 DOI: 10.1016/j.psychres.2015.07.052]

207   **Genovese T**, Dalrymple K, Chelminski I, Zimmerman M. Subjective anger and overt aggression in psychiatric outpatients. *Compr Psychiatry* 2017; **73**: 23-30 [PMID: 27855338 DOI: 10.1016/j.comppsych.2016.10.008]

208   **Mancke F**, Herpertz SC, Bertsch K. Correlates of Aggression in Personality Disorders: an Update. *Curr Psychiatry Rep* 2018; **20**: 53 [PMID: 30032442 DOI: 10.1007/s11920-018-0929-4]

209   **Coid J**, Yang M, Tyrer P, Roberts A, Ullrich S. Prevalence and correlates of personality disorder in Great Britain. *Br J Psychiatry* 2006; **188**: 423-431 [PMID: 16648528 DOI: 10.1192/bjp.188.5.423]

210   **Timmerman IG**, Emmelkamp PM.   The prevalence and comorbidity of Axis I and Axis II pathology in a group of forensic patients. Int J Offender Ther Comp Criminol 2001; 45: 198-213 [DOI: 10.1177/0306624X01452006]

211   **Yu R**, Geddes JR, Fazel S. Personality disorders, violence, and antisocial behavior: a systematic review and meta-regression analysis. *J Pers Disord* 2012; **26**: 775-792 [PMID: 23013345 DOI: 10.1521/pedi.2012.26.5.775]

212   **Newhill CE**, Eack SM, Mulvey EP. Violent behavior in borderline personality. *J Pers Disord* 2009; **23**: 541-554 [PMID: 20001173 DOI: 10.1521/pedi.2009.23.6.541]

213   **Soloff PH**, Meltzer CC, Becker C, Greer PJ, Kelly TM, Constantine D. Impulsivity and prefrontal hypometabolism in borderline personality disorder. *Psychiatry Res* 2003; **123**: 153-163 [PMID: 12928103 DOI: 10.1016/s0925-4927(03)00064-7]

214   **de Barros DM**, de Pádua Serafim A. Association between personality disorder and violent behavior pattern. *Forensic Sci Int* 2008; **179**: 19-22 [PMID: 18524516 DOI: 10.1016/j.forsciint.2008.04.013]

215   **Látalová K**, Prasko J. Aggression in borderline personality disorder. *Psychiatr Q* 2010; **81**: 239-251 [PMID: 20390357 DOI: 10.1007/s11126-010-9133-3]

216   **Stepp SD**, Smith TD, Morse JQ, Hallquist MN, Pilkonis PA. Prospective associations among borderline personality disorder symptoms, interpersonal problems, and aggressive behaviors. *J Interpers Violence* 2012; **27**: 103-124 [PMID: 21859760 DOI: 10.1177/0886260511416468]

217   **Herr NR**, Keenan-Miller D, Rosenthal MZ, Feldblum J. Negative interpersonal events mediate the relation between borderline features and aggressive behavior: findings from a nonclinical sample of undergraduate women. *Personal Disord* 2013; **4**: 254-260 [PMID: 23647075 DOI: 10.1037/a0032212]

218   **Gunderson JG**, Lyons-Ruth K. BPD's interpersonal hypersensitivity phenotype: a gene-environment-developmental model. *J Pers Disord* 2008; **22**: 22-41 [PMID: 18312121 DOI: 10.1521/pedi.2008.22.1.22]

219   **Mancke F**, Herpertz SC, Bertsch K. Aggression in borderline personality disorder: A multidimensional model. *Personal Disord* 2015; **6**: 278-291 [PMID: 26191822 DOI: 10.1037/per0000098]

220   **Wagner AW**, Linehan MM. Facial expression recognition ability among women with borderline personality disorder: implications for emotion regulation? *J Pers Disord* 1999; **13**: 329-344 [PMID: 10633314 DOI: 10.1521/pedi.1999.13.4.329]

221   **von Ceumern-Lindenstjerna IA**, Brunner R, Parzer P, Mundt C, Fiedler P, Resch F. Initial orienting to emotional faces in female adolescents with borderline personality disorder. *Psychopathology* 2010; **43**: 79-87 [PMID: 20068378 DOI: 10.1159/000274176]

222   **Tikkanen R**, Holi M, Lindberg N, Tiihonen J, Virkkunen M. Recidivistic offending and mortality in alcoholic violent offenders: a prospective follow-up study. *Psychiatry Res* 2009; **168**: 18-25 [PMID: 19467714 DOI: 10.1016/j.psychres.2008.02.009]

223   **Allen A**, Links PS. Aggression in borderline personality disorder: evidence for increased risk and clinical predictors. *Curr Psychiatry Rep* 2012; **14**: 62-69 [PMID: 22033830 DOI: 10.1007/s11920-011-0244-9]

224   **Mancke F**, Bertsch K, Herpertz SC. Gender differences in aggression of borderline personality disorder. *Borderline Personal Disord Emot Dysregul* 2015; **2**: 7 [PMID: 26401309 DOI: 10.1186/s40479-015-0028-7]

225   **Kernis MH**, Cornell DP, Sun CR, Berry A, Harlow T. There's more to self-esteem than whether it is high or low: the importance of stability of self-esteem. *J Pers Soc Psychol* 1993; **65**: 1190-1204 [PMID: 8295118 DOI: 10.1037//0022-3514.65.6.1190]

226   **Halmai T**, Tényi T.   Személyiségzavarok - igazságügyi pszichiátriai vonatkozások. In: Tényi T. Személyiségzavarok - klinikum és kutatás. Budapest: Medicina Könyvkiadó, 2017: 267-294

227   **Walsh Z**, Swogger MT, Kosson DS. Psychopathy and instrumental violence: facet level relationships. *J Pers Disord* 2009; **23**: 416-424 [PMID: 19663661 DOI: 10.1521/pedi.2009.23.4.416]

228   **Declercq F**, Willemsen J, Audenaert K, Verhaeghe P.   Psychopathy and predatory violence in homicide, violent, and sexual offences: Factor and facet relations. Legal Criminol Psychol 2012; 17:

59-74 [DOI: 10.1348/135532510X527722]

229   **Azevedo J**, Vieira-Coelho M, Castelo-Branco M, Coelho R, Figueiredo-Braga M. Impulsive and premeditated aggression in male offenders with antisocial personality disorder. *PLoS One* 2020; **15**: e0229876 [PMID: 32142531 DOI: 10.1371/journal.pone.0229876]

230   **Lambe S**, Hamilton-Giachritsis C, Garner E, Walker J. The Role of Narcissism in Aggression and Violence: A Systematic Review. *Trauma Violence Abuse* 2018; **19**: 209-230 [PMID: 27222500 DOI: 10.1177/1524838016650190]

231   **Walker JS**, Bright JA.   False inflated self-esteem and violence: A systematic review and cognitive model. J Forens Psychiatry Psychol 2009; 20: 1-32 [DOI: 10.1080/14789940701656808]

232   **Crocker AG**, Mercier C, Lachapelle Y, Brunet A, Morin D, Roy ME. Prevalence and types of aggressive behaviour among adults with intellectual disabilities. *J Intellect Disabil Res* 2006; **50**: 652-661 [PMID: 16901292 DOI: 10.1111/j.1365-2788.2006.00815.x]

233   **Tenneij NH**, Didden R, Stolker JJ, Koot HM. Markers for aggression in inpatient treatment facilities for adults with mild to borderline intellectual disability. *Res Dev Disabil* 2009; **30**: 1248-1257 [PMID: 19464143 DOI: 10.1016/j.ridd.2009.04.006]

234   **Tsiouris JA**, Kim SY, Brown WT, Cohen IL. Association of aggressive behaviours with psychiatric disorders, age, sex and degree of intellectual disability: a large-scale survey. *J Intellect Disabil Res* 2011; **55**: 636-649 [PMID: 21492292 DOI: 10.1111/j.1365-2788.2011.01418.x]

235   **van den Akker N**, Kroezen M, Wieland J, Pasma A, Wolkorte R. Behavioural, psychiatric and psychosocial factors associated with aggressive behaviour in adults with intellectual disabilities: A systematic review and narrative analysis. *J Appl Res Intellect Disabil* 2021; **34**: 327-389 [PMID: 33073443 DOI: 10.1111/jar.12809]

236   **Embregts PJ**, Didden R, Huitink C, Schreuder N. Contextual variables affecting aggressive behaviour in individuals with mild to borderline intellectual disabilities who live in a residential facility. *J Intellect Disabil Res* 2009; **53**: 255-264 [PMID: 19178616 DOI: 10.1111/j.1365-2788.2008.01132.x]

237   **Lundqvist LO**. Prevalence and risk markers of behavior problems among adults with intellectual disabilities: a total population study in Örebro County, Sweden. *Res Dev Disabil* 2013; **34**: 1346-1356 [PMID: 23417139 DOI: 10.1016/j.ridd.2013.01.010]

238   **Crocker AG**, Prokić A, Morin D, Reyes A. Intellectual disability and co-occurring mental health and physical disorders in aggressive behaviour. *J Intellect Disabil Res* 2014; **58**: 1032-1044 [PMID: 23952483 DOI: 10.1111/jir.12080]

239   **Cooper SA**, Smiley E, Jackson A, Finlayson J, Allan L, Mantry D, Morrison J. Adults with intellectual disabilities: prevalence, incidence and remission of aggressive behaviour and related factors. *J Intellect Disabil Res* 2009; **53**: 217-232 [PMID: 19178617 DOI: 10.1111/j.1365-2788.2008.01127.x]

240   **Borthwick-Duffy SA**.   Prevalence of destructive behaviors. A study of aggression, self-injury, and property destruction. In: Thompson T, Gray DB. Destructive Behavior in Developmental Disabilities: Diagnoses and Treatment. Thousand Oaks, CA: Sage, 1994: 3-23

241   **Jacobson JW**. Problem behavior and psychiatric impairment within a developmentally disabled population I: behavior frequency. *Appl Res Ment Retard* 1982; **3**: 121-139 [PMID: 7125639 DOI: 10.1016/0270-3092(82)90002-9]

242   **Drieschner KH**, Marrozos I, Regenboog M. Prevalence and risk factors of inpatient aggression by adults with intellectual disabilities and severe challenging behaviour: a long-term prospective study in two Dutch treatment facilities. *Res Dev Disabil* 2013; **34**: 2407-2418 [PMID: 23711630 DOI: 10.1016/j.ridd.2013.04.008]

243   **McClintock K**, Hall S, Oliver C. Risk markers associated with challenging behaviours in people with intellectual disabilities: a meta-analytic study. *J Intellect Disabil Res* 2003; **47**: 405-416 [PMID: 12919191 DOI: 10.1046/j.1365-2788.2003.00517.x]

244   **Hemmings CP**, Gravestock S, Pickard M, Bouras N. Psychiatric symptoms and problem behaviours in people with intellectual disabilities. *J Intellect Disabil Res* 2006; **50**: 269-276 [PMID: 16507031 DOI: 10.1111/j.1365-2788.2006.00827.x]

245   **Crocker AG**, Mercier C, Allaire JF, Roy ME. Profiles and correlates of aggressive behaviour among adults with intellectual disabilities. *J Intellect Disabil Res* 2007; **51**: 786-801 [PMID: 17803497 DOI: 10.1111/j.1365-2788.2007.00953.x]

246   **Cohen IL**, Tsiouris JA, Flory MJ, Kim SY, Freedland R, Heaney G, Pettinger J, Brown WT. A large scale study of the psychometric characteristics of the IBR Modified Overt Aggression Scale: findings and evidence for increased self-destructive behaviors in adult females with autism spectrum disorder. *J Autism Dev Disord* 2010; **40**: 599-609 [PMID: 19941156 DOI: 10.1007/s10803-009-0908-z]

247   **Bruininks RH**, Olson KM, Larson SA, Lakin KC.   Challenging behaviors among persons with mental retardation in residential settings. In: Thompson T, Gray DB. Destructive Behavior in Developmental Disabilities: Diagnoses and Treatment. Thousand Oaks, CA: Sage, 1994: 24-48

248   **Lloyd BP**, Kennedy CH. Assessment and treatment of challenging behaviour for individuals with intellectual disability: a research review. *J Appl Res Intellect Disabil* 2014; **27**: 187-199 [PMID: 24464965 DOI: 10.1111/jar.12089]

249   **Vojt G**, Marshall LA, Thomson LD.   The assessment of imminent inpatient aggression: A validation study of the DASA-IV in Scotland. J Forens Psychiatry Psychol 2010; 21: 789-800 [DOI: 10.1080/14789949.2010.489952]

250 **Ravyts SG**, Perez E, Donovan EK, Soto P, Dzierzewski JM. Measurement of aggression in older adults. *Aggress Violent Behav* 2021; **57** [PMID: 34025202 DOI: 10.1016/j.avb.2020.101484]

251 **Suris A**, Lind L, Emmett G, Borman PD, Kashner M, Barratt ES. Measures of aggressive behavior: Overview of clinical and research instruments. Aggress Violent Behav 2004; 9: 165-227 [DOI: 10.1016/S1359-1789(03)00012-0]

252 **Krakowski MI**, Czobor P. The denial of aggression in violent patients with schizophrenia. *Schizophr Res* 2012; **141**: 228-233 [PMID: 23010487 DOI: 10.1016/j.schres.2012.08.037]

253 **Dickens GL**, O'Shea LE, Christensen M. Structured assessments for imminent aggression in mental health and correctional settings: Systematic review and meta-analysis. *Int J Nurs Stud* 2020; **104**: 103526 [PMID: 32062051 DOI: 10.1016/j.ijnurstu.2020.103526]

254 **Ogloff JR**, Daffern M. The dynamic appraisal of situational aggression: an instrument to assess risk for imminent aggression in psychiatric inpatients. *Behav Sci Law* 2006; **24**: 799-813 [PMID: 17171770 DOI: 10.1002/bsl.741]

255 **Daffern M**, Howells K, Hamilton L, Mannion A, Howard R, Lilly M. The impact of structured risk assessments followed by management recommendations on aggression in patients with personality disorder. J Forens Psychiatry Psychol 2009; 20: 661-679 [DOI: 10.1080/14789940903173990]

256 **Douglas KS**, Hart SD, Webster CD, Belfrage H. HCR-20: Assessing risk for violence (Version 3). Burnaby, BC: Vancouver, Canada: Mental Health, Law, and Policy Institute, Simon Fraser University, 2013

257 **Douglas KS**, Hart SD, Webster CD, Belfrage H, Guy LS, Wilson CM. Historical-clinical-risk management-20, version 3 (HCR-20V3): development and overview. Int J Forensic Ment Health 2014; 13: 93-108 [DOI: 10.1080/14999013.2014.906519]

258 **Neil C**, O'Rourke S, Ferreira N, Flynn L. Protective factors in violence risk assessment: Predictive validity of the SAPROF and HCR-20V3. Int J Forensic Ment Health 2020; 19: 84-102 [DOI: 10.1080/14999013.2019.1643811]

259 **Doyle M**, Power LA, Coid J, Kallis C, Ullrich S, Shaw J. Predicting post-discharge community violence in England and Wales using the HCR-20V3. Int J Forensic Ment Health 2014; 13: 140-147 [DOI: 10.1080/14999013.2014.906517]

260 **Almvik R**, Woods P, Rasmussen K. The Brøset Violence Checklist: sensitivity, specificity, and interrater reliability. J Interpers Violence 2000; 15: 1284-1296 [DOI: 10.1177/088626000015012003]

261 **Woods P**, Almvik R. The Brøset violence checklist (BVC). *Acta Psychiatr Scand Suppl* 2002; 103-105 [PMID: 12072138 DOI: 10.1034/j.1600-0447.106.s412.22.x]

262 **Nijman HL**, Muris P, Merckelbach HL, Palmstierna T, Wistedt B, Vos AM, Rixtel VA, Allertz W. The staff observation aggression scale-revised (SOAS-R). Aggress Behav 1999; 25: 197-209 [DOI: 10.1002/(SICI)1098-2337(1999)25:3<197::AID-AB4>3.0.CO;2-C]

263 **Nijman HL**, Palmstierna T, Almvik R, Stolker JJ. Fifteen years of research with the Staff Observation Aggression Scale: a review. *Acta Psychiatr Scand* 2005; **111**: 12-21 [PMID: 15636589 DOI: 10.1111/j.1600-0447.2004.00417.x]

264 **Knoedler DW**. The Modified Overt Aggression Scale. *Am J Psychiatry* 1989; **146**: 1081-1082 [PMID: 2750991 DOI: 10.1176/ajp.146.8.1081b]

265 **Yudofsky SC**, Silver JM, Jackson W, Endicott J, Williams D. The Overt Aggression Scale for the objective rating of verbal and physical aggression. *Am J Psychiatry* 1986; **143**: 35-39 [PMID: 3942284 DOI: 10.1176/ajp.143.1.35]

266 **Steinert T**, Wölfle M, Gebhardt RP. Measurement of violence during in-patient treatment and association with psychopathology. *Acta Psychiatr Scand* 2000; **102**: 107-112 [PMID: 10937782 DOI: 10.1034/j.1600-0447.2000.102002107.x]

267 **Margari F**, Matarazzo R, Casacchia M, Roncone R, Dieci M, Safran S, Fiori G, Simoni L; EPICA Study Group. Italian validation of MOAS and NOSIE: a useful package for psychiatric assessment and monitoring of aggressive behaviours. *Int J Methods Psychiatr Res* 2005; **14**: 109-118 [PMID: 16175880 DOI: 10.1002/mpr.22]

268 **Huang HC**, Wang YT, Chen KC, Yeh TL, Lee IH, Chen PS, Yang YK, Lu RB. The reliability and validity of the Chinese version of the Modified Overt Aggression Scale. *Int J Psychiatry Clin Pract* 2009; **13**: 303-306 [PMID: 24916941 DOI: 10.3109/13651500903056533]

269 **BUSS AH**, DURKEE A. An inventory for assessing different kinds of hostility. *J Consult Psychol* 1957; **21**: 343-349 [PMID: 13463189 DOI: 10.1037/h0046900]

270 **Vassar M**, Hale W. Reliability reporting across studies using the Buss Durkee Hostility Inventory. *J Interpers Violence* 2009; **24**: 20-37 [PMID: 18378813 DOI: 10.1177/0886260508314931]

271 **Ronan GF**, Dreer L, Maurelli K, Ronan D, Gerhart J. Practitioner's guide to empirically supported measures of anger, aggression, and violence. Springer Science & Business Media, 2013 [DOI: 10.1007/978-3-319-00245-3]

272 **Buss AH**, Perry M. The aggression questionnaire. *J Pers Soc Psychol* 1992; **63**: 452-459 [PMID: 1403624 DOI: 10.1037//0022-3514.63.3.452]

273 **Buss AH**, Warren WL. Aggression questionnaire: (AQ). Torrence, CA: Western Psychological Services, 2000

274 **Spielberger CD**. Professional manual for the State-Trait Anger Expression Inventory-2 (STAXI-2). Odessa, FL: Psychological Assessment Resources, 1999

275 **Borteyrou X**, Bruchon-Schweitzer M, Spielberger CD. [The French adaptation of the STAXI-2, C.D. Spielberger's State-trait anger expression inventory]. *Encephale* 2008; **34**: 249-255 [PMID:

18558145 DOI: 10.1016/j.encep.2007.06.001]

276   **Culhane SE**, Morera OF.   Reliability and validity of the Novaco Anger Scale and Provocation Inventory (NAS-PI) and State-Trait Anger Expression Inventory-2 (STAXI-2) in hispanic and non-hispanic white student samples. Hisp J Behav Sci 2010; 32: 586-606 [DOI: 10.1177/0739986310381458]

277   **Etzler SL**, Rohrmann S, Brandt H.   Validation of the STAXI-2: A study with prison inmates. Psychol Test Assess Model 2014; 56: 178-194

278   **Redondo N**, Peña ME, Graña JL, Andreu JM. Psychometric properties of the Aggression Questionnaire: A replication in a sample of partner-assaultive men in psychological treatment. *Psicothema* 2017; **29**: 584-589 [PMID: 29048322 DOI: 10.7334/psicothema2016.390]

Resilience to the effects of social stress on vulnerability to developing drug addiction

Claudia Calpe-López, Maria A Martínez-Caballero, Maria P García-Pardo, Maria A Aguilar

ORCID number: Claudia Calpe-López 0000-0001-9926-8485; Maria A Martínez-Caballero 0000-0001-9838-5831; Maria P García-Pardo 0000-0003-2730-0145; Maria A Aguilar 0000-0002-1935-6619.

Claudia Calpe-López, Maria A Martínez-Caballero, Maria A Aguilar, Department of Psychobiology, University of Valencia, Valencia 46010, Spain

Maria P García-Pardo, Faculty of Social and Human Sciences, University of Zaragoza, Teruel 44003, Spain

Corresponding author: Maria A Aguilar, PhD, Full Professor, Department of Psychobiology, University of Valencia, Avda, Blasco Ibáñez 21, Valencia 46010, Spain. asuncion.aguilar@uv.es

Abstract

We review the still scarce but growing literature on resilience to the effects of social stress on the rewarding properties of drugs of abuse. We define the concept of resilience and how it is applied to the field of drug addiction research. We also describe the internal and external protective factors associated with resilience, such as individual behavioral traits and social support. We then explain the physiological response to stress and how it is modulated by resilience factors. In the subsequent section, we describe the animal models commonly used in the study of resilience to social stress, and we focus on the effects of chronic social defeat (SD), a kind of stress induced by repeated experience of defeat in an agonistic encounter, on different animal behaviors (depression- and anxiety-like behavior, cognitive impairment and addiction-like symptoms). We then summarize the current knowledge on the neurobiological substrates of resilience derived from studies of resilience to the effects of chronic SD stress on depression- and anxiety-related behaviors in rodents. Finally, we focus on the limited studies carried out to explore resilience to the effects of SD stress on the rewarding properties of drugs of abuse, describing the current state of knowledge and suggesting future research directions.

Key Words: Resilience; Stress; Depression; Drug addiction; Animal models; Social defeat

Core Tip: Preclinical research on drug addiction has focused on the factors that enhance vulnerability to develop drug addiction. Recent studies of resilience have determined

the neurobehavioral traits that confer protection against developing an addictive disorder after stress exposure. Active coping strategies to face the stressor and the absence of depression-like symptoms are consistently associated with resilience to the stress-induced potentiation of the rewarding effects of cocaine and alcohol. Unravelling the neurobiological substrates of resilience is key to developing pharmacological and psychological interventions to enhance stress resilience in order to prevent the development of addiction and other stress-related disorders.

INTRODUCTION

The noun resilience derives from the Latin *resiliens,* the present participle of resilire (re-"back" + salire "to jump"), and was first used by Cicero and Francis Bacon (among others) as a synonym of rebound[1]. From the nineteen century on, material science has also used the word resilience to indicate the flexibility of a material or its ability to resist stress (force being applied) without permanent deformation. In the context of psychology, resilience can be defined as "the process of adapting well in the face of adversity, trauma, or other significant sources of stress"[2,3]. Besides the rebound of the equilibrium, resilience often implies an increase in mental resistance.

Although resilience is sometimes considered an extraordinary capacity of some individuals, research indicates that it is a common trait. The majority of individuals exposed to trauma or stressful events adapt to and overcome stress and maintain normal psychological and physical functioning without developing stress-related disorders[4]. Approximately 50% of people experience trauma in their life, but the prevalence of post-traumatic stress disorder (PTSD) is about 8%[5]. Resilience is an innate capacity, although it is not a stable trait, it is a dynamic process[6,7] that changes through a life span and can be enhanced by different factors.

RESILIENCE TO STRESS AND DRUG ADDICTION

Most research on resilience has focused on the biological and behavioral profile of individuals who are resilient to developing psychiatric illnesses such as depression and PTSD after exposure to stress. However, studies on resilience to the effects of stress on the initiation, maintenance and relapse to addictive disorders are very limited. In fact, almost all research regarding substance use disorders (SUD) has focused on risk; *i.e.*, the factors that predispose an individual to develop an addictive disorder. Vulnerability to the effects of drugs of abuse depends on multiple factors, including biologic factors such as genetic load, which are modified by life experiences and the environment in which the individual lives. Stressful experiences have a profound impact on the brain[8], for this reason, stress can increase vulnerability to addiction. Exposure to stress, especially in early life and adolescence, induces long-term modifications in the physiological response to stress, emotional reactivity, the brain reward system and cognitive processing, all of which contribute to the increased vulnerability to develop a SUD[9]. However, as commented on before, most people are resilient to stress. Consequently, only a small percentage of individuals that experience a traumatic event or are exposed to chronic stress develop an addictive disorder.

In recent years there has been an important impulse in the study of resilience to develop a SUD or an addictive behavior. In fact, until 2010, literature related to resilience and addiction was scarce, while in the last ten years the number of works on the subject has increased exponentially (Figure 1). Epidemiologic studies indicate a clear association between low resilience (often during adolescence) and the increment of addictive behaviors[10,11]. Resilience is a factor moderating the relationship between stress and alcohol use disorders (AUD)[12] and is strongly associated with a

Studies on resilience and addiction
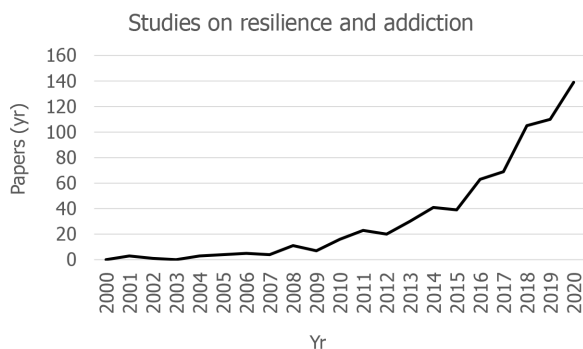
Figure 1 Results from the search "resilience and addiction" in the PubMed database (https://pubmed.ncbi.nlm.nih.gov, accessed on December 15, 2021). Number of papers published each year from 2000 until 2020.

reduction in the risk of AUD, though there is not a direct causal relationship but rather an overlapping of genetic and environmental influences[13]. Animal models used to study the impact of stress on drug addiction[14,15] are also being incorporated into research to identify the behavioral and physiological traits that characterize animals' resilience to the effects of stress on the rewarding properties of drugs of abuse, as well as the neurobiological substrates of the resilience process.

Addressing the perspective of resilience in the study of addictive behaviors is promising as a way of enhancing knowledge regarding the neuroscience of addiction. However, as Rudzinski *et al*[16] noted, there are difficulties in the use of the concept of resilience in the field of drug addiction, especially regarding its definition and operationalization as a trait, as a process or, as is more common, as an outcome (for example, the absence of SUD). In addition, it is important to distinguish between resilience (a concept with multiple meanings) and resiliency, which is a personality trait that has been linked to alcohol/drug problems and is defined as "the ability to flexibly adapt impulse control relative to contextual demand"[17]. Some studies define resilience as the capacity to maintain abstinence and not relapse to drug use during a recovery period[18,19]. In this sense, neuroimaging studies have shown that conserved prefrontal cortex (PFC) morphology and heightened neural PFC engagement are linked to abstinence and resilience against relapse in alcohol-dependent patients[19]. Other studies consider drug use as a stressor or risk factor for resilience (for example [20]), while some studies do not evaluate resilience to stress. In the last case, the concept of resilience is used to design a reduced response to the drugs of abuse in rodents that have been exposed to a genetic or pharmacological manipulation[21,22].

In the present review we mainly focus on research that has studied resilience to the effects of stressful experiences on subsequent drug use/abuse in animal models. First, we succinctly comment on the protective factors associated with resilience in studies with humans and explain the relationship between the physiological response to stress and resilience, since most human studies have focused on the neuroendocrine changes that are predictive of resilience. We then discuss the main animal models used to study resilience to social stress and review advances concerning the neurobiological substrates of resilience in said studies. Finally, we discuss research that specifically addresses resilience to the effects of repeated social defeat (SD) on the rewarding properties of drugs of abuse and lay out future research directions and conclusions.

BEHAVIORAL TRAITS AND PROTECTIVE FACTORS ASSOCIATED WITH RESILIENCE

Different protective factors associated with resilience can be identified on biological, psychological, and social levels. Among the internal factors are stable predispositions (such as genotype or personality traits) and the influence of skills or capacities acquired through interaction with stressors (emotion-regulation abilities, appraisal styles, *etc.*). Resilient people are more prone to experience positive emotions, realistic optimism, cognitive reappraisal (ability to replace negative thoughts with more positive ones), secure attachment, an active coping with stress, high coping self-efficacy, self-esteem, empathy, prosocial behavior and altruism, a healthy lifestyle (for example, physical exercise) and a sense of coherence (moral compass that gives

meaning of life)[4,16,23,24].

There are also external factors related with resilience at three levels[16]: Family (parental supervision, setting boundaries, bonding, support, *etc*.), school (positive environment, good relationships with teachers and peers, school engagement and extra-curricular activities involvement, *etc*.) and community (positive relationships with friends or neighbors, participation in religious practices, community engagement, community support, *etc*.). All these internal strengths and external resources help to prevent maladaptive responses to adversity[9]. Longitudinal studies have indicated several key factors related with resilience and a successful transition from childhood and adolescence to adulthood, such as social support (family, peer relationships, romantic partners, *etc*.), self-discipline, and good cognitive and executive functioning (planification, cognitive flexibility, *etc*.)[25]. Children exposed to war show increased risk of PTSD in adulthood, but some protective factors against the deleterious impact of war have been identified, including a loving and supportive environment (family, peers, teachers, *etc*.), a shared sense of values and religious beliefs, positive thinking and generosity[26]. Similarly, in patients with psychiatric disorders (depression and/or anxiety), factors predictive of low resilience include lack of purpose in life, less frequent physical exercise and low spirituality[27]. A study with fire-workers indicated that the trait of mindfulness (concentration on and moment-to-moment awareness of bodily activities and feelings) contributed to resilience, thus reducing avoidant coping in response to stress. Fire-workers with this trait reported less alcohol problems and reduced physical, depressive and PTSD symptoms[28].

As mentioned before, resilience is a dynamic process that raises individuals up from life's adversities and allows them to successfully overcome stressful events. The phenomenon known as "stress inoculation" occurs when a person exposed to mild or moderate stressors develops an adaptive stress response and shows a higher resilience to the negative effects of a variety of subsequent stressors[5,29]. As demonstrated by the group of McEwen, the behavioral effects of stress follow an inverted U–shape curve; low and high stress levels induced impairing effects, but intermediate levels promote better coping responses[30]. In the same way as a vaccine induces immunity against disease[2], stress inoculation is a form of immunity or protection against later stress that may be a result of neuroplasticity in the PFC[29]. The "Systematic Self-reflection model" proposes that engaging with moderate stressors can have positive consequences on mental health if sca□olded in self-reflection, a meta-cognitive skill (consisting of an honest reflection on the individual's coping and emotion regulatory practices) that leads to a cognitive maturity and on-going adaptation of the capacity of resilience[31]. On the other hand, substance use and other adjustment problems (depression, anxiety, rule-breaking, *etc*.) have been observed in adolescents from affluent families that have not been exposed to identified stressful experiences. These individuals are now considered as a group at risk that needs to build resilience through positive changes in parenting, construction and maintenance of supportive social networks, promotion of coping self-efficacy and self-esteem, *etc*[32].

PHYSIOLOGICAL RESPONSE TO STRESS AND RESILIENCE

Exposure to a physically or psychologically stressful stimulus immediately activates a physiological response characterized by a cascade of hormones in the hypothalamus-pituitary-adrenal (HPA) axis that prepare the body for fight or flight. The paraventricular nucleus of the hypothalamus releases corticotropin-releasing factor (CRF), which leads to the release of adrenocorticotropic hormone (ACTH) by the adenohypophysis, which in turn stimulates the release of glucocorticoids (cortisol in humans and corticosterone in rodents) by the cortex of adrenal glands. There are negative feedback mechanisms in the HPA axis; for example, glucocorticoids suppress CRF and ACTH production. In addition, stress activates the sympathetic nervous system (SNS), which induces the adrenomedullary release of noradrenaline (NA). Stress also stimulates the brain's noradrenergic system, resulting in the release of NA from the locus coeruleus (LC) to the amygdala, hippocampus, hypothalamus and PFC [33,34]. Dopamine (DA) release is also altered by stress, with an increase in the PFC and a reduction in the nucleus accumbens (NAcc)[35], and acute stress increases serotonin turnover in the amygdala, hippocampus, PFC and NAcc[36-38], although other studies have shown a lack of an effect of acute stress on serotonin turnover in the amygdala, NAcc, striatum[39] and hypothalamic paraventricular nucleus[38].

Glucocorticoid elevation may cause damage and atrophy of neurons in different brain areas involved in memory and emotional behavior, such as the hippocampus

and amygdala, inducing physical and psychological problems. Moreover, chronic stress interferes with the activity of neurotrophic factors that are responsible for the formation and strengthening of new neurons and synaptic connections, especially in the hippocampus, such as brain-derived neural factor (BDNF). The volume of this structure and the levels of BDNF are reduced in subjects exposed to prolonged stress, which could be a risk factor for the development of PTSD[40-42]. Resilience can avoid these negative effects of stress, for example, through the release of substances that block the physiological stress response. Neuropeptide Y (NPY) and dehydroepi-androsterone (DHEA) counteract CRF and cortisol, respectively[43,44]. Higher levels of NPY in response to acute stress predict less psychological distress and fewer symptoms of dissociation[45]. Furthermore, the brain of resilient people produces more BDNF, which also decreases levels of glucocorticoids in the hippocampus, and BDNF-mediated plasticity increases attention and memory and accelerates recovery from adversity. Resilient people have been shown to exhibit an adaptive stress response, rapid stress recovery (levels of cortisol decreasing fast after adversity) and lower susceptibility to stress-related physical and mental pathology[4].

There is an interface between the endocrine stress response and the immune system. Communication between neural, hormonal and immune systems is mediated by cytokines and chemokines, small molecules that mediate inflammatory processes, corticosteroids, pituitary hormones, catecholamines and neuropeptides[46,47]. Feedback between the peripheral immune system and the brain contributes to individual differences in the behavioral response to stress[48,49]. Resilient subjects display reduced neuroinflammation, which facilitates habituation to and recovery from stressful events and explains the lower incidence of medical and psychiatric diseases amongst these individuals[49,50,51]. Resilient people have lower systemic inflammation, and the psychosocial factors associated with resilience mitigate the impact of stress on systemic inflammation[51]. These bidirectional relationships between resilience and immunity are modulated by the gut microbiota[52]. There is an interaction between the gut and the brain that involves neural, endocrine, and immune pathways. It seems that the stress-induced activation of the HPA axis stimulates the immune system and causes changes in microbial diversity[53]. The gut microbiota has been associated with a wide range of physiological processes, including the response to stress[54]. Oral intake of Bifidobacterium was shown to significantly increase the number of mice that were resilient after repeated SD stress with respect to control animals not receiving treatment[55]. Moreover, administration of Lactobacillus was found to decrease anxiety-like behavior induced by repeated SD stress and to improve the immune response[56].

ANIMAL MODELS AND BEHAVIORAL PARADIGMS TO STUDY RESILIENCE TO SOCIAL STRESS

Animal models are necessary to understand the different aspects of human resilience, such as physiological or behavioral changes. As mentioned before, after exposure to stress, some humans develop a psychopathological disorder, such as depression or anxiety, while others are resilient to such effects. These disorders are complex and multifactorial and affect many aspects of human life; thus, no animal model can mimic the complexity of human disorder. However, animal models are useful for simulating some of the psychiatric symptoms[57] or behavioral dimensions that characterize a disorder[58]. After exposure to chronic stress, some animals develop depression– and anxiety–like symptoms and other behavioral alterations (susceptible or vulnerable animals), while others exhibit clear resistance to at least some of the maladaptive sequelae of stress (resilient animals). In addition, animal models also contribute to our understanding of the mechanisms underlying the development of resilience, such as the therapeutic effects of the inoculation of stress[59].

In this section, we first describe the animal models and behavioral tests used to study resilience to the symptoms of stress-related disorders, such as anxiety, depression, cognitive impairment or drug addiction and then the models used to induce stress in experimental animals. This is not an exhaustive review of these models, but only a brief description of the main paradigms used in preclinical studies of resilience. We focus on the model of SD stress in rodents, and on the behavioral paradigms that have been used to evaluate its short- and long-term consequences.

ANIMAL MODELS OF STRESS EXPOSURE

There are multiple techniques to induce stress in experimental rodents. Some of them use pharmacological stressors, such as daily administration of corticosterone[60], or physical stressors, such as restraint or immobilization[61]. Another model is based on a combination of physical and psychosocial stressors (chronic unpredictable stress (UCS) or chronic "mild" stress (CMS) paradigm)[62]. In the CMS, most animals (about 70%) show anhedonia–like symptoms (less sucrose consumption), reduction of hippocampal volume and alterations in glutamate metabolism, although there is a subset of resilient animals that do not exhibit these changes[62]. Resilience to stress has also been studied with the model known as "predator odor", in which the stress response is induced by exposing animals to the odor of a predator[63]. Usually, rats are classified into 3 groups according to the number and type of behavioral deficits observed as extremely, partially, or minimally disrupted. Anxiety–like symptoms, increased acoustic startle responses and reductions in NPY are observed in animals that are extremely disrupted, while partially and minimally disrupted animals exhibit mixed deficits within these domains[63].

The paradigm of learned helplessness is an animal model of depression that is also employed to induce stress and study resilience by exposing animals to the stress induced by an inescapable, unpredictable and uncontrollable foot shock[60,64,65]. After such exposure to stress, a subset of susceptible animals develops learned helplessness (coping deficits to deal with the inescapable shocks), while another subset of resilient animals displays escape responses with latencies similar to those of non-stressed animals[64]. Results are in function of the severity, duration and control over cessation of the footshock, the last variable of which promotes resilience[65].

As commented on before, in the present work we focus on the model of chronic SD stress because it is the most used animal model to study resilience to the effects of stress and has more ethological and ecological validity. In fact, the most frequent type of stress faced by humans is the chronic social stress derived from problems with social interaction (family or friend relationships, work-place stress, bullying, *etc.*). In the chronic SD model, brief episodes of aggression from a more aggressive conspecific in the resident-intruder paradigm result in the defeat of the experimental animal (intruder), which usually shows anxiety- and depression-like symptoms[15,66-69]. In the most widely employed SD model, rats or mice are exposed to SD for 10 days. Each day, the experimental animal undergoes 10 min of physical attack by the aggressive opponent, followed by 24 h of sensory contact. The consequences of this kind of stress are also a function of the severity and duration of the defeat episodes but chronic SD exposure induced an escalation of cocaine and alcohol consumption. To study resilience, genetically inbred C57BL6/J male mice are usually employed. Following chronic SD stress, all mice exhibit heightened reactivity of the HPA axis, deficits in exploration (interpreted as increased anxiety) and polydipsia[70]. However, there are differences between susceptible and resilient mice regarding other consequences of chronic SD. Resilient mice do not exhibit social avoidance, hyperthermia elicited by social interactions, anhedonia–like symptoms, or metabolic syndrome, characterized by over–eating, obesity, and leptin resistance[70,71]. Approximately 35% of C57BL6/J mice are resilient, although the relative distribution of resilience differs across strains [72]. Similarly, wild-type Groningen rats have better coping strategies and are more resilient to SD stress than Wistar rats[73].

A variation of the classical 10-day SD paradigm consists of exposing animals to intermittent repeated SD (IRSD); usually, four episodes of defeat separated by intervals of 72 h. The IRSD model is frequently employed in studies on the influence of social stress on vulnerability to developing drug addiction. Exposure to IRSD has also been shown to increase the rewarding effects of drugs of abuse[14,74,75,76]. In our laboratory, mice exposed to IRSD during adolescence or adulthood exhibit a long-term enhanced sensitivity to the rewarding effects of drug of abuse such as cocaine and MDMA[77,78,79].

To study the phenomenon of "stress inoculation" several types of moderate stressors have been used, including exposure to intermittent foot shocks[80] and brief intermittent maternal separations during early periods of life[81] or a combination of maternal separation and UCS[81]. Infant rats exposed to intermittent foot shocks subsequently respond more effectively than non-stressed control rats when confronted with novel situations[80]. The combination of maternal deprivation during early life with UCS during adolescence promotes greater resilience in adulthood than maternal deprivation alone or when combined with UCS[81].

During chronic exposure to stress, behavioral strategies that limit the experience of stress may promote resilience[5]. During chronic SD, animals that engage in less submissive postures when threatened and attacked by the opponent show less social avoidance, suggesting that this behavioral coping strategy reduces the effects of the stress[82]. Behavioral manipulations have also been used to reduce the effects of stress and increase resilience; for example, exposure to physical exercise[83,84] or environmental enrichment[85].

BEHAVIORAL PARADIGMS TO STUDY STRESS-RELATED PSYCHIATRIC DISORDERS

Behavioral tests of anxiety- and depression-like symptoms

The forced swim test (FST) is a classic behavioral test of depression-like symptomatology in which animals are placed into a cylinder filled with water and forced to swim during a period lasting a few minutes. Initially animals attempt to escape and swim, but afterwards they stop fighting and become passive. Immobility (passive floating with minor movements necessary to keep the head above water) is interpreted as a failure to persist in escape-directed behavior, hopelessness, negative mood and depressive-like behavior. The FST is frequently used to evaluate resilience since SD increases immobility in this test in susceptible but not in resilient animals[60,86,87,88]. Similar to the FST, the tail suspension test (TST) measures immobility, which is considered to represent despair and depressive-like behavior[89]. Rodents are hung in an uncontrollable fashion by their tail for a few minutes[90] and, after initial escape-oriented movements, develop an immobile posture. The effects of SD exposure in the TST are unclear, and it has been suggested that this paradigm models the stress-coping strategy from which depressive-like behavior is inferred[91]. An increase in immobility is observed in animals reared in a limited bedding and nesting environment, which induces erratic maternal care and social stress[92]. Similarly, exposure to chronic mild stress (CMS) has been shown to increase immobility in anhedonia-susceptible animals[87]. However, our group has recently observed a reduction of immobility after IRSD exposure, which could be interpreted as an enhanced reactivity of defeated mice to the situation of moderate inescapable stress that the TST represents[93].

Anhedonia– or depressive-like symptoms are also frequently evaluated by measuring sucrose consumption. During training, after some hours of food and water deprivation, a bottle containing a sucrose solution is made available in the home cage. Sucrose intake is measured at different intervals during stress exposure and is reduced in vulnerable but not resilient stressed animals[70,71,88,94,95]. The splash test consists of spraying a 10% sucrose solution on the dorsal coat of a rodent to stimulate grooming behavior. An increase in the latency of grooming and a decrease in the time and/or frequency of grooming is interpreted as depressive-like behavior[96]. This test has also been used to evaluate resilience to the consequences of SD stress[60,93].

In the social interaction test, animals are placed within an open field in two trials (2.5-10 min), in the absence (no target) and presence (target) of a conspecific animal contained in a perforated Plexiglas cage, in order to allow for social interaction while preventing confrontation. Social avoidance is considered to take place when the experimental animal spends less time in the area immediately surrounding the enclosure containing the opponent (interaction zone) and more time in the corners of the open field. Social avoidance is associated with depressive-like behaviors and is frequently observed after SD exposure in susceptible but not in resilient animals[70,71,93,97,98].

The novelty suppressed feeding test is based on the innate fear of rodents of novelty and the inhibition of feeding behavior when exposed to a novel environment. Animals' access to food is restricted for 12-24 h. Animals are placed in a corner of a box containing a pellet of food and the latency to begin eating is recorded. Immediately after this, animals are placed in its home cage and the amount of food consumed in 5 min is measured. This test detects behaviors related to depression and anxiety, because a conflict appears between the anxiogenic environment and hunger-induced behavior[60,99].

The elevated plus maze (EPM) is one of the most used paradigms to measure anxiety in rodents. This test is based on the natural aversion of rodents to open elevated areas and the exploratory behavior that they exhibit in novel environments. The apparatus, elevated about 50 cm above floor level, consists of two open arms and two enclosed arms, and the junction of the four arms forms a central platform. Subjects

are placed on the central platform and allowed to explore the maze for 5 min. The total time spent in and the number of entries into the open (and closed) arms, and the percentage of time and entries into the open arms are measured. Anxiety levels are considered to be lower when the measurements in the open arms are higher and those in the closed arms are lower, and vice versa[100,101]. Mice exposed to chronic SD exhibit higher anxiety levels in this paradigm[93,97,102]. The EPM is also frequently used in studies of resilience to the effects of social stress on anxiety[60,92,102]. In a recent study in our laboratory, we observed that mice that were resilient to the effects of stress on cocaine reward spent less time in the open arms[93].

In the open field/exploration test, the animal is placed into an open-field arena for several min and its locomotor activity is evaluated by measuring distance travelled and velocity. A reduction of these measures is indicative of anxiety[103]. Sometimes the open field is divided into a center and a surrounding area, with thigmotaxis being indicative of anxiety. Maternal separation decreases the time that mice remain in the center of the open field[104]. SD induces deficits in exploration that are not observed in resilient animals[60,70,71,102].

The hole-board test is used to evaluate anxiety-related and novelty-seeking behavior of rodents. This test is carried out in a square box with equidistant holes in the floor. The animal is placed in a corner of the box and is allowed to freely explore the apparatus for a few minutes. Head-dipping represents exploratory tendencies that are distinct from general locomotor activity; thus, the latency to perform the first head-dip and the frequency of dips is recorded. Stress exposure elevates anxiety-related behavior in the hole-board test in rats and mice[105,106]. In our laboratory, we have observed that mice with low novelty-seeking are resilient to the effects of SD on cocaine reward[93].

Behavioral tests to evaluate cognitive impairment

The novel object recognition test evaluates episodic memory in rodents[107] and has been used to measure cognitive dysfunction according to deficits in object-context identification[108]. The task is performed in an open field box and consists of three phases: habituation (free exploration of the empty box), training (exploration of the box, which contains two small river stones) and test (one of the stones is replaced with a small plastic toy). In the training and test sessions, separated for a memory retention interval (1 min), the exploration of the objects is measured for 3 min. It is assumed that if the animal recognizes the stone, it has spent more time exploring the new object. Exposure to different paradigms of stress induces cognitive deficits in recognition memory[94,104,105,109]. Acute[110] and chronic[97] SD impairs performance of the object recognition task. This task has also been used to study resilience to the impairing effects of social stress on cognition[88,94,97,111,112].

The Morris water maze task measures spatial memory that is dependent on the hippocampus[113]. The apparatus consists of a circular swimming pool, divided into 4 equal quadrants (NW, NE, SE and SW), with an escape platform placed 1 cm below the water surface. Several visual cues surrounding the maze are placed on the walls. During the training phase the animal is placed in the water inside one of the quadrants and allowed to swim freely until it locates and climbs onto the platform. If the animal fails to locate the platform, it is guided to the platform by the experimenter and allowed to stand on it for several seconds. The training is performed over 4-5 consecutive days (3 trials per day), measuring the escape latency (the time taken to locate the platform in each trial). The test is performed 24 h after the last training session (the platform is removed and the time spent in each quadrant is measured). If the animal recalls the placement of the hidden platform it will spend more time in that quadrant. Unpredicted CMS impairs performance of the water maze[114], but chronic SD stress does not affect this task[102]. The water maze has also been used to study resilience to the effects of stress on cognitive processes[114,115]. An interesting study [115] showed that rats that emitted ultrasonic vocalizations during intermittent swim stress later showed resilience in the Morris water maze and an instrumental swim escape test.

The Y-maze is a spatial task that requires intact hippocampal function[116]. The Y-maze apparatus has three identical and symmetrical arms that radiate out from the center. Explicit cues are presented outside the maze (located on the walls around the room). In the first trial, the animal is placed in one arm, designated as the "start" arm, while another arm is blocked so that the animal can only explore the start and the other arm. After 4 h, in the second trial, animals are placed in the start arm and can freely explore all three arms. The number of entries and the time spent in each arm is measured. If the animal recalls the arms previously explored in trial 1, it will spend more time in the "novel" arm in trial 2 (discrimination performance). CMS induces

deficits in the performance of the Y-maze among vulnerable anhedonic-rats[88]. Acute[110] but not chronic[117] SD stress also impairs performance in the Y-maze. However, the combination of chronic SD with a slight peripheral infection (produced by injection of a sub-threshold of LPS) impairs the performance of susceptible mice in the Y-maze[111].

The radial arm maze is a model of hippocampus-dependent memory. Animals are food-restricted (approximately 85.0% of their previous body weight) and pre-trained to associate the maze with a food reward placed at the end of all 8 arms. Subsequently, the animals are trained for several consecutive days. In each trial the animal is placed in the central chamber of the maze for habituation and can then freely explore the arms until it consumes all food reward or until a maximum time. The measurement of memory is the number of errors committed, defined as entries in a previously visited arm[118,119]. Chronic stress induced by visual and olfactory exposure to a predator (Long Evan rat) without direct physical contact impairs performance in the radial maze[118]. Similarly, maternal separation induces an overall impairment in the performance of the radial maze in adulthood; however, this impairment is observed in susceptible, but not in resilient mice[119]. On the other hand, adult rats exposed to maternal deprivation perform better in the radial maze, an effect probably related with the phenomenon of inoculation of stress[120].

The radial arm water maze also evaluates spatial ability in rodents[121,122,123]. In this case, the radial arm maze is filled with cloudy water to conceal a platform placed in one of the eight arms, and there are prominent extra-maze cues on the walls of the room. The animals perform several trials in three days, which consists of placing the animal into an arm (the start arm, which does not contain the platform). When the animal reaches the hidden platform it remains on it for several seconds to visualize the room spatially. If the animal fails to find the hidden platform, it is guided there by the experimenter. The number of entrances is measured in each trial. Two types of errors are considered in each trial; reference memory errors (number of first-time entries into arms that did not contain the platform) and working memory errors (number of repeat entries into an arm that did not contain the platform). Chronic restraint stress impairs radial arm water maze performance[122,123], but this effect recedes with time[124] and is prevented by environmental enrichment[85].

It is important to note that chronic stressors do not affect the performance of females in most of these tests (spatial object recognition, radial arm maze, Morris water maze, Y-maze), while males show stress-induced impairments in all of them[125]. These sex-dependent differences include the use of different strategies by the sexes to solve cognitive tasks and may be related to estradiol levels[87].

Animal models of addiction-like symptoms

The animal models of drug reward and addiction-like symptoms are essential to progress in understanding the biological basis of SUD and for the identification of new therapeutic targets. Drug addiction is a neuropsychiatric disorder characterized by loss of control over drug-seeking and drug-taking, the presence of a negative emotional state and an intense craving for the drug when it is not available, and a high propensity to relapse even after long-term periods of abstinence[126]. Drug addiction represents a profound disruption of different neural circuits, including a deficit of the brain reward system, an over-activation of the stress systems, aberrant associative learning (which confers exaggerated incentive salience to stimuli or contexts associated with the drug), and a dysfunction of the PFC, resulting in the inability to inhibit drug-taking behavior. The transition from an initial recreational and controlled drug use to compulsive consumption is also related with a change from the ventral to the dorsal striatum in the control of drug use behavior, with the consequent development of rigid stimulus-response habits[127,128].

Drug addiction has a multifactorial nature, since environmental and biological factors interact to confer vulnerability or resilience to the development of this disorder. The complexity of addictive behavior cannot be captured by an animal model, but they are useful in modelling some specific aspects of drug addiction. The two main models to study vulnerability or resilience to drug addiction are the self-administration (SA) paradigm, which is based on the primary hedonic effects produced by the consumption of a drug of abuse, and the conditioned place preference (CPP) paradigm, which focuses on the component of reward related to associative or incentive learning.

The intravenous SA paradigm is the most important procedure for assessing the primary intrinsic reinforcing effect of drugs, and is the most commonly used in rodents[129,130]. In this paradigm animals are trained in daily sessions to obtain the drug by performing an operant response; for example, by pressing a lever or performing a nose-poke. This response is reinforced by injection of the drug, usually

according to a fixed response (FR) program in which the animal must perform a fixed number of responses in order to obtain the dose of the drug. Variable or progressive response programs are also used to measure motivation of the animal for the drug. The oral SA paradigm, frequently used for alcohol, is similar regardless of the way in which the substance is ingested by the animal. Pharmacological and methodological factors may influence the results obtained with the SA paradigm, such as the drug, dose and rate of infusion, duration of the SA session, the requirements of response, the sex and age of the animal, *etc.*

The SA paradigm is also used to study extinction and reinstatement of drug-seeking behavior. During the extinction phase, the drug of abuse is not presented after responding, and as a consequence, a progressive decrease in the operant response takes place[131-133]. When extinction has been completed, reinstatement of the operant response by several stimuli is observed. Reinstatement of drug SA is a model of relapse to drug consumption after a period of abstinence. As in humans, administration of the drug of abuse (priming), re-exposure to drug-associated stimuli, or exposure to stress reinstates the initially learned operant response[134]. Indeed, some researchers have adapted the SA paradigm in order to model the main features of addiction in humans based on the DSM-5 criteria: loss of control or persistence in drug seeking (active responses during periods in which the reinforcer is not available), high motivation for the drug (using a progressive reinforcement schedule), and maintenance of consumption despite its negative outcomes (association between reinforcement and a foot shock)[135]. The SA model has excellent predictive and face validity; however, it also has some drawbacks related with the complexity of the technique (surgical implantation of an intravenous catheter or previous familiarization with the drug for intravenous or oral SA, respectively) and the training of the animals until they effectively acquire operant response.

Using the SA paradigm, it has been demonstrated that exposure to social stress increases the reinforcing effects of drugs of abuse[136-139]. Recently, resilience to these effects has also been studied using different types of social stress and drugs of abuse, such as cocaine[140-143], methamphetamine[144] and alcohol[145-147].

The CPP is a paradigm that evaluates the conditioned rewarding effects of a drug of abuse, since some contextual stimuli acquire appetitive properties when associated with the drug[148-151]. This paradigm is characterized by its methodological simplicity and is thus frequently used. Animals are conditioned in a box with two or three compartments that are clearly distinct in terms of the stimuli present in each compartment; for example, they have different colored walls and floor textures. Before conditioning, a pre-conditioning phase takes place to evaluate the time spent by the animal in each compartment without any treatment. During conditioning the animal receives the drug (usually 4 injections in 4 or 8 days) in a specific compartment (without access to the other compartment) and physiological saline in the opposite compartment. Later, in the post-conditioning phase (equal to pre-conditioning) it is evaluated whether the animal has learned to associate the rewarding effects of the drug with the environmental cues present in the drug-paired compartment. If the animal spends more time in this compartment (in comparison to the time spent in pre-conditioning or to the time spent in the saline-paired compartment), it is considered that the animal has acquired CPP. All drugs abused by humans induce CPP in rodents [150].

As described for the SA paradigm, the CPP procedure can also be used to evaluate other processes besides acquisition, such as extinction and reinstatement of motivated behavior[148]. To induce extinction, animals are placed in the CPP box and perform daily or weekly sessions similarly to pre- and post-conditioning (*i.e.*, they are exposed to the previously drug-paired compartment without administration of the drug). Progressively, the association between the reinforcing value and environmental cues weakens, and the CPP is finally extinguished. The period needed for extinction of CPP is influenced by different factors, including exposure to stressful events. For example, exposure to SD before each acquisition session[152], or 3-weeks before the initiation of the CPP procedure[78], slows the extinction of MDMA-induced CPP. After extinction, an injection of the drug of abuse (priming) or exposure to stress induces the reinstatement of CPP. In this paradigm, reinstatement refers to the recovery of the conditioned response and involves renewed memory of the association - learned during conditioning - between the reinforcing effect of the drug and the environmental cues associated with its pleasant effects. In our laboratory we have observed that SD exposure induces reinstatement of the CPP induced by cocaine[153,154].

The CPP has been widely used to evaluate the influence of social stress on the conditioned rewarding effects of different drugs of abuse, including alcohol, cocaine and MDMA[15]. In our laboratory, the animals are exposed to SD three weeks before

initiation of the CPP procedure. We have seen that exposure to SD induces a long-term increase in the rewarding effects of cocaine, since defeated mice acquire CPP with doses that are ineffective in inducing place conditioning in control mice[77]. Furthermore, we have observed how SD induces a long-term enhancement in the vulnerability of mice to priming-induced reinstatement of the CPP induced by cocaine [155] and MDMA[78]. In addition, the CPP model has been used to study resilience to the effects of social stress on the rewarding effects of methamphetamine[156], MDMA [157] and cocaine[93,143,158,159,160-163].

Finally, the effects of social stress on alcohol intake and resilience to these effects have been studied in the two-bottle choice test, a paradigm of voluntary consumption, in which animals can choose freely, during a limited time, to drink from one of the two bottles placed in the home cage: one containing water and the other containing alcohol [92,164].

ADVANCES CONCERNING THE NEUROBIOLOGICAL SUBSTRATES OF RESILIENCE

The study of the neurobiology of resilience is a relatively young area of scientific investigation[24,35]. Research carried out with animal models in the last decade has identified several behavioral, hormonal, neural and molecular mechanisms underlying the development and enhancement of resilience, mainly in relation with the reduced susceptibility to develop psychiatric disorders, such as depression or PTSD, after stress or trauma (Figure 2). As Russo *et al*[5] noted, resilience is mediated not only by the absence of neurobiological abnormalities that occur in susceptible animals after stress exposure (passive resilience), but also by the presence of neuroadaptations which occur in individuals that are resilient to stress, which help them to maintain normal functioning (active resilience). In this section we review the main results obtained in studies using electrophysiological, optogenetic, pharmacological, and molecular profiling techniques to unravel the neurobiological substrates of resilience to the negative consequences of chronic SD stress, mainly social avoidance and anhedonia. Advances in this field may guide ongoing research regarding the neurobiological substrates of resilience to the effects of SD on addiction disorders.

Glutamatergic system

The glutamatergic system seems to play an important role in resilience to stress[165]. Chronic stress reduces the dendritic spine density of glutamatergic neurons in the PFC and hippocampus, while it increases it in the amygdala and NAcc[166]. In the chronic predator and SD stress paradigms, resilient mice show greater expression of immediate early genes (c–Fos, FosB, or ΔFosB) in glutamatergic neurons of the medial PFC[106,167,168] and in medium spiny neurons (MSN) of the NAcc, inducing expression of the AMPA glutamate receptor subunit GluA2[169]. Optogenetic stimulation of either medial PFC or amygdala glutamate afferents to the NAcc induces resilience[168,170], while attenuation of glutamatergic transmission from the ventral hippocampus to the NAcc is pro-resilient, and reduced activity in the ventral hippocampus is observed in mice that are resilient to the effects of chronic SD[170]. Furthermore, several environmental manipulations that promote resilience to stress–induced depression– and anxiety–like behaviors, such as early intermittent maternal separation and environmental enrichment, increase the volume of ventro-medial PFC[171], the dendritic spine density of hippocampal and PFC neurons[172], and expression of FosB and ΔFosB in medial PFC[167]. All these results suggest that increased neuronal activation of mPFC represent pro–resilience adaptation[5].

NMDA receptors have been implicated in stress resilience[165]. Mice susceptible to chronic SD stress exhibit low activity of hippocampal extrasynaptic NMDA receptors, and enhancement in the function of these receptors prevents social avoidance behavior in defeated mice[173]. The NMDA antagonist ketamine protects against the long-term consequences of different types of stress in animal models[165,174]. For example, administration of ketamine protects mice against SD-induced depressive sympto-matology in the FST and against learned helplessness-induced coping deficits when dealing with inescapable shocks, although it did not protect against the anxiety-like phenotype in the EPM[60]. Reducing brain D-serine, an endogenous co-agonist at the glycine site of the NMDA receptors, may also improve stress resilience[175], and NMDA receptor blockade in the right medial PFC facilitates resilience to SDS-induced anxiety in mice[176]. Furthermore, we have observed that the NMDA antagonist memantine increases resilience to the effects of IRSD on the CPP induced by cocaine in
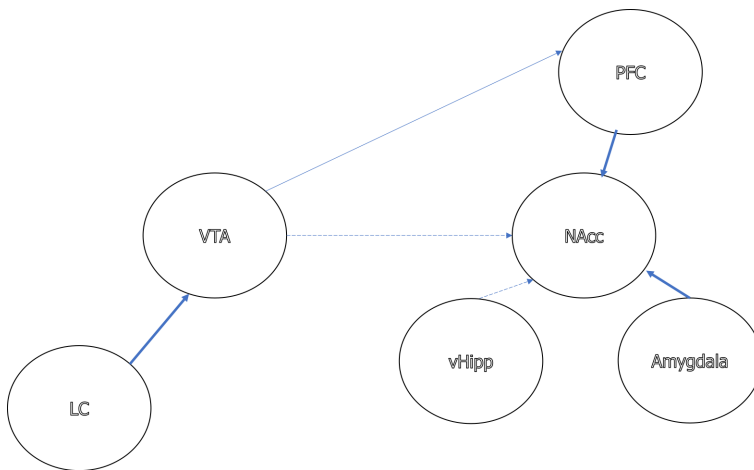
Figure 2 Simplified diagram of the neurobiological substrates of resilience to the effects of social defeat in rodents. Resilience is induced by activation of the pathways indicated with gross lines and by inhibition or normalization of the pathways represented with dashed lines. LC: Locus coeruleus; VTA: Ventral tegmental area; PFC: Prefrontal cortex; NAcc: Nucleus accumbens; vHipp: Ventral hippocampus; Amyg: Amygdala.

mice[77].

Some subunits of AMPA receptors might be involved in resilience. For instance, mice resilient to developing social avoidance after chronic SD show increased GluR2 mRNA expression compared to control mice, while susceptible mice display a decrease in GluR2 levels in the NAcc[169]. In addition, AMPA agonists prevent increases in corticosterone and latency to feed in the novelty-suppressed feeding induced by chronic stress[177].

The role of metabotropic glutamate receptors in stress resilience remains uncertain [165]. After 3 days exposure to learned helplessness or SD, mGluR5 KO mice exhibit enhanced susceptibility to stress-induced depression, social avoidance, and anhedonia. In addition, susceptible mice exhibit less mGluR5 in the NAcc than both resilient and control mice[178]. Finally, blockade of mGlu2/3 and deletion of mGlu2, but not mGlu3, promotes stress resilience, including protection against stress-induced depressive-like symptoms[179].

GABAergic system

There are a limited number of studies on the role of GABA in resilience to the effects of chronic SD, and the effects observed to date have been in the function of the brain area containing GABA neurons and the subtype of receptor studied.

Chronic SD defeat activates GABA neurons of the dorsal raphe nucleus (DRN) and strengthens inhibition of 5-HT neurons in susceptible mice, but this effect is not observed in resilient mice without a social interaction deficit; accordingly, optogenetic inhibition of DRN GABA neurons was shown to disinhibit 5-HT neurons and promote resilience[180]. Conversely, SD stress impairs the inhibitory tone in the NAcc. Stress-susceptible mice exhibit reduced levels of inhibitory synaptic markers and protein expression (vesicular GABA transporters (vGAT) and gephyrin) in the NAcc that are not observed in resilient mice[181]. GABA (B) receptors in the habenular nuclei are also down-regulated in susceptible mice, which display elevated c-Fos expression in this structure; furthermore, intra-habenular injection of baclofen and CGP36216 (GABA (B) agonist and antagonist, respectively) reverses social avoidance[182]. Studies with KO mice have also indicated the role of GABA in resilience to the effects of SD. GAT-1-deficient mice demonstrate an increase in resilience to the effects of acute stress on depressive- and anxiety-like symptoms[183,184]. Moreover, GABA(B1a) KO mice are more susceptible, whereas GABA(B1b) KO mice are more resilient to both stress-induced anhedonia and psychosocial stress-induced social avoidance[185].

Dopaminergic system

Adaptations within the brain reward system, and in particular in the mesolimbic DA circuit, are closely associated with resilience to the effects of chronic SD stress. The firing rate of ventral tegmental area (VTA) DA neurons has been shown to be increased in susceptible animals exposed to chronic SD; conversely, resilient mice show an increase in K + channels that normalizes hyperexcitability of VTA DA

neurons and prevents social avoidance and sucrose preference deficit[70,186,187]. A further increase in the hyperactivity of VTA DA neurons in susceptible mice produced by optogenetics or pharmacological treatments induces homeostatic plasticity and reverses depression-related behaviors[187,188]. Such studies bring to light the self-stabilizing capacity of midbrain DA neurons of the brain reward system[187]. A recent study has demonstrated that a baseline level of physical activity (voluntary wheel running), mediated by the tyrosine hydroxylase (TH) neurons in the VTA, affects susceptibility and resilience to chronic SD. Mice with low levels of physical activity showed lower TH expression in the VTA and were susceptible to SD, while mice with high levels of activity showed higher TH expression and were resilient to SD; activation of TH neurons in the VTA of mice with lower levels of activity increased resilience, while inhibition of these neurons increased susceptibility to SD[189].

Different MSN subtypes of the NAcc (D1-MSN and D2-MSN, with predominant expression of DA D1 and D2 receptors, respectively) are also involved in susceptibility and resilience to chronic SD stress. Susceptible mice that develop depression-like behaviors after SD showed decreased frequency of excitatory synaptic input in D1-MSN (but an increase in D2-MSN); in addition, enhancing the activity[190] or the spine density[191] of D1-MSN has been shown to induce resilience. Fosb-targeted histone methylation in D1-MSN or histone acetylation in D2-MSN promote a susceptible, depressive-like phenotype, while histone acetylation in D1-MSN or histone methylation in D2-MSN increase resilience[192]. Resilient animals also display an upregulation of synaptic strength at dendritic spines of D1-MSN and a concomitant downregulation in D2-MSN[193]. In addition, chronic SD selectively reduces NLGN-2, a neuronal postsynaptic cell adhesion protein, in DA D1-MSN of susceptible mice [181]. D1-MSN activity prior to stress is also a predictor of resilience, as mice that will later become resilient display increased baseline D1-MSN activity[194].

Single and repeated SD stress induces D1 receptor-mediated changes in medial PFC neurons. A single SD was shown to increase arborization and the spines of apical dendrites of pyramidal neurons in the medial PFC, whereas repeated SD reduced dendritic lengths of these neurons[195]. Optogenetic inhibition of the DA VTA neurons projecting to the medial PFC promotes susceptibility[188]. DA D1 receptors in medial PFC excitatory neurons plays a role in suppressing susceptibility to stress, since repeated SD reduces the expression of these receptors in susceptible mice, while its genetic deletion facilitates the induction of social avoidance[195].

DA transmission in other brain areas is also involved in susceptibility or resilience to stress, although results are contradictory. Vulnerable mice were reported to display increased expression of DA D2 receptors in the amygdala[102,196] and increased levels of DA in the hippocampus and PFC[197]. However, another study found that hippocampal dopaminergic activity was inversely correlated with the level of social avoidance induced by SD and chronic treatment with hop bitter acids enhanced stress resilience[198]. Similarly, treatment with caffeine (from 14 days before until the end of SD) reverses social avoidance and anhedonia, and this pro-resilience effect of caffeine is reversed by the antagonism of DA D1 (but not D2) receptors[199].

Noradrenergic system

Noradrenergic (NA) neurons in the LC have direct connections within the VTA and regulate vulnerability to SD through inhibitory control of VTA DA neurons[200]. NA LC neurons projecting to the VTA exhibit enhanced firing activity in resilient, but not susceptible, mice, and optogenetic activation of LC neurons in susceptible mice reverses depression-related behaviors[201]. α1- and β3-adrenergic receptors are highly expressed in VTA neurons projecting to the NAcc, and the antagonism of these receptors blocks the effects of the optogenetic and pharmacologic activation of LC neurons; *i.e.*, it reverses hyperactivity and homeostatic plasticity in the VTA-NAcc pathway in susceptible mice[201].

Serotonergic system

Plasticity of the serotonergic system also contributes to susceptibility or resilience to the effects of SD stress, although the role of serotonin depends on the brain area under consideration. As commented on before, inhibition of GABA neurons of DRN disinhibits 5-HT neurons and promotes resilience to social avoidance induced by SD in mice[180]. In fact, the mechanism underlying SD-induced social avoidance is a hyposerotonergic state in the DRN, which results from the activation of p38α mitogen-activated protein kinase (MAPK), the consequent translocation of the SERT to the membrane, and the increase in the rate of serotonin uptake[202]. Down-regulation of the 5-HT1A auto-receptors in 5-HT neurons of DRN (which can result in increased 5HT release), improves behavioral resilience to SD[203]. On the other hand, rats

susceptible to stress-induced anhedonia, but not resilient rats, display an increased number of neurons expressing tryptophan-hydroxylase-2 (TPH2, the enzyme for serotonin synthesis) in the ventral subnucleus of the DRN (DRNv), while activation of the CRF containing neurons of the amygdala induce resilience, suppressing the increase of TPH2 positive neurons in the DRNv and ameliorating anhedonia in susceptible rats[204]. Mice resilient to the effects of chronic SD also display a reduction of serotonin in the hippocampus[197].

Cholinergic system

ACh signaling in the hippocampus may be related with differential responses to SD stress. Interference with hippocampal AChE activity increases anxiety- and depression-like behaviors and decreases resilience to repeated SD stress[205]. In addition, nicotinic cholinergic (nACh) signaling in the basolateral amygdala seems to play a role in the effects of SD, since β2 nAChR subunit knockdown undermines resilience to SD stress and c-fos immunoreactivity in this structure[206].

Endogenous opioids

Chronic SD stress increases μ and κ opioid receptors and reduces δ opioid receptors in the PFC of susceptible mice (with social avoidance), while resilient mice show no alteration in the levels of opioid receptors and increased p38 MAPK phosphorylation [207]. Besides the increased mRNA expression of the opioid μ and κ receptors in the frontal cortex, susceptible mice also show a reduction in the expression of μ receptors in the hippocampus and a reduction of κ receptors in the basolateral amygdala[208, 209]. Conversely, mRNA of dynorphin is increased in the shell of NAcc in susceptible rats and in the striatum of resilient animals[208].

Chronic SD also decreases mRNA levels of δ opioid receptors and enkephalins in the basolateral amygdala and in the ventral hippocampus (CA1) of vulnerable mice [209]. Administration of an agonist of δ receptors increases resilience and reduces oxidative stress markers in CA1 neurons, a mechanism that may be involved in the pro-resilient effect of enkephalin signaling[210]. Similarly, susceptible animals display reduced enkephalin levels in the NAcc and enkephalinase inhibitors, while intra-NAcc infusion of a δ receptor agonist induces resilience and increases phosphorylation of extracellular signal-regulated kinase (ERK), which is downregulated by SD stress[211].

μ-opioid receptor G-allele carriers express less submissive behavior and exhibit resilience to SD, demonstrated by a lack of subsequent social avoidance and reductions in anhedonia; moreover, the resilience in question was associated with a greater induction of c-fos in the NAcc and periaqueductal gray[212].

Neuropeptide Y

Neuropeptide Y (NPY) is a neuropeptide that is widely distributed in the brain and promotes protective responses in the face of stress[213,214] by inducing anxiolytic effects and counteracting the anxiogenic effects of CRF. Multiple studies indicate a positive correlation between NPY levels and resilience to the deleterious effects of stress in humans and animal models. A significant down-regulation of NPY in the amygdala and hippocampus has been observed in animals with PTSD-like symptoms, and administration of NPY reversed the negative behavioral effects of predator-scent stress[63]. Mice susceptible to the effects of chronic SD also show a down-regulation of NPY and NPY2R in the hippocampus[215]. Administration of NPY significantly reduces submissive/defensive behaviors in socially defeated hamsters, although this effect is not mediated by the Y1 receptor[216]. Such results demonstrate that NPY may function as an important factor in resilience against the impairing effects of SD, and a recent study has suggested that deficiency of NPY plays a role in the impairing effects of stress on hippocampal function and the processes mediated by this structure[217].

Orexins

Orexins (OX) produced in the lateral hypothalamus also play an important role in the response to stress[218,219]. Chronic SD stress-susceptible and -resilient mice (with or without deficits in social interaction) display different levels of prepro-OX in the hypothalamus[220] and basolateral amygdala, with increased OX1 and decreased OX2 observed in susceptible mice[221]. Brain infusion of OX A was found to induce an antidepressant-like effect only in susceptible mice, while co-infusion of OX A and B induced an anxiogenic effect only in resilient mice[220]. In addition, knocking down the OX2 receptors in the basolateral amygdala increases social avoidance and reduces the time spent in the center of an open field[221]. Similarly, after SD stress, resilient (actively coping) rats express lower prepro-OX mRNA levels than passively coping

rats, while inhibition of OX before each SD episode increases social interaction and decreases depressive-like behavior in vulnerable rats[222]. These results suggest that lower levels of OX contribute to resilience to repeated SD, although in this context it is important to consider the different types of OX receptors. A recent study indicated that OX1 and OX2 receptors exert opposite functions and that the agonism of OX2 receptors promotes resilience to the anxiety and depression induced by exposure to SD stress in mice[223,224].

Neurotrophic factors

Neurotrophic factors and their signaling pathways, such as BDNF or ERK1/2, have been implicated in the neuroadaptations that take place in response to stress.

ERK is reduced after SD stress in both susceptible and resilient mice[207]. SD also decreases phosphorylation of ERK[211] and the pERK/ERK ratio[225]. Overexpression of ERK2 in the VTA increases susceptibility to SD stress in mice, while blockade of VTA ERK2 activity promotes behavioral resilience and decreases the frequency of firing of the VTA DA neurons, an important electrophysiological hallmark of resilience [226]. Phosphorylation of ERK is enhanced by treatments that induce resilience, such as the intra-NAcc infusion of a delta opioid receptor agonist or enkephalinase inhibitors[211].

BDNF is expressed in the amygdala, hippocampus, PFC and basal forebrain, and acts through its two main receptors, TrkB and p75[227]. BDNF has antidepressant-like effects and enhances hippocampal neurogenesis[228,229], which suggests an important role of this factor in the potentiation of resilience. Chronic SD stress decreases BDNF/TrkB in the PFC, the dentate gyrus (DG), and the CA3 region of the hippocampus, but increases BDNF/TrkB in the NAcc[175,225]. A differential expression of BDNF has been observed in susceptible and resilient mice in function of the brain area studied. Susceptible mice have higher levels of BDNF mRNA in the VTA than resilient and control mice, suggesting that this increase is associated with depressive-like behavior induced by SD[230]. An increase of BDNF-4 has been observed in the PFC of susceptible mice exposed to chronic SD, but the same animals also showed a selective reduction of BDNF-6 transcript in the hippocampus[231]. Conversely, in another study with mice exposed to chronic SD stress, levels of BDNF in the medial PFC and hippocampus were lower in susceptible mice than in control and resilient animals[232]. Finally, several studies support the contribution of hippocampal BDNF expression to resilience to chronic stress[233]. In rodents exposed to SD, activation of hippocampal BDNF/TRKB signaling (by means of branched-chain amino acids, exercise and high protein diets) induces resilience to social avoidance [234,235,236]. In addition, enhancement of BDNF and TRKB levels and signaling has been implicated in the nicotine-induced resilience to the social deficit induced by SD [237].

Hormones of the HPA axis

Stress activates the HPA axis and the release of stress hormones that regulate the individual response to stress. SD stress induces hypercortisolemia and adrenal hypertrophy in susceptible mice, but not in resilient rodents[48,238]. In addition, susceptible mice exhibit reduced glucocorticoid (GR) receptor expression in the hippocampus in comparison to resilient mice, suggesting that up-regulation of GR and enhancement of GR nuclear translocation in the hippocampus play an important role in resilience to chronic SD stress[238]. Susceptible mice show higher plasma corticosterone concentrations 2 h and 48 h after single and chronic SD stress, respectively; and administration of corticosterone *via* drinking water enhances susceptibility while a GR antagonist alleviates the negative consequences of chronic stress[239]. A single dose of ketamine that improved depressive-like behaviors was shown to decrease plasma corticosterone levels and rescue GR expression and nuclear translocation in the hippocampus of susceptible mice[239].

Resilient rats (with proactive behavior in resisting defeat) show decreased efficacy of CRF[82]. Similarly, mice in which CRF is deleted from GABAergic forebrain neurons were found to display a resilient phenotype[240], and PFC mRNA expression of CRF was stronger in susceptible mice than in resilient counterparts[48]. However, another study showed that increasing CRF neuronal activity in a subtype of GABAergic inhibitory interneurons in the medial PFC promoted lasting resilience to SD stress[241,226].

Epigenetic factors

A wide variety of genetic factors - polymorphisms of genes of NPY, CRFR1, catecholamines (COMT, DAT, DAR1, DAR4), serotonin (SERT, 5-HTR1A, 5-HTR3A, 5-

HTR2C), BDNF, among others - have been implicated in resilience (for a review see[4, 242]). Like all aspects of psychological function, resilience results from the interaction between genes and environment. Epigenetic factors are functional modifications to the genome (such as DNA methylation and demethylation, and histone methylation, acetylation, and phosphorylation) that regulate gene expression and phenotype without changing the DNA sequence. Different epigenetic mechanisms have been linked to resilience[243]. For instance, changes in gene expression and chromatin modifications in specific brain regions are associated with resilience to chronic SD stress[70,231,244,245]. In particular, histone methyltransferases are up-regulated in the NAcc of resilient mice, which exhibit low depression-like symptoms after chronic SD [246], while susceptible mice show reduced g9a mRNA levels in the hippocampus, and a reduction of HDAC-5 and DNMT3a mRNA levels in the PFC[231].

HDAC inhibitors may also regulate stress-related behaviors independently of their action on histones, through prevention of glucocorticoid signaling in serotonin pathways. Deletion of HDAC6 in serotonin neurons prevents the electrophysiological and morphological changes induced by chronic SD in these neurons and blocks the expression of social avoidance[247]. In one study, lower acetylated Hsp90 levels, higher GR-Hsp90 association, and enhanced GR translocation were observed in the DRN of vulnerable mice after chronic SD stress, and a HDAC6-selective inhibitor or the serotonin-selective viral overexpression of the acetylation-mimic mutant of Hsp90 in DRN neurons promoted resilience to chronic SD stress[248].

Immune system

Inflammation may underlie individual differences in vulnerability and resilience to chronic SD stress[249,250].

Exposure to SD increases inflammatory markers, but the enhancement of proinflammatory proteins is more pronounced in susceptible rats (with passive coping during defeats and anhedonia) than in active coping rats[236]. In addition, only susceptible rats exhibit elevated levels of inflammatory proteins (IL-1β, TNF-α, GM-CSF) in the LC [251], and higher systemic levels of interleukin-6 (IL-6)[252]. Rats with short-defeat latencies (vulnerable rats) exhibit increased anxiety- and depression-like behaviors, and inflammation in the ventral hippocampus[253]. On the other hand, selective KO of the miR-106b~25 cluster in peripheral leukocytes promotes behavioral resilience to chronic SD stress[254]. Preexisting individual differences in the sensitivity of the peripheral immune system (IL-6) may predict vulnerability or resilience to social stress [250].

Gut microbiota, important activators of inflammatory substances, have emerged as a putative mechanism for promoting stress vulnerability[253]. For example, in one study, mice that were most susceptible to the behavioral effects of chronic SD (reflected by severe social avoidance behaviors) displayed the greatest changes within particular sets of bacteria in the phylum and genus taxonomic ranks[255].

RESILIENCE TO THE EFFECTS OF SOCIAL DEFEAT ON THE REWARDING PROPERTIES OF DRUGS OF ABUSE

There is a well-known link between stress and the development of AUD/SUD, and preclinical studies have shown that early life stress, social rank stress, and SD stress impact on vulnerability and resilience to alcohol, cocaine and other drugs of abuse[14, 15,256]. However, as mentioned previously, there are few works studying resilience to the effects of social stress on the rewarding properties of drugs of abuse. For example, in the search "social defeat, addiction, resilience" in PubMed we identified only 18 papers, and some of these studies did not employ any paradigm of drug reward or addiction. After an exhaustive search and review of the literature we found only 8 papers on resilience to the consequences of repeated or chronic SD for the rewarding effects of cocaine, alcohol or methamphetamine.

In a classic preclinical study of resilience, Krishnan *et al*[70] demonstrated for the first time that, following exposure to chronic SD stress, mice can be classified as susceptible or resilient according to their differential response to stress. Susceptible mice exhibited anhedonia, social avoidance and anxiety-like behavior in the EPM, while resilient mice did not show such symptoms. This study was also pioneering in demonstrating differences between susceptible and resilient mice in sensitivity to the rewarding effects of cocaine. Only susceptible mice showed CPP after conditioning with a low dose of cocaine, while resilient or non-stressed mice did not acquire CPP [70]. Surprisingly, until recently, no other studies have addressed this issue.

In our laboratory, we have studied the influence of IRSD stress on the rewarding properties of cocaine in the CPP paradigm. Exposure to four episodes of SD during late adolescence (on post-natal day (PND) 47-56) subsequently increased the sensitivity of adult mice to a low dose of cocaine. In particular, 1 mg/kg of cocaine induced CPP in defeated mice but not in non-stressed control mice[77]. In a recent study, we evaluated whether some animals were resilient to the effects of IRSD. Overall, exposure to SD decreased all measurements related to the open arms of the EPM, immobility in the TST, social contact in the social interaction test, and grooming in the splash test. IRSD exposure also increased the sensitivity of the mice to the rewarding effects of cocaine, since only defeated animals acquired CPP. However, the potentiation of cocaine CPP was not observed in all the defeated mice, as some of them were resilient to the effects of IRSD on cocaine reward[93]. In the same study we characterized the behavioral profile of vulnerable and resilient mice during defeat episodes and in several behavioral paradigms shortly after SD. Vulnerable mice that showed CPP also exhibited depressive-like behavior, in line with the results of Krishnan *et al*[70]. In comparison with vulnerable mice, resilient mice displayed different behavioral traits, such as less submissive behavior during episodes of defeat, a lower percentage of time in the open arms of an EPM, lower novelty-seeking in the hole board, higher social interaction, greater immobility in the TST, and higher frequency of grooming in the splash test. These results indicate that the behavioral profile of resilient mice is characterized by an active coping response during defeat episodes, a reduced short-term response to SD (lesser reactivity to moderate unavoidable stress, enhanced concern in a potentially dangerous environment and absence of depressive symptoms), and a lack of long-term responses to SD, as evidenced by the absence of cocaine CPP[93].

Two similar studies also showed that control mice do not develop CPP with a low dose of cocaine, while defeated mice did overall develop a preference for the drug-paired compartment[143,162]. Among the defeated animals, two populations could be distinguished - resilient (did not develop preference) and susceptible mice (developed preference) - and they differed in their active or passive behavior during the SD sessions. As the authors stated, "resilient animals showed less flight and submission behaviors than susceptible mice and they presented attack behaviors towards the residents, thereby showing their resistance to being defeated"[162]. Besides passive coping behavior during SD episodes, susceptible mice (which showed cocaine CPP) also displayed social avoidance and higher IL-6 levels in the striatum and hippocampus after the last SD episode[143]. The results of all these studies suggest that an active coping style can protect the individual from the negative consequences of social stress. It is important to note that differences in the responses to cocaine between susceptible and resilient mice were not always observed, since both subgroups of defeated mice showed similar levels of cocaine SA[143].

Rats exposed to repeated SD (five episodes) and social isolation (approximately 12 wk) can also be classified as SD-prone or SD-resilient, based on their affective (depression-like behavior) and cognitive performance. In one study, although SD was shown to increase alcohol SA in both groups, only SD-prone rats displayed heightened motivation for alcohol, persistent alcohol-seeking despite unavailability, resistance to extinction, and increased cue-induced reinstatement of alcohol SA[145]. Similarly, among rats exposed to SD stress, there was a subpopulation in which SD exposure increased anxiety-like behavior and induced escalation of alcohol SA. In comparison with resilient rats, vulnerable rats showed a strong upregulation of vasopressin and oxytocin that correlated positively with the magnitude of the anxiety-like behavior and alcohol SA[146]. These studies suggest that proneness to depression or anxiety enhances vulnerability to AUD, while resilience to mental disorders induced by stress can protect the individual from the development of AUD.

No studies have evaluated resilience to the effects of SD on the rewarding effects of drugs of abuse other than cocaine and alcohol, although one did show that a single SD episode combined with drug priming potentiated the reinstatement of methamphetamine SA (in comparison with priming alone). Interestingly, the defeat latency during the episode of SD correlated with reinstatement values and c-Fos-immunoreactivity in the basolateral amygdala; priming-induced reinstatement and c-Fos were both potentiated in rapidly defeated rats. Conversely, these effects were not observed in rats that were undefeated during the social encounter, but inactivation of the basolateral amygdala induced potentiation of reinstatement, suggesting that this structure mediates resilience against SD stress[144]. The positive correlation between reinstatement and passive coping (high values of reinstatement in animals with lower latency defeat) was reported in another study, although the authors questioned its real meaning, and proposed that active coping behaviors during SD episodes were

associated with the magnitude of reinstatement[257]. In the study in question animals were exposed to SD-predictive cues (discrete environmental stimuli present during the SD stress experience) or not (control group) before reinstatement. Animals exposed to SD-predictive cues exhibited stronger reinstatement of cocaine SA and increased serum corticosterone with respect to the control group. Reinstatement magnitude was positively and significantly correlated with the time spent in a "submissive supine posture", considered a "passive" coping response. However, there was a narrow (though non-significant) correlation between the magnitude of resilience and three behavioral categories indicative of active coping responses; "aggressive allogrooming", "dominant posture", and "retreat". Further studies are needed to determine the real nature of the correlation between the coping strategy of mice during defeat and subsequent vulnerability to reinstatement.

Although scarce, there is research on resilience to the effects of stress on drug reward carried out with other paradigms of social stress. Mice segregated according to whether they are vulnerable or resilient (socially-submissive or socially-dominant mice, respectively) were exposed to CMS for 4 wk; vulnerable, submissive mice displayed a marked increase in cocaine preference after stress, whereas the preference of resilient, dominant mice did not change. In addition, vulnerable mice displayed an increase in the expression of CRF and a reduction in the expression of DA D1 and D2 receptors in the hippocampus[159]. Following exposure to predator odor stress, animals were classified as susceptible or resilient based on EPM behavior and context avoidance; as expected, susceptible animals showed heightened motivation to self-administer cocaine[141]. With the same model, female and male rats were classified according to their stress-reactive behavior (digging and immobility during exposure to the predator odor); no different subgroups could be distinguished in males because all presented the same profile, but female rats were composed of two different populations - high digging/low immobility *vs* low digging/high immobility - and the former showed increased alcohol SA[147].

Early-life adversity consisting of rearing mouse pups in a limited bedding and nesting environment facilitates the escalation of ethanol intake in males at an earlier stage of exposure to alcohol, while females are insensitive to both stress and alcohol. In the study in question, stressed males exposed to alcohol showed reduced open arm exploration in the EPM and increased immobility in the TST compared to alcohol-naïve mice, although they did not differ in grooming response in the splash test, novel object recognition test or corticosterone levels. There were also no differences among control-reared males exposed or not to alcohol. The authors concluded that early stress accelerates the transition from moderate to excessive alcohol drinking and produces anxiety- and depression-like symptoms during alcohol withdrawal[92].

Finally, foot shock stress has been shown to increase two-bottle drinking in some mice, although others show resilience to this effect, displaying higher G-CSF, IL-13, and leptin levels[164]. All these studies suggest that differences in the ability to cope with stressful situations or in the response to stress results in varying tendencies to develop addictive behaviors.

Stress and drug use can lead to common alterations in synaptic plasticity that may contribute to the ability of stress to elicit relapse. For example, disruption of PKC-mediated GluA2 phosphorylation increases vulnerability to both SD-induced enhancement of social avoidance and stress-induced reinstatement of cocaine AA and CPP[258]. Study of resilience to the reinstating effects of SD stress may help to identify therapies that prevent stress-induced relapse. In line with this, Bruchas et al[202] demonstrated that SD stress produced reinstatement of cocaine-induced CPP in wild-type mice, but not in mice with a selective deletion of p38α MAPK in DRN serotonergic neurons. The antagonism of DA D3 receptors also prevents the SD-induced reinstatement of cocaine CPP and the increase in corticosterone provoked by SD[259]. Similarly, elimination of Rgs7 (a regulator of G-protein-coupled receptors) in striatal neurons induces a resilient phenotype, since mice do not show SD-induced reinstatement of cocaine CPP and exhibit an anxiolytic- and antidepressant-like profile [163]. Finally, our group has demonstrated that cannabidiol can prevent SD-induced reinstatement of cocaine CPP[154]. Altogether, these studies suggest that resilience to the effects of social stress on relapse to cocaine seeking can be pharmacologically enhanced.

FUTURE RESEARCH DIRECTIONS

An important variable in the development of resilience is sex. Studies on resilience to

stress in animal models have been performed almost exclusively in males, although the prevalence of stress-related disorders clearly differ between males and females [260]. Some studies have shown sex differences in vulnerability and resilience to stress through a lifetime. Prenatal or early stress affects males more than females, inducing problems in social interaction, attention and cognition; conversely, adolescent stress induces more effects in females, increasing the risk of depression, anxiety and PTSD [261]. Thus, research suggests that hormonal activation during puberty, pregnancy or perimenopause highlights the risk associated with stress in females. Furthermore, in comparison with males, female rodents are more resilient to the effects of stress on cognitive processes (for example, in the object recognition task), but are more susceptible to the effects of stress in emotional domains (for example, in the sucrose preference and the FST)[86,87]. In fact, the effects of stress on cognition depend on both sex and the learning task. For example, stress improves the performance of radial arm maze, Morris water maze, Y–maze, non–associative learning, and object placement tasks in females, but impairs it in males[262-264]. Conversely, stress enhances learning of aversive conditioning in males but impairs it in females[265,266]. These data point to the possibility that males and females use different coping strategies in the face of stress[5]. Females are more resilient than males to the impairing effects of chronic unpredictable intermittent restraint on spatial memory, suggesting that chronic stress negatively impairs hippocampal-dependent function in males, but not in females[125]. Sexual differences in the consequences of stress on corticolimbic areas[267], including the brain reward system and the NAcc[202,250], and on the NA LC system[109] have also been reported. In fact, there are sex differences in the effects of ketamine on resilience to chronic stress, as this drug is only effective in males[268]. Research on sex differences in vulnerability and resilience to stress in general and in the field of drug abuse in particular should be a priority of future research. The knowledge obtained by studies with females is critical to the development of effective treatments customized for each sex, which may improve psychological disorders derived from or related with stress, including drug addiction.

Age is another essential variable to be taken into account in the study of resilience to the effects of stress. Adolescents are particularly sensitive to environmental influences, since DA circuitries in the PFC undergo maturational changes at this age. This can render adolescents more vulnerable to the effects of SD. For example, we have observed how SD exposure during adolescence induces a long-term increase in vulnerability to reinstatement[78,155]. A recent study has compared adolescent and adult mice according to their resilience or susceptibility to social avoidance behavior after SD exposure. Although the majority of adolescent mice were resilient, they exhibited risk-taking behavior, alterations in PFC DA connectivity and deficits in inhibitory control when they reached adulthood. Conversely, the majority of adult mice were susceptible (they exhibited social avoidance), but did not show alterations in anxiety-like traits, PFC connectivity or cognition[269]. Chronic SD stress in adolescent mice has a profound impact on the development and plasticity of reward circuitry, inducing alterations in the glutamatergic development of the NAcc and mesolimbic DA system [270]. In our laboratory we are now studying the behavioral traits that characterize resilient mice exposed to IRSD stress during early adolescence, with the objective of comparing the results with those of our previous study in adult mice. As maternal experience promotes resilience to the effects of stress on cognition[271], we believe it could be interesting to evaluate how maternity modifies resilience to the effects of SD on drug reward and other behavioral outcomes. The study of stress resilience in the context of aging is very limited[165] but necessary, because the likelihood of the mood and cognitive disorders frequently associated with drug addiction increases in older adults. Thus, future research on resilience must be extended to cover the whole lifespan, with a special focus on critical periods such as prenatal or early life, adolescence, maternity and old age. In addition, it is essential to determine if resilience is a stable trait or changes with time. In this context, a recent study has analyzed the behavior of stressed mice after chronic SD at early and late stages of their lives and has found very dynamic courses of behavior: there are those that are consistently resilient or susceptible over time; those that are susceptible in the short term after stress, but recover with time; and there are animals that are initially resilient but develop vulnerability at a later date[112].

Another area of future research in the field of resilience to the effects of stress on drug addiction is that which explores the behavioral or pharmacological manipulations that increase or promote resilience to the effects of stress on drug reward. Regarding behavioral manipulations, we have observed that mice allowed to perform voluntary physical exercise before exposure to IRSD become resilient to the effects of stress on cocaine-induced CPP (Calpe-López *et al*[93], in preparation). Positive social

conditions, such as paired housing, also increase stress resilience and reverse the potentiation of cocaine reward induced by IRSD, effects that are mediated by oxytocin [161]. In addition, it is essential to improve our understanding of the phenomenon of stress inoculation in order to define the right type and level of stress and the influence of age and sex variables. In recent studies we have tested the effects of different types of stress inoculation, which can modulate the subsequent response of mice to IRSD. In particular, a brief maternal separation (6 h on PND 9) or exposure during adolescence (PND 27) to immobilization, to a single SD or a vicarious defeat experience all induced resilience, and mice did not show cocaine-induced CPP (Calpe-López *et al*[93], in preparation).

Regarding pharmacological manipulations, preclinical studies have shown the effectiveness of several pharmacological treatments in models of resilience to the effects of stress on depressive- and anxiety-like symptoms and in animal models of drug addiction. These studies have highlighted the potential of several drugs that may increase resilience to some of the effects of social stress, including cannabidiol, NMDA antagonists and NOS inhibitors, NPY, galanin, and OX receptor modulators. Thus, it may be interesting to test whether these compounds are a therapeutic target to increase resilience to the effects of stress on drug addiction. Among these compounds, we would highlight cannabidiol, which is effective in reducing PTSD[272] and the effects of cocaine and other drugs of abuse[273,274,275]. A recent study in our laboratory demonstrated that cannabidiol prevents the stress-induced reinstatement of cocaine CPP[154]. Thus, it would be interesting to test the potential of cannabidiol to promote resilience to the effects of stress on the rewarding properties of drugs of abuse. We consider this drug to be a promising pro-resilience compound. Similarly, several studies have demonstrated that the NMDA antagonist ketamine exerts protective effects against the long-term consequences of different kinds of stress in animal models[165,174]. We believe this drug may prevent the long-term effects of stress on drug addiction, as we have demonstrated that another NMDA antagonist, memantine, induces resilience to the effects of social stress on the CPP induced by cocaine in mice[77]. In the same way, the effects of nitric oxide (NO) modulators need to be evaluated, since exposure to stressful events activates NO synthase (NOS), while pharmacological inhibition of NOS reduces depressive and anxious behaviors in animal models[276]. Furthermore, previous studies have demonstrated that NO is also involved in the rewarding effects of drugs of abuse[79,277], and NOS inhibition has been shown to prevent the effects of social stress on the rewarding properties of MDMA in the CPP paradigm[157].

The role of several neuropeptides in the effects of stress in animal models of drug addiction must also be evaluated. As commented on in the previous section, NPY is involved in the regulation of stress responses and plays an important role in emotional behaviors, mediating PTSD and addictive disorders[213-214]. Thus, NPY, as well as galanin[83,84], could induce resilience and prevent the effects of stress on drug addiction. OX play an important role in the response to stress and drugs of abuse [219]. In particular, OX-A activates the HPA axis and induces ACTH and corticos-terone release[218]. Furthermore, the antagonism of OX1 receptor blocks the stress-induced reinstatement of cocaine seeking[224,278], and the genetic manipulation of animals to induce a deficiency of OX has been shown to reduce cocaine-seeking after a withdrawal period and responsivity to cocaine-associated cues[22]. Conversely, agonism of the OX2 receptor promotes resilience to the anxiety- and depression-like symptoms induced by SD[224]. Thus, it would be of interest to test whether OX1 antagonists or OX2 agonists increase resilience to the effects of SD in animal models of drug addiction. Finally, p38 MAPKs are key signaling molecules in response to stress, regulation of pro-inflammatory cytokines and drug addiction. For these reasons, p38 MAPK and HDAC6 inhibitors are promising drugs, because they might increase resilience against stress and addiction relapse induced by adverse experiences[160].

It is vital that future research focus on other drugs of abuse, since, with the exception of one study on methamphetamine, cocaine and alcohol are the only drugs to have been evaluated. It is also important to study the relationship between different aspects of resilience (for example, between resilience to the development of depressive symptomatology and resilience against developing drug addiction after stress exposure). Frequently, resilience to a particular effect of stress does not imply resilience to another effect. For example, inhibition of 5-HT synthesis provides resilience against the effects of CMS in the open field, but not in the EPM[103]. Pre-treatment with ketamine before SD protects mice against depressive-like behavior in the FST but does not prevent anxiety-like behavior in the EPM[60]. A recent study showed that susceptibility to SD-induced social avoidance is unrelated to suscept-ibility to develop a deficit in appetitive, goal-directed motivation after SD; however,

motivational impairments were related to ventral hippocampus hyperactivity, since successful task completion in resilient animals was associated with suppression of ventral hippocampal neural activity[279]. Similarly, rats displaying high cognitive competence in the Y-maze and radial arm maze are also resilient to the negative effects of the FST[280]. Resilience to the effects of SD on cocaine and alcohol reward frequently correlates with the absence of depressive-like symptoms[70,93,143,145].

Finally, translational studies of potential cognitive treatments to increase resilience are essential. For example, cognitive training in humans reduces vulnerability in the face of environmental stress. Similarly, it has been observed that a brief 9-day cognitive training can promote long-term resilience to the CPP induced by cocaine in mice, thus accelerating the extinction of CPP[158]. Coordination between human and animal studies is also required to understand the neural circuit of resilience, and neuroimaging techniques in humans can be combined with classic or more innovative methods in animals.

CONCLUSION

In the fields of medicine and psychology, the concept of resilience has implied a change of paradigm, placing the focus on factors that maintain health and promote wellness. The majority of research on drug addiction aims to identify individual and environmental factors that enhance the vulnerability of a subject to drug addiction. From our point of view, the incorporation of the concept of resilience - a complex, multidimensional construct - will allow scientists to unravel the neurobehavioral traits that confer protection against developing an addictive disorder after exposure to stressful or traumatic events, as well as permitting the underlying neurobiological substrates of resilience to be determined.

Overall, our understanding of the neurobiology of resilience is still at an early stage, but research in the last decade has made leaps and bounds by identifying genetic, epigenetic, molecular, neurochemical, psychological and environmental factors that protect individuals from the neuropsychiatric disorders related to stress[9,281-284]. Currently, resilience is considered an active and dynamic process that can be enhanced to allow individuals to adapt positively to a stressful context that, in other cases, could increase the risk of developing a psychiatric disorder. This concept of resilience has fueled the number of studies focused on specific protective factors and how the neurobiological mechanisms of resilience (HPA axis, GABA, serotonin, glutamate, DA, NA, acetylcholine, endocannabinoids, BDNF-TrkB, OX/hypocretin, NPY, galanin, *etc.*) can be manipulated to increase stress resilience in high-risk individuals and thus prevent the development of psychiatric disorders related to stress[165,219,281,284-286]. However, as stated before, most studies to date have focused on resilience to the development of emotional and anxiety disorders, while those on resilience to addictive disorders are few and far between. The members of our research team are pioneers in the study of resilience to stress in the context of drug addiction. Besides identifying behavioral traits that predict resilience in mice[93], we have highlighted behavioral manipulations (papers in preparation) and pharmacological treatments that increase resilience to the effects of stress in preclinical models of drug addiction. In particular, antagonism of glutamate receptors and inhibition of NOS reverses the effects of IRSD on cocaine and MDMA CPP[77,157,287], while cannabidiol reduces the effects of cocaine[154,273,274] and blocks SD-induced reinstatement of cocaine CPP[154].

Although promising, research on resilience to developing drug addiction after stress in animal models is not devoid of limitations; namely, the difficulty of determining the intensity and duration of exposure to adversity, and the definition of a concrete criterion to consider an animal resilient (absence or reduction of substance use; resistance to developing a SUD or to reinstatement of drug seeking, *etc.*). In addition, the incorporation of females and rodents at different developmental ages is crucial if the realities of resilience are to be fully understood.

From a translational point of view, understanding how an individual develops resilience is of paramount relevance to the design of training programs that increase this ability and promote coping mechanisms, especially in subjects with a maladaptive stress response. There is a well-known link between stress and the development of AUD/SUD, anxiety and depression disorders. Comorbidity between these disorders is frequent and associated with more severe symptoms and poor treatment outcomes. Besides reducing addictive behaviors, resilience training may have positive effects on mental health, reducing vulnerability to the development of anxiety, depressive, and cognitive disorders. Advances in the identification of neurobiological substrates of

resilience will help in the development of pharmacological and psychological interventions for enhancing resilience to adversity and stress.

REFERENCES

1   **Alexander DE**. Resilience and disaster risk reduction: an etymological journey. *Nat Hazards Earth Syst Sci* 2013; 13: 2707-2716 [DOI: 10.5194/nhess-13-2707-2013]

2   **Rutter M**. Resilience: some conceptual considerations. *J Adolesc Health* 1993; **14**: 626-631, 690 [PMID: 8130234 DOI: 10.1016/1054-139x(93)90196-v]

3   **Rutter M**. Annual Research Review: Resilience-clinical implications. *J Child Psychol Psychiatry* 2013; **54**: 474-487 [PMID: 23017036 DOI: 10.1111/j.14697610.2012.02615.x]

4   **Wu G**, Feder A, Cohen H, Kim JJ, Calderon S, Charney DS, Mathé AA. Understanding resilience. *Front Behav Neurosci* 2013; **7**: 10 [PMID: 23422934 DOI: 10.3389/fnbeh.2013.00010]

5   **Russo SJ**, Murrough JW, Han MH, Charney DS, Nestler EJ. Neurobiology of resilience. *Nat Neurosci* 2012; **15**: 1475-1484 [PMID: 23064380 DOI: 10.1038/nn.3234]

6   **Rutter M**. Resilience as a dynamic concept. *Dev Psychopathol* 2012; **24**: 335-344 [PMID: 22559117 DOI: 10.1017/S0954579412000028]

7   **Kalisch R**, Cramer AOJ, Binder H, Fritz J, Leertouwer I, Lunansky G, Meyer B, Timmer J, Veer IM, van Harmelen AL. Deconstructing and Reconstructing Resilience: A Dynamic Network Approach. *Perspect Psychol Sci* 2019; **14**: 765-777 [PMID: 31365841 DOI: 10.1177/1745691619855637]

8   **McEwen BS**. In pursuit of resilience: stress, epigenetics, and brain plasticity. *Ann N Y Acad Sci* 2016; **1373**: 56-64 [PMID: 26919273 DOI: 10.1111/nyas.13020]

9   **al'Absi M**. The influence of stress and early life adversity on addiction: Psychobiological mechanisms of risk and resilience. *Int Rev Neurobiol* 2020; **152**: 71-100 [PMID: 32451001 DOI: 10.1016/bs.irn.2020.03.012]

10   **Kennedy B**, Chen R, Fang F, Valdimarsdottir U, Montgomery S, Larsson H, Fall K. Low stress resilience in late adolescence and risk of smoking, high alcohol consumption and drug use later in life. *J Epidemiol Community Health* 2019; **73**: 496-501 [PMID: 30718261 DOI: 10.1136/jech-2018-211815]

11   **Yen JY**, Lin HC, Chou WP, Liu TL, Ko CH. Associations Among Resilience, Stress, Depression, and Internet Gaming Disorder in Young Adults. *Int J Environ Res Public Health* 2019; **16** [PMID: 31480445 DOI: 10.3390/ijerph16173181]

12   **Morgan JK**, Brown J, Bray RM. Resilience as a moderating factor between stress and alcohol-related consequences in the Army National Guard. *Addict Behav* 2018; **80**: 22-27 [PMID: 29310003 DOI: 10.1016/j.addbeh.2018.01.002]

13   **Long EC**, Lönn SL, Ji J, Lichtenstein P, Sundquist J, Sundquist K, Kendler KS. Resilience and Risk for Alcohol Use Disorders: A Swedish Twin Study. *Alcohol Clin Exp Res* 2017; **41**: 149-155 [PMID: 27918840 DOI: 10.1111/acer.13274]

14   **Aguilar MA**, García-Pardo MP, Montagud-Romero S, Miñarro J, Do Couto BR. Impact of social stress in addiction to psychostimulants: what we know from animal models. *Curr Pharm Des* 2013; **19**: 7009-7025 [PMID: 23574439 DOI: 10.2174/13816128194013109124708]

15   **Vannan A**, Powell GL, Scott SN, Pagni BA, Neisewander JL. Animal Models of the Impact of Social Stress on Cocaine Use Disorders. *Int Rev Neurobiol* 2018; **140**: 131-169 [PMID: 30193703 DOI: 10.1016/bs.irn.2018.07.005]

16   **Rudzinski K**, McDonough P, Gartner R, Strike C. Is there room for resilience? *Subst Abuse Treat Prev Policy* 2017; **12**: 41 [PMID: 28915841 DOI: 10.1186/s13011-017-0125-2]

17   **Weiland BJ**, Nigg JT, Welsh RC, Yau WY, Zubieta JK, Zucker RA, Heitzeg MM. Resiliency in adolescents at high risk for substance abuse: flexible adaptation *via* subthalamic nucleus and linkage to drinking and drug use in early adulthood. *Alcohol Clin Exp Res* 2012; **36**: 1355-1364 [PMID: 22587751 DOI: 10.1111/j.1530-0277.2012.01741.x]

18   **Harris KJ**, Smock SA, Wilkes MT. Relapse resilience: a process model of addiction and recovery. *J Fam Psychother* 2011; 22: 265-74 [DOI: 10.1080/08975353.2011.602622]

19   **Charlet K**, Rosenthal A, Lohoff FW, Heinz A, Beck A. Imaging resilience and recovery in alcohol dependence. *Addiction* 2018; **113**: 1933-1950 [PMID: 29744956 DOI: 10.1111/add.14259]

20   **Pearce ME**, Jongbloed KA, Richardson CG, Henderson EW, Pooyak SD, Oviedo-Joekes E, Christian WM, Schechter MT, Spittal PM; Cedar Project Partnership. The Cedar Project: resilience in the face of HIV vulnerability within a cohort study involving young Indigenous people who use drugs in three Canadian cities. *BMC Public Health* 2015; **15**: 1095 [PMID: 26510467 DOI: 10.1186/s12889-015-2417-7]

21   **Kallupi M**, Scuppa G, de Guglielmo G, Calò G, Weiss F, Statnick MA, Rorick-Kehn LM, Ciccocioppo R. Genetic Deletion of the Nociceptin/Orphanin FQ Receptor in the Rat Confers Resilience to the Development of Drug Addiction. *Neuropsychopharmacology* 2017; **42**: 695-706 [PMID: 27562376 DOI: 10.1038/npp.2016.171]

22   **Steiner N**, Rossetti C, Sakurai T, Yanagisawa M, de Lecea L, Magistretti PJ, Halfon O, Boutrel B. Hypocretin/orexin deficiency decreases cocaine abuse liability. *Neuropharmacology* 2018; **133**: 395-403 [PMID: 29454841 DOI: 10.1016/j.neuropharm.2018.02.010]

23   **Gloria CT**, Steinhardt MA. Relationships Among Positive Emotions, Coping, Resilience and Mental Health. *Stress Health* 2016; **32**: 145-156 [PMID: 24962138 DOI: 10.1002/smi.2589]

24   **Southwick SM**, Vythilingam M, Charney DS. The psychobiology of depression and resilience to stress: implications for prevention and treatment. *Annu Rev Clin Psychol* 2005; **1**: 255-291 [PMID: 17716089 DOI: 10.1146/annurev.clinpsy.1.102803.143948]

25   **Burt KB**, Paysnick AA. Resilience in the transition to adulthood. *Dev Psychopathol* 2012; **24**: 493-505 [PMID: 22559126 DOI: 10.1017/S0954579412000119]

26   **Werner EE**. Children and war: risk, resilience, and recovery. *Dev Psychopathol* 2012; **24**: 553-558 [PMID: 22559130 DOI: 10.1017/S0954579412000156]

27   **Min JA**, Jung YE, Kim DJ, Yim HW, Kim JJ, Kim TS, Lee CU, Lee C, Chae JH. Characteristics associated with low resilience in patients with depression and/or anxiety disorders. *Qual Life Res* 2013; **22**: 231-241 [PMID: 22485024 DOI: 10.1007/s11136-012-0153-3]

28   **Smith BW**, Ortiz JA, Steffen LE, Tooley EM, Wiggins KT, Yeater EA, Montoya JD, Bernard ML. Mindfulness is associated with fewer PTSD symptoms, depressive symptoms, physical symptoms, and alcohol problems in urban firefighters. *J Consult Clin Psychol* 2011; **79**: 613-617 [PMID: 21875175 DOI: 10.1037/a0025189]

29   **Southwick SM**, Charney DS. The science of resilience: implications for the prevention and treatment of depression. *Science* 2012; **338**: 79-82 [PMID: 23042887 DOI: 10.1126/science.1222942]

30   **McEwen BS**, Gianaros PJ. Stress- and allostasis-induced brain plasticity. *Annu Rev Med* 2011; **62**: 431-445 [PMID: 20707675 DOI: 10.1146/annurev-med-052209-100430]

31   **Crane MF**, Searle BJ, Kangas M, Nwiran Y. How resilience is strengthened by exposure to stressors: the systematic self-reflection model of resilience strengthening. *Anxiety Stress Coping* 2019; **32**: 1-17 [PMID: 30067067 DOI: 10.1080/10615806.2018.1506640]

32   **Luthar SS**, Barkin SH. Are affluent youth truly "at risk"? *Dev Psychopathol* 2012; **24**: 429-449 [PMID: 22559123 DOI: 10.1017/S0954579412000089]

33   **Aston-Jones G**, Cohen JD. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annu Rev Neurosci* 2005; **28**: 403-450 [PMID: 16022602 DOI: 10.1146/annurev.neuro.28.061604.135709]

34   **Strawn JR**, Geracioti TD Jr. Noradrenergic dysfunction and the psychopharmacology of posttraumatic stress disorder. *Depress Anxiety* 2008; **25**: 260-271 [PMID: 17354267 DOI: 10.1002/da.20292]

35   **Charney DS**. Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. *Am J Psychiatry* 2004; **161**: 195-216 [PMID: 14754765 DOI: 10.1176/appi.ajp.161.2.195]

36   **Feder A**, Nestler EJ, Charney DS. Psychobiology and molecular genetics of resilience. *Nat Rev Neurosci* 2009; **10**: 446-457 [PMID: 19455174 DOI: 10.1038/nrn2649]

37   **Miura H**, Qiao H, Ohta T. Attenuating effects of the isolated rearing condition on increased brain serotonin and dopamine turnover elicited by novelty stress. *Brain Res* 2002; **926**: 10-17 [PMID: 11814401 DOI: 10.1016/s0006-8993(01)03201-2]

38   **Culman J**, Mühlenhoff S, Blume A, Hedderich J, Lützen U, Hunt SP, Rupniak NMJ, Zhao Y. The Hypothalamic-Pituitary-Adrenal Axis and Serotonin Metabolism in Individual Brain Nuclei of Mice with Genetic Disruption of the NK1 Receptor Exposed to Acute Stress. *Cell Mol Neurobiol* 2018; **38**: 1271-1281 [PMID: 29948553 DOI: 10.1007/s10571-018-0594-5]

39   **De La Garza R 2nd**, Mahoney JJ 3rd. A distinct neurochemical profile in WKY rats at baseline and in response to acute stress: implications for animal models of anxiety and depression. *Brain Res* 2004; **1021**: 209-218 [PMID: 15342269 DOI: 10.1016/j.brainres.2004.06.052]

40   **Duman RS**. Neuronal damage and protection in the pathophysiology and treatment of psychiatric illness: stress and depression. *Dialogues Clin Neurosci* 2009; **11**: 239-255 [PMID: 19877493]

41   **Tural Ü**, Aker AT, Önder E, Sodan HT, Ünver H, Akansel G. Neurotrophic factors and hippocampal activity in PTSD. *PLoS One* 2018; **13**: e0197889 [PMID: 29799860 DOI: 10.1371/journal.pone.0197889]

42   **Kozlovsky N**, Matar MA, Kaplan Z, Kotler M, Zohar J, Cohen H. Long-term down-regulation of BDNF mRNA in rat hippocampal CA1 subregion correlates with PTSD-like behavioural stress response. *Int J Neuropsychopharmacol* 2007; **10**: 741-758 [PMID: 17291374 DOI: 10.1017/S1461145707007560]

43   **Sajdyk TJ**, Shekhar A, Gehlert DR. Interactions between NPY and CRF in the amygdala to regulate emotionality. *Neuropeptides* 2004; **38**: 225-234 [PMID: 15537374 DOI: 10.1016/j.npep.2004.05.006]

44   **Jones T**, Moller MD. Implications of hypothalamic-pituitary-adrenal axis functioning in posttraumatic stress disorder. *J Am Psychiatr Nurses Assoc* 2011; **17**: 393-403 [PMID: 22142976 DOI: 10.1177/1078390311420564]

45   **Morgan CA 3rd**, Rasmusson AM, Wang S, Hoyt G, Hauger RL, Hazlett G. Neuropeptide-Y, cortisol, and subjective distress in humans exposed to acute stress: replication and extension of previous report. *Biol Psychiatry* 2002; **52**: 136-142 [PMID: 12114005 DOI: 10.1016/s0006-3223(02)01319-7]

46   **Bottaccioli AG**, Bottaccioli F, Minelli A. Stress and the psyche-brain-immune network in psychiatric diseases based on psychoneuroendocrineimmunology: a concise review. *Ann N Y Acad Sci* 2019; **1437**: 31-42 [PMID: 29762862 DOI: 10.1111/nyas.13728]

47   **Verburg-van Kemenade BM**, Van der Aa LM, Chadzinska M. Neuroendocrine-immune interaction: regulation of inflammation *via* G-protein coupled receptors. *Gen Comp Endocrinol* 2013; **188**: 94-101 [PMID: 23201149 DOI: 10.1016/j.ygcen.2012.11.010]

48   **Gururajan A**, van de Wouw M, Boehme M, Becker T, O'Connor R, Bastiaanssen TFS, Moloney GM, Lyte JM, Ventura Silva AP, Merckx B, Dinan TG, Cryan JF. Resilience to chronic stress is associated with specific neurobiological, neuroendocrine and immune responses. *Brain Behav Immun* 2019; **80**: 583-594 [PMID: 31059807 DOI: 10.1016/j.bbi.2019.05.004]

49   **Tsyglakova M**, McDaniel D, Hodes GE. Immune mechanisms of stress susceptibility and resilience: Lessons from animal models. *Front Neuroendocrinol* 2019; **54**: 100771 [PMID: 31325456 DOI: 10.1016/j.yfrne.2019.100771]

50   **Ménard C**, Pfau ML, Hodes GE, Russo SJ. Immune and Neuroendocrine Mechanisms of Stress Vulnerability and Resilience. *Neuropsychopharmacology* 2017; **42**: 62-80 [PMID: 27291462 DOI: 10.1038/npp.2016.90]

51   **Feder A**, Fred-Torres S, Southwick SM, Charney DS. The Biology of Human Resilience: Opportunities for Enhancing Resilience Across the Life Span. *Biol Psychiatry* 2019; **86**: 443-453 [PMID: 31466561 DOI: 10.1016/j.biopsych.2019.07.012]

52   **Dantzer R**, Cohen S, Russo SJ, Dinan TG. Resilience and immunity. *Brain Behav Immun* 2018; **74**: 28-42 [PMID: 30102966 DOI: 10.1016/j.bbi.2018.08.010]

53   **Makris AP**, Karianaki M, Tsamis KI, Paschou SA. The role of the gut-brain axis in depression: endocrine, neural, and immune pathways. *Hormones (Athens)* 2021; **20**: 1-12 [PMID: 32827123 DOI: 10.1007/s42000-020-00236-4]

54   **Cathomas F**, Murrough JW, Nestler EJ, Han MH, Russo SJ. Neurobiology of Resilience: Interface Between Mind and Body. *Biol Psychiatry* 2019; **86**: 410-420 [PMID: 31178098 DOI: 10.1016/j.biopsych.2019.04.011]

55   **Yang C**, Fujita Y, Ren Q, Ma M, Dong C, Hashimoto K. Bifidobacterium in the gut microbiota confer resilience to chronic social defeat stress in mice. *Sci Rep* 2017; **7**: 45942 [PMID: 28368029 DOI: 10.1038/srep45942]

56   **Bharwani A**, Mian MF, Surette MG, Bienenstock J, Forsythe P. Oral treatment with Lactobacillus rhamnosus attenuates behavioural deficits and immune changes in chronic social stress. *BMC Med* 2017; **15**: 7 [PMID: 28073366 DOI: 10.1186/s12916-016-0771-7]

57   **Harris JC**. Experimental animal modeling of depression and anxiety. *Psychiatr Clin North Am* 1989; **12**: 815-836 [PMID: 2690027]

58   **Frazer A**, Morilak DA. What should animal models of depression model? *Neurosci Biobehav Rev* 2005; **29**: 515-523 [PMID: 15893377 DOI: 10.1016/j.neubiorev.2005.03.006]

59   **Ayash S**, Schmitt U, Lyons DM, Müller MB. Stress inoculation in mice induces global resilience. *Transl Psychiatry* 2020; **10**: 200 [PMID: 32561821 DOI: 10.1038/s41398-020-00889-0]

60   **Brachman RA**, McGowan JC, Perusini JN, Lim SC, Pham TH, Faye C, Gardier AM, Mendez-David I, David DJ, Hen R, Denny CA. Ketamine as a Prophylactic Against Stress-Induced Depressive-like Behavior. *Biol Psychiatry* 2016; **79**: 776-786 [PMID: 26037911 DOI: 10.1016/j.biopsych.2015.04.022]

61   **Ono Y**, Lin HC, Tzen KY, Chen HH, Yang PF, Lai WS, Chen JH, Onozuka M, Yen CT. Active coping with stress suppresses glucose metabolism in the rat hypothalamus. *Stress* 2012; **15**: 207-217 [PMID: 21936685 DOI: 10.3109/10253890.2011.614296]

62   **Delgado y Palacios R**, Campo A, Henningsen K, Verhoye M, Poot D, Dijkstra J, Van Audekerke J, Benveniste H, Sijbers J, Wiborg O, Van der Linden A. Magnetic resonance imaging and spectroscopy reveal differential hippocampal changes in anhedonic and resilient subtypes of the chronic mild stress rat model. *Biol Psychiatry* 2011; **70**: 449-457 [PMID: 21762877 DOI: 10.1016/j.biopsych.2011.05.014]

63   **Cohen H**, Liu T, Kozlovsky N, Kaplan Z, Zohar J, Mathé AA. The neuropeptide Y (NPY)-ergic system is associated with behavioral resilience to stress exposure in an animal model of post-traumatic stress disorder. *Neuropsychopharmacology* 2012; **37**: 350-363 [PMID: 21976046 DOI: 10.1038/npp.2011.230]

64   **Berton O**, Covington HE 3rd, Ebner K, Tsankova NM, Carle TL, Ulery P, Bhonsle A, Barrot M, Krishnan V, Singewald GM, Singewald N, Birnbaum S, Neve RL, Nestler EJ. Induction of deltaFosB in the periaqueductal gray by stress promotes active coping responses. *Neuron* 2007; **55**: 289-300 [PMID: 17640529 DOI: 10.1016/j.neuron.2007.06.033]

65   **Fleshner M**, Maier SF, Lyons DM, Raskind MA. The neurobiology of the stress-resistant brain. *Stress* 2011; **14**: 498-502 [PMID: 21790482 DOI: 10.3109/10253890.2011.596865]

66   **Bartolomucci A**, Cabassi A, Govoni P, Ceresini G, Cero C, Berra D, Dadomo H, Franceschini P, Dell'Omo G, Parmigiani S, Palanza P. Metabolic consequences and vulnerability to diet-induced obesity in male mice under chronic social stress. *PLoS One* 2009; **4**: e4331 [PMID: 19180229 DOI: 10.1371/journal.pone.0004331]

67   **Nestler EJ**, Hyman SE. Animal models of neuropsychiatric disorders. *Nat Neurosci* 2010; **13**: 1161-1169 [PMID: 20877280 DOI: 10.1038/nn.2647]

68   **Hollis F**, Kabbaj M. Social defeat as an animal model for depression. *ILAR J* 2014; **55**: 221-232 [PMID: 25225302 DOI: 10.1093/ilar/ilu002]

69   **Czéh B**, Fuchs E, Wiborg O, Simon M. Animal models of major depression and their clinical implications. *Prog Neuropsychopharmacol Biol Psychiatry* 2016; **64**: 293-310 [PMID: 25891248 DOI: 10.1016/j.pnpbp.2015.04.004]

70   **Krishnan V**, Han MH, Graham DL, Berton O, Renthal W, Russo SJ, Laplant Q, Graham A, Lutter M, Lagace DC, Ghose S, Reister R, Tannous P, Green TA, Neve RL, Chakravarty S, Kumar A, Eisch AJ, Self DW, Lee FS, Tamminga CA, Cooper DC, Gershenfeld HK, Nestler EJ. Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. *Cell* 2007; **131**: 391-404 [PMID: 17956738 DOI: 10.1016/j.cell.2007.09.018]

71   **Lutter M**, Sakata I, Osborne-Lawrence S, Rovinsky SA, Anderson JG, Jung S, Birnbaum S, Yanagisawa M, Elmquist JK, Nestler EJ, Zigman JM. The orexigenic hormone ghrelin defends against depressive symptoms of chronic stress. *Nat Neurosci* 2008; **11**: 752-753 [PMID: 18552842 DOI: 10.1038/nn.2139]

72   **Golden SA**, Covington HE 3rd, Berton O, Russo SJ. A standardized protocol for repeated social defeat stress in mice. *Nat Protoc* 2011; **6**: 1183-1191 [PMID: 21799487 DOI: 10.1038/nprot.2011.361]

73   **Vidal J**, Buwalda B, Koolhaas JM. Male Wistar rats are more susceptible to lasting social anxiety than Wild-type Groningen rats following social defeat stress during adolescence. *Behav Processes* 2011; **88**: 76-80 [PMID: 21854839 DOI: 10.1016/j.beproc.2011.08.005]

74   **Ellenbroek BA**, van der Kam EL, van der Elst MC, Cools AR. Individual differences in drug dependence in rats: the role of genetic factors and life events. *Eur J Pharmacol* 2005; **526**: 251-258 [PMID: 16253227 DOI: 10.1016/j.ejphar.2005.09.032]

75   **Burke AR**, Watt MJ, Forster GL. Adolescent social defeat increases adult amphetamine conditioned place preference and alters D2 dopamine receptor expression. *Neuroscience* 2011; **197**: 269-279 [PMID: 21933700 DOI: 10.1016/j.neuroscience.2011.09.008]

76   **Newman EL**, Leonard MZ, Arena DT, de Almeida RMM, Miczek KA. Social defeat stress and escalation of cocaine and alcohol consumption: Focus on CRF. *Neurobiol Stress* 2018; **9**: 151-165 [PMID: 30450381 DOI: 10.1016/j.ynstr.2018.09.007]

77   **García-Pardo MP**, Calpe-López C, Miñarro J, Aguilar MA. Role of N-methyl-D-aspartate receptors in the long-term effects of repeated social defeat stress on the rewarding and psychomotor properties of cocaine in mice. *Behav Brain Res* 2019; **361**: 95-103 [PMID: 30557580 DOI: 10.1016/j.bbr.2018.12.025]

78   **García-Pardo MP**, Blanco-Gandía MC, Valiente-Lluch M, Rodríguez-Arias M, Miñarro J, Aguilar MA. Long-term effects of repeated social stress on the conditioned place preference induced by MDMA in mice. *Prog Neuropsychopharmacol Biol Psychiatry* 2015; **63**: 98-109 [PMID: 26093344 DOI: 10.1016/j.pnpbp.2015.06.006]

79   **García-Pardo MP**, De la Rubia Ortí JE, Aguilar Calpe MA. Differential effects of MDMA and cocaine on inhibitory avoidance and object recognition tests in rodents. *Neurobiol Learn Mem* 2017; **146**: 1-11 [PMID: 29081371 DOI: 10.1016/j.nlm.2017.10.013]

80   **LEVINE S**. Plasma-free corticosteroid response to electric shock in rats stimulated in infancy. *Science* 1962; **135**: 795-796 [PMID: 14464660 DOI: 10.1126/science.135.3506.795-a]

81   **Ricon T**, Toth E, Leshem M, Braun K, Richter-Levin G. Unpredictable chronic stress in juvenile or adult rats has opposite effects, respectively, promoting and impairing resilience. *Stress* 2012; **15**: 11-20 [PMID: 21682654 DOI: 10.3109/10253890.2011.572207]

82   **Wood SK**, Walker HE, Valentino RJ, Bhatnagar S. Individual differences in reactivity to social stress predict susceptibility and resilience to a depressive phenotype: role of corticotropin-releasing factor. *Endocrinology* 2010; **151**: 1795-1805 [PMID: 20160137 DOI: 10.1210/en.2009-1026]

83   **Holmes PV**. Trophic Mechanisms for Exercise-Induced Stress Resilience: Potential Role of Interactions between BDNF and Galanin. *Front Psychiatry* 2014; **5**: 90 [PMID: 25120496 DOI: 10.3389/fpsyt.2014.00090]

84   **Sciolino NR**, Smith JM, Stranahan AM, Freeman KG, Edwards GL, Weinshenker D, Holmes PV. Galanin mediates features of neural and behavioral stress resilience afforded by exercise. *Neuropharmacology* 2015; **89**: 255-264 [PMID: 25301278 DOI: 10.1016/j.neuropharm.2014.09.029]

85   **Hutchinson KM**, McLaughlin KJ, Wright RL, Bryce Ortiz J, Anouti DP, Mika A, Diamond DM, Conrad CD. Environmental enrichment protects against the effects of chronic stress on cognitive and morphological measures of hippocampal integrity. *Neurobiol Learn Mem* 2012; **97**: 250-260 [PMID: 22266288 DOI: 10.1016/j.nlm.2012.01.003]

86   **Luine V**. Sex differences in chronic stress effects on memory in rats. *Stress* 2002; **5**: 205-216 [PMID: 12186683 DOI: 10.1080/1025389021000010549]

87   **Luine V**, Gomez J, Beck K, Bowman R. Sex differences in chronic stress effects on cognition in rodents. *Pharmacol Biochem Behav* 2017; **152**: 13-19 [PMID: 27566290 DOI: 10.1016/j.pbb.2016.08.005]

88   **Fu W**, Xie H, Laudon M, Zhou S, Tian S, You Y. Piromelatine ameliorates memory deficits associated with chronic mild stress-induced anhedonia in rats. *Psychopharmacology (Berl)* 2016; **233**: 2229-2239 [PMID: 27007604 DOI: 10.1007/s00213-016-4272-3]

89   **Pollak DD**, Rey CE, Monje FJ. Rodent models in depression research: classical strategies and new directions. *Ann Med* 2010; **42**: 252-264 [PMID: 20367120 DOI: 10.3109/07853891003769957]

90   **Cryan JF**, Mombereau C, Vassout A. The tail suspension test as a model for assessing antidepressant activity: review of pharmacological and genetic studies in mice. *Neurosci Biobehav Rev* 2005; **29**: 571-625 [PMID: 15890404 DOI: 10.1016/j.neubiorev.2005.03.009]

91   **Commons KG**, Cholanians AB, Babb JA, Ehlinger DG. The Rodent Forced Swim Test Measures Stress-Coping Strategy, Not Depression-like Behavior. *ACS Chem Neurosci* 2017; 8: 955-960 [DOI:

10.1021/acschemneuro.7b00042]

92   **Okhuarobo A**, Bolton JL, Igbe I, Zorrilla EP, Baram TZ, Contet C. A novel mouse model for vulnerability to alcohol dependence induced by early-life adversity. *Neurobiol Stress* 2020; **13**: 100269 [PMID: 33344722 DOI: 10.1016/j.ynstr.2020.100269]

93   **Calpe-López C**, García-Pardo MP, Martínez-Caballero MA, Santos-Ortíz A, Aguilar MA. Behavioral Traits Associated With Resilience to the Effects of Repeated Social Defeat on Cocaine-Induced Conditioned Place Preference in Mice. *Front Behav Neurosci* 2019; **13**: 278 [PMID: 31998090 DOI: 10.3389/fnbeh.2019.00278]

94   **Rimmerman N**, Schottlender N, Reshef R, Dan-Goor N, Yirmiya R. The hippocampal transcriptomic signature of stress resilience in mice with microglial fractalkine receptor (CX3CR1) deficiency. *Brain Behav Immun* 2017; **61**: 184-196 [PMID: 27890560 DOI: 10.1016/j.bbi.2016.11.023]

95   **Park J**, Lee J, Choi K, Kang HJ. Regulation of behavioral response to stress by microRNA-690. *Mol Brain* 2021; **14**: 7 [PMID: 33422095 DOI: 10.1186/s13041-021-00728-3]

96   **Bergner CL**, Smolinsky AN, Hart PC, Dufour BD, Egan RJ, LaPorte JL, Kalueff AV. Mouse Models for Studying Depression-Like States and Antidepressant Drugs. *Methods Mol Biol* 2016; **1438**: 255-269 [PMID: 27150095 DOI: 10.1007/978-1-4939-3661-8_15]

97   **Duque A**, Vinader-Caerols C, Monleón S. Indomethacin counteracts the effects of chronic social defeat stress on emotional but not recognition memory in mice. *PLoS One* 2017; 12: e0173182 [DOI: 10.1371/journal.pone.0173182]

98   **Andoh C**, Nishitani N, Hashimoto E, Nagai Y, Takao K, Miyakawa T, Nakagawa T, Mori Y, Nagayasu K, Shirakawa H, Kaneko S. TRPM2 confers susceptibility to social stress but is essential for behavioral flexibility. *Brain Res* 2019; **1704**: 68-77 [PMID: 30273551 DOI: 10.1016/j.brainres.2018.09.031]

99   **Blasco-Serra A**, González-Soler EM, Cervera-Ferri A, Teruel-Martí V, Valverde-Navarro AA. A standardization of the Novelty-Suppressed Feeding Test protocol in rats. *Neurosci Lett* 2017; **658**: 73-78 [PMID: 28803957 DOI: 10.1016/j.neulet.2017.08.019]

100   **Rodgers RJ**, Johnson NJ. Factor analysis of spatiotemporal and ethological measures in the murine elevated plus-maze test of anxiety. *Pharmacol Biochem Behav* 1995; **52**: 297-303 [PMID: 8577794 DOI: 10.1016/0091-3057(95)00138-m]

101   **Rodgers RJ**, Dalvi A. Anxiety, defence and the elevated plus-maze. *Neurosci Biobehav Rev* 1997; **21**: 801-810 [PMID: 9415905 DOI: 10.1016/s0149-7634(96)00058-9]

102   **Prabhu VV**, Nguyen TB, Cui Y, Oh YE, Lee KH, Bagalkot TR, Chung YC. Effects of social defeat stress on dopamine D2 receptor isoforms and proteins involved in intracellular trafficking. *Behav Brain Funct* 2018; **14**: 16 [PMID: 30296947 DOI: 10.1186/s12993-018-0148-5]

103   **Gutknecht L**, Popp S, Waider J, Sommerlandt FM, Göppner C, Post A, Reif A, van den Hove D, Strekalova T, Schmitt A, Colaço MB, Sommer C, Palme R, Lesch KP. Interaction of brain 5-HT synthesis deficiency, chronic stress and sex differentially impact emotional behavior in Tph2 knockout mice. *Psychopharmacology (Berl)* 2015; **232**: 2429-2441 [PMID: 25716307 DOI: 10.1007/s00213-015-3879-0]

104   **Hidaka C**, Kashio T, Uchigaki D, Mitsui S. Vulnerability or resilience of motopsin knockout mice to maternal separation stress depending on adulthood behaviors. *Neuropsychiatr Dis Treat* 2018; **14**: 2255-2268 [PMID: 30233183 DOI: 10.2147/NDT.S170281]

105   **Binder E**, Malki K, Paya-Cano JL, Fernandes C, Aitchison KJ, Mathé AA, Sluyter F, Schalkwyk LC. Antidepressants and the resilience to early-life stress in inbred mouse strains. *Pharmacogenet Genomics* 2011; **21**: 779-789 [PMID: 22016050 DOI: 10.1097/FPC.0b013e32834b3f35]

106   **Adamec R**, Toth M, Haller J, Halasz J, Blundell J. A comparison of activation patterns of cells in selected prefrontal cortical and amygdala areas of rats which are more or less anxious in response to predator exposure or submersion stress. *Physiol Behav* 2012; **105**: 628-638 [PMID: 21971366 DOI: 10.1016/j.physbeh.2011.09.016]

107   **Ennaceur A**, Delacour J. A new one-trial test for neurobiological studies of memory in rats. 1: Behavioral data. *Behav Brain Res* 1988; **31**: 47-59 [PMID: 3228475 DOI: 10.1016/0166-4328(88)90157-x]

108   **Broadbent NJ**, Squire LR, Clark RE. Spatial memory, recognition memory, and the hippocampus. *Proc Natl Acad Sci U S A* 2004; **101**: 14515-14520 [PMID: 15452348 DOI: 10.1073/pnas.0406344101]

109   **Atmore KH**, Stein DJ, Harvey BH, Russell VA, Howells FM. Differential effects of social isolation rearing on glutamate- and GABA-stimulated noradrenaline release in the rat prefrontal cortex and hippocampus. *Eur Neuropsychopharmacol* 2020; **36**: 111-120 [PMID: 32553548 DOI: 10.1016/j.euroneuro.2020.05.007]

110   **Jene T**, Gassen NC, Opitz V, Endres K, Müller MB, van der Kooij MA. Temporal profiling of an acute stress-induced behavioral phenotype in mice and role of hippocampal DRR1. *Psychoneuroendocrinology* 2018; **91**: 149-158 [PMID: 29555365 DOI: 10.1016/j.psyneuen.2018.03.004]

111   **Tzeng WY**, Su CC, Sun LH, Cherng CG, Yu L. Synergistic Effects of Psychosocial Stress and Mild Peripheral Infection on Inducing Microglial Activation in the Hippocampal Dentate Gyrus and Long-Lasting Deficits in Hippocampus-Related Memory. *Chin J Physiol* 2018; **61**: 106-117 [PMID: 29660975 DOI: 10.4077/CJP.2018.BAG569]

112   **Wendelmuth M**, Willam M, Todorov H, Radyushkin K, Gerber S, Schweiger S. Dynamic

longitudinal behavior in animals exposed to chronic social defeat stress. *PLoS One* 2020; **15**: e0235268 [PMID: 32701959 DOI: 10.1371/journal.pone.0235268]

113   **Vorhees CV**, Williams MT. Value of water mazes for assessing spatial and egocentric learning and memory in rodent basic research and regulatory studies. *Neurotoxicol Teratol* 2014; **45**: 75-90 [PMID: 25116937 DOI: 10.1016/j.ntt.2014.07.003]

114   **Qu N**, Wang XM, Zhang T, Zhang SF, Li Y, Cao FY, Wang Q, Ning LN, Tian Q. Estrogen Receptor α Agonist is Beneficial for Young Female Rats Against Chronic Unpredicted Mild Stress-Induced Depressive Behavior and Cognitive Deficits. *J Alzheimers Dis* 2020; **77**: 1077-1093 [PMID: 32804146 DOI: 10.3233/JAD-200486]

115   **Drugan RC**, Warner TA, Papallo TA, Castracane LL, Stafford NP. Ultrasonic vocalizations during intermittent swim stress forecasts resilience in subsequent forced swim and spatial learning tests. *Behav Brain Res* 2014; **259**: 41-44 [PMID: 24475493 DOI: 10.1016/j.bbr.2013.10.029]

116   **Conrad CD**, Galea LA, Kuroda Y, McEwen BS. Chronic stress impairs rat spatial memory on the Y maze, and this effect is blocked by tianeptine pretreatment. *Behav Neurosci* 1996; **110**: 1321-1334 [PMID: 8986335 DOI: 10.1037//0735-7044.110.6.1321]

117   **McAllister BB**, Wright DK, Wortman RC, Shultz SR, Dyck RH. Elimination of vesicular zinc alters the behavioural and neuroanatomical effects of social defeat stress in mice. *Neurobiol Stress* 2018; **9**: 199-213 [PMID: 30450385 DOI: 10.1016/j.ynstr.2018.10.003]

118   **Bhakta A**, Gavini K, Yang E, Lyman-Henley L, Parameshwaran K. Chronic traumatic stress impairs memory in mice: Potential roles of acetylcholine, neuroinflammation and corticotropin releasing factor expression in the hippocampus. *Behav Brain Res* 2017; **335**: 32-40 [PMID: 28797603 DOI: 10.1016/j.bbr.2017.08.013]

119   **Tractenberg SG**, Orso R, Creutzberg KC, Malcon LMC, Lumertz FS, Wearick-Silva LE, Viola TW, Riva MA, Grassi-Oliveira R. Vulnerable and resilient cognitive performance related to early life stress: The potential mediating role of dopaminergic receptors in the medial prefrontal cortex of adult mice. *Int J Dev Neurosci* 2020; **80**: 13-27 [PMID: 31907967 DOI: 10.1002/jdn.10004]

120   **Kambali MY**, Anshu K, Kutty BM, Muddashetty RS, Laxmi TR. Effect of early maternal separation stress on attention, spatial learning and social interaction behaviour. *Exp Brain Res* 2019; **237**: 1993-2010 [PMID: 31154461 DOI: 10.1007/s00221-019-05567-2]

121   **Diamond DM**, Park CR, Heman KL, Rose GM. Exposing rats to a predator impairs spatial working memory in the radial arm water maze. *Hippocampus* 1999; **9**: 542-552 [PMID: 10560925 DOI: 10.1002/(SICI)1098-1063(1999)9:5<542::AID-HIPO8>3.0.CO;2-N]

122   **Hoffman AN**, Krigbaum A, Ortiz JB, Mika A, Hutchinson KM, Bimonte-Nelson HA, Conrad CD. Recovery after chronic stress within spatial reference and working memory domains: correspondence with hippocampal morphology. *Eur J Neurosci* 2011; **34**: 1023-1030 [PMID: 21884554 DOI: 10.1111/j.1460-9568.2011.07820.x]

123   **Ortiz JB**, Mathewson CM, Hoffman AN, Hanavan PD, Terwilliger EF, Conrad CD. Hippocampal brain-derived neurotrophic factor mediates recovery from chronic stress-induced spatial reference memory deficits. *Eur J Neurosci* 2014; **40**: 3351-3362 [PMID: 25156382 DOI: 10.1111/ejn.12703]

124   **Ortiz JB**, Anglin JM, Daas EJ, Paode PR, Nishimura K, Conrad CD. BDNF and TrkB Mediate the Improvement from Chronic Stress-induced Spatial Memory Deficits and CA3 Dendritic Retraction. *Neuroscience* 2018; **388**: 330-346 [PMID: 30076998 DOI: 10.1016/j.neuroscience.2018.07.049]

125   **Peay DN**, Saribekyan HM, Parada PA, Hanson EM, Badaruddin BS, Judd JM, Donnay ME, Padilla-Garcia D, Conrad CD. Chronic unpredictable intermittent restraint stress disrupts spatial memory in male, but not female rats. *Behav Brain Res* 2020; **383**: 112519 [PMID: 32006567 DOI: 10.1016/j.bbr.2020.112519]

126   **Koob GF**, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry* 2016; **3**: 760-773 [PMID: 27475769 DOI: 10.1016/S2215-0366(16)00104-8]

127   **Everitt BJ**. Neural and psychological mechanisms underlying compulsive drug seeking habits and drug memories--indications for novel treatments of addiction. *Eur J Neurosci* 2014; **40**: 2163-2182 [PMID: 24935353 DOI: 10.1111/ejn.12644]

128   **Everitt BJ**, Robbins TW. From the ventral to the dorsal striatum: devolving views of their roles in drug addiction. *Neurosci Biobehav Rev* 2013; **37**: 1946-1954 [PMID: 23438892 DOI: 10.1016/j.neubiorev.2013.02.010]

129   **Moser P**, Wolinsky T, Duxon M, Porsolt RD. How good are current approaches to nonclinical evaluation of abuse and dependence? *J Pharmacol Exp Ther* 2011; **336**: 588-595 [PMID: 21098089 DOI: 10.1124/jpet.110.169979]

130   **Yahyavi-Firouz-Abadi N**, See RE. Anti-relapse medications: preclinical models for drug addiction treatment. *Pharmacol Ther* 2009; **124**: 235-247 [PMID: 19683019 DOI: 10.1016/j.pharmthera.2009.06.014]

131   **Epstein DH**, Preston KL, Stewart J, Shaham Y. Toward a model of drug relapse: an assessment of the validity of the reinstatement procedure. *Psychopharmacology (Berl)* 2006; **189**: 1-16 [PMID: 17019567 DOI: 10.1007/s00213-006-0529-6]

132   **Shaham Y**, Shalev U, Lu L, de Wit H, Stewart J. The reinstatement model of drug relapse: history, methodology and major findings. *Psychopharmacology (Berl)* 2003; **168**: 3-20 [PMID: 12402102 DOI: 10.1007/s00213-002-1224-x]

133   **Stewart J**. Pathways to relapse: the neurobiology of drug- and stress-induced relapse to drug-taking. *J Psychiatry Neurosci* 2000; **25**: 125-136 [PMID: 10740986]

134   **Soria G**, Barbano MF, Maldonado R, Valverde O. A reliable method to study cue-, priming-, and

stress-induced reinstatement of cocaine self-administration in mice. *Psychopharmacology (Berl)* 2008; **199**: 593-603 [PMID: 18488200 DOI: 10.1007/s00213-008-1184-x]

135   **Deroche-Gamonet V**, Piazza PV. Psychobiology of cocaine addiction: Contribution of a multi-symptomatic animal model of loss of control. *Neuropharmacology* 2014; **76** Pt B: 437-449 [PMID: 23916478 DOI: 10.1016/j.neuropharm.2013.07.014]

136   **Rodriguez-Arias M**, Navarrete F, Blanco-Gandia MC, Arenas MC, Bartoll-Andrés A, Aguilar MA, Rubio G, Miñarro J, Manzanares J. Social defeat in adolescent mice increases vulnerability to alcohol consumption. *Addict Biol* 2016; **21**: 87-97 [PMID: 25219790 DOI: 10.1111/adb.12184]

137   **Reguilón MD**, Ferrer-Pérez C, Ballestín R, Miñarro J, Rodríguez-Arias M. Voluntary wheel running protects against the increase in ethanol consumption induced by social stress in mice. *Drug Alcohol Depend* 2020; **212**: 108004 [PMID: 32408137 DOI: 10.1016/j.drugalcdep.2020.108004]

138   **Reguilón MD**, Ferrer-Pérez C, Miñarro J, Rodríguez-Arias M. Oxytocin reverses ethanol consumption and neuroinflammation induced by social defeat in male mice. *Horm Behav* 2021; **127**: 104875 [PMID: 33069753 DOI: 10.1016/j.yhbeh.2020.104875]

139   **Montagud-Romero S**, Reguilón MD, Pascual M, Blanco-Gandía MC, Guerri C, Miñarro J, Rodríguez-Arias M. Critical role of TLR4 in uncovering the increased rewarding effects of cocaine and ethanol induced by social defeat in male mice. *Neuropharmacology* 2021; **182**: 108368 [PMID: 33132187 DOI: 10.1016/j.neuropharm.2020.108368]

140   **Bock R**, Shin JH, Kaplan AR, Dobi A, Markey E, Kramer PF, Gremel CM, Christensen CH, Adrover MF, Alvarez VA. Strengthening the accumbal indirect pathway promotes resilience to compulsive cocaine use. *Nat Neurosci* 2013; **16**: 632-638 [PMID: 23542690 DOI: 10.1038/nn.3369]

141   **Brodnik ZD**, Black EM, Clark MJ, Kornsey KN, Snyder NW, España RA. Susceptibility to traumatic stress sensitizes the dopaminergic response to cocaine and increases motivation for cocaine. *Neuropharmacology* 2017; **125**: 295-307 [PMID: 28778834 DOI: 10.1016/j.neuropharm.2017.07.032]

142   **Lee JH**, Ribeiro EA, Kim J, Ko B, Kronman H, Jeong YH, Kim JK, Janak PH, Nestler EJ, Koo JW, Kim JH. Dopaminergic Regulation of Nucleus Accumbens Cholinergic Interneurons Demarcates Susceptibility to Cocaine Addiction. *Biol Psychiatry* 2020; **88**: 746-757 [PMID: 32622465 DOI: 10.1016/j.biopsych.2020.05.003]

143   **Ballestín R**, Alegre-Zurano L, Ferrer-Pérez C, Cantacorps L, Miñarro J, Valverde O, Rodríguez-Arias M. Neuroinflammatory and behavioral susceptibility profile of mice exposed to social stress towards cocaine effects. *Prog Neuropsychopharmacol Biol Psychiatry* 2021; **105**: 110123 [PMID: 33002518 DOI: 10.1016/j.pnpbp.2020.110123]

144   **Blouin AM**, Pisupati S, Hoffer CG, Hafenbreidel M, Jamieson SE, Rumbaugh G, Miller CA. Social stress-potentiated methamphetamine seeking. *Addict Biol* 2019; **24**: 958-968 [PMID: 30105771 DOI: 10.1111/adb.12666]

145   **Riga D**, Schmitz LJM, van Mourik Y, Hoogendijk WJG, De Vries TJ, Smit AB, Spijker S. Stress vulnerability promotes an alcohol-prone phenotype in a preclinical model of sustained depression. *Addict Biol* 2020; **25**: e12701 [PMID: 30561063 DOI: 10.1111/adb.12701]

146   **Barchiesi R**, Chanthongdee K, Domi E, Gobbo F, Coppola A, Asratian A, Toivainen S, Holm L, Augier G, Xu L, Augier E, Heilig M, Barbier E. Stress-induced escalation of alcohol self-administration, anxiety-like behavior, and elevated amygdala Avp expression in a susceptible subpopulation of rats. *Addict Biol* 2021; e13009 [PMID: 33565224 DOI: 10.1111/adb.13009]

147   **Ornelas LC**, Tyler RE, Irukulapati P, Paladugu S, Besheer J. Increased alcohol self-administration following exposure to the predator odor TMT in active coping female rats. *Behav Brain Res* 2021; **402**: 113068 [PMID: 33333108 DOI: 10.1016/j.bbr.2020.113068]

148   **Aguilar MA**, Rodríguez-Arias M, Miñarro J. Neurobiological mechanisms of the reinstatement of drug-conditioned place preference. *Brain Res Rev* 2009; **59**: 253-277 [PMID: 18762212 DOI: 10.1016/j.brainresrev.2008.08.002]

149   **Bardo MT**, Bevins RA. Conditioned place preference: what does it add to our preclinical understanding of drug reward? *Psychopharmacology (Berl)* 2000; **153**: 31-43 [PMID: 11255927 DOI: 10.1007/s002130000569]

150   **Tzschentke TM**. Measuring reward with the conditioned place preference paradigm: a comprehensive review of drug effects, recent progress and new issues. *Prog Neurobiol* 1998; **56**: 613-672 [PMID: 9871940 DOI: 10.1016/s0301-0082(98)00060-4]

151   **Tzschentke TM**. Measuring reward with the conditioned place preference (CPP) paradigm: update of the last decade. *Addict Biol* 2007; **12**: 227-462 [PMID: 17678505 DOI: 10.1111/j.1369-1600.2007.00070.x]

152   **García-Pardo MP**, Rodríguez-Arias M, Maldonado C, Manzanedo C, Miñarro J, Aguilar MA. Effects of acute social stress on the conditioned place preference induced by MDMA in adolescent and adult mice. *Behav Pharmacol* 2014; **25**: 532-546 [PMID: 25050816 DOI: 10.1097/FBP.0000000000000065]

153   **Titomanlio F**, Manzanedo C, Rodríguez-Arias M, Mattioli L, Perfumi M, Miñarro J, Aguilar MA. Rhodiola rosea Impairs Acquisition and Expression of Conditioned Place Preference Induced by Cocaine. *Evid Based Complement Alternat Med* 2013; **2013**: 697632 [PMID: 24174979 DOI: 10.1155/2013/697632]

154   **Calpe-López C**, Gasparyan A, Navarrete F, Manzanares J, Miñarro J, Aguilar MA. Cannabidiol prevents priming- and stress-induced reinstatement of the conditioned place preference induced by cocaine in mice. *J Psychopharmacol* 2021; **35**: 864-874 [PMID: 33427014 DOI:

10.1177/0269881120965952]

155 **Montagud-Romero S**, Aguilar MA, Maldonado C, Manzanedo C, Miñarro J, Rodríguez-Arias M. Acute social defeat stress increases the conditioned rewarding effects of cocaine in adult but not in adolescent mice. *Pharmacol Biochem Behav* 2015; **135**: 1-12 [PMID: 25989047 DOI: 10.1016/j.pbb.2015.05.008]

156 **Ueno M**, Yamada K, Ichitani Y. The relationship between fear extinction and resilience to drug-dependence in rats. *Neurosci Res* 2017; **121**: 37-42 [PMID: 28322983 DOI: 10.1016/j.neures.2017.03.006]

157 **García-Pardo MP**, LLansola M, Felipo V, De la Rubia Ortí JE, Aguilar MA. Blockade of nitric oxide signalling promotes resilience to the effects of social defeat stress on the conditioned rewarding properties of MDMA in mice. *Nitric Oxide* 2020; **98**: 29-32 [PMID: 32142901 DOI: 10.1016/j.niox.2020.03.001]

158 **Boivin JR**, Piscopo DM, Wilbrecht L. Brief cognitive training interventions in young adulthood promote long-term resilience to drug-seeking behavior. *Neuropharmacology* 2015; **97**: 404-413 [PMID: 26066577 DOI: 10.1016/j.neuropharm.2015.05.036]

159 **Yanovich C**, Kirby ML, Michaelevski I, Yadid G, Pinhasov A. Social rank-associated stress vulnerability predisposes individuals to cocaine attraction. *Sci Rep* 2018; **8**: 1759 [PMID: 29379100 DOI: 10.1038/s41598-018-19816-x]

160 **El Rawas R**, Amaral IM, Hofer A. Is p38 MAPK Associated to Drugs of Abuse-Induced Abnormal Behaviors? *Int J Mol Sci* 2020; **21** [PMID: 32650599 DOI: 10.3390/ijms21144833]

161 **Ferrer-Pérez C**, Reguilón MD, Miñarro J, Rodríguez-Arias M. Endogenous oxytocin is essential for the buffering effects of pair housing against the increase in cocaine reward induced by social stress. *Physiol Behav* 2020; **221**: 112913 [PMID: 32298668 DOI: 10.1016/j.physbeh.2020.112913]

162 **Ródenas-González F**, Blanco-Gandía MDC, Miñarro López J, Rodriguez-Arias M. Behavioral and neuroimmune characterization of resilience to social stress: rewarding effects of cocaine. *Adicciones* 2020; **0**: 1348 [PMID: 32100047 DOI: 10.20882/adicciones.1348]

163 **Sutton LP**, Khalatyan N, Savas JN, Martemyanov KA. Striatal RGS7 Regulates Depression-Related Behaviors and Stress-Induced Reinstatement of Cocaine Conditioned Place Preference. *eNeuro* 2021; **8** [PMID: 33402347 DOI: 10.1523/ENEURO.0365-20.2020]

164 **Steinman MQ**, Kirson D, Wolfe SA, Khom S, D'Ambrosio SR, Spierling Bagsic SR, Bajo M, Vlkolinský R, Hoang NK, Singhal A, Sureshchandra S, Oleata CS, Messaoudi I, Zorrilla EP, Roberto M. Importance of sex and trauma context on circulating cytokines and amygdalar GABAergic signaling in a comorbid model of posttraumatic stress and alcohol use disorders. *Mol Psychiatry* 2020 [PMID: 33087855 DOI: 10.1038/s41380-020-00920-2]

165 **Faye C**, Mcgowan JC, Denny CA, David DJ. Neurobiological Mechanisms of Stress Resilience and Implications for the Aged Population. *Curr Neuropharmacol* 2018; **16**: 234-270 [PMID: 28820053 DOI: 10.2174/1570159X15666170818095105]

166 **Christoffel DJ**, Golden SA, Russo SJ. Structural and synaptic plasticity in stress-related disorders. *Rev Neurosci* 2011; **22**: 535-549 [PMID: 21967517 DOI: 10.1515/RNS.2011.044]

167 **Lehmann ML**, Herkenham M. Environmental enrichment confers stress resiliency to social defeat through an infralimbic cortex-dependent neuroanatomical pathway. *J Neurosci* 2011; **31**: 6159-6173 [PMID: 21508240 DOI: 10.1523/JNEUROSCI.0577-11.2011]

168 **Covington HE 3rd**, Lobo MK, Maze I, Vialou V, Hyman JM, Zaman S, LaPlant Q, Mouzon E, Ghose S, Tamminga CA, Neve RL, Deisseroth K, Nestler EJ. Antidepressant effect of optogenetic stimulation of the medial prefrontal cortex. *J Neurosci* 2010; **30**: 16082-16090 [PMID: 21123555 DOI: 10.1523/JNEUROSCI.1731-10.2010]

169 **Vialou V**, Robison AJ, Laplant QC, Covington HE 3rd, Dietz DM, Ohnishi YN, Mouzon E, Rush AJ 3rd, Watts EL, Wallace DL, Iñiguez SD, Ohnishi YH, Steiner MA, Warren BL, Krishnan V, Bolaños CA, Neve RL, Ghose S, Berton O, Tamminga CA, Nestler EJ. DeltaFosB in brain reward circuits mediates resilience to stress and antidepressant responses. *Nat Neurosci* 2010; **13**: 745-752 [PMID: 20473292 DOI: 10.1038/nn.2551]

170 **Bagot RC**, Parise EM, Peña CJ, Zhang HX, Maze I, Chaudhury D, Persaud B, Cachope R, Bolaños-Guzmán CA, Cheer JF, Deisseroth K, Han MH, Nestler EJ. Ventral hippocampal afferents to the nucleus accumbens regulate susceptibility to depression. *Nat Commun* 2015; **6**: 7062 [PMID: 25952660 DOI: 10.1038/ncomms8062]

171 **Katz M**, Liu C, Schaer M, Parker KJ, Ottet MC, Epps A, Buckmaster CL, Bammer R, Moseley ME, Schatzberg AF, Eliez S, Lyons DM. Prefrontal plasticity and stress inoculation-induced resilience. *Dev Neurosci* 2009; **31**: 293-299 [PMID: 19546566 DOI: 10.1159/000216540]

172 **Kozorovitskiy Y**, Gross CG, Kopil C, Battaglia L, McBreen M, Stranahan AM, Gould E. Experience induces structural and biochemical changes in the adult primate brain. *Proc Natl Acad Sci U S A* 2005; **102**: 17478-17482 [PMID: 16299105 DOI: 10.1073/pnas.0508817102]

173 **Tse YC**, Lopez J, Moquin A, Wong SA, Maysinger D, Wong TP. The susceptibility to chronic social defeat stress is related to low hippocampal extrasynaptic NMDA receptor function. *Neuropsychopharmacology* 2019; **44**: 1310-1318 [PMID: 30723288 DOI: 10.1038/s41386-019-0325-8]

174 **Rincón-Cortés M**, Grace AA. Antidepressant effects of ketamine on depression-related phenotypes and dopamine dysfunction in rodent models of stress. *Behav Brain Res* 2020; **379**: 112367 [PMID: 31739001 DOI: 10.1016/j.bbr.2019.112367]

175 **Dong C**, Zhang JC, Ren Q, Ma M, Qu Y, Zhang K, Yao W, Ishima T, Mori H, Hashimoto K.

Deletion of serine racemase confers D-serine -dependent resilience to chronic social defeat stress. *Neurochem Int* 2018; **116**: 43-51 [PMID: 29550603 DOI: 10.1016/j.neuint.2018.03.008]

176   **Victoriano G**, Santos-Costa N, Mascarenhas DC, Nunes-de-Souza RL. Inhibition of the left medial prefrontal cortex (mPFC) prolongs the social defeat-induced anxiogenesis in mice: Attenuation by NMDA receptor blockade in the right mPFC. *Behav Brain Res* 2020; **378**: 112312 [PMID: 31629003 DOI: 10.1016/j.bbr.2019.112312]

177   **Schmidt MV**, Trümbach D, Weber P, Wagner K, Scharf SH, Liebl C, Datson N, Namendorf C, Gerlach T, Kühne C, Uhr M, Deussing JM, Wurst W, Binder EB, Holsboer F, Müller MB. Individual stress vulnerability is predicted by short-term memory and AMPA receptor subunit ratio in the hippocampus. *J Neurosci* 2010; **30**: 16949-16958 [PMID: 21159965 DOI: 10.1523/JNEUROSCI.4668-10.2010]

178   **Shin S**, Kwon O, Kang JI, Kwon S, Oh S, Choi J, Kim CH, Kim DG. mGluR5 in the nucleus accumbens is critical for promoting resilience to chronic stress. *Nat Neurosci* 2015; **18**: 1017-1024 [PMID: 26005851 DOI: 10.1038/nn.4028]

179   **Highland JN**, Zanos P, Georgiou P, Gould TD. Group II metabotropic glutamate receptor blockade promotes stress resilience in mice. *Neuropsychopharmacology* 2019; **44**: 1788-1796 [PMID: 30939596 DOI: 10.1038/s41386-019-0380-1]

180   **Challis C**, Boulden J, Veerakumar A, Espallergues J, Vassoler FM, Pierce RC, Beck SG, Berton O. Raphe GABAergic neurons mediate the acquisition of avoidance after social defeat. *J Neurosci* 2013; **33**: 13978-13988, 13988a [PMID: 23986235 DOI: 10.1523/JNEUROSCI.2383-13.2013]

181   **Heshmati M**, Christoffel DJ, LeClair K, Cathomas F, Golden SA, Aleyasin H, Turecki G, Friedman AK, Han MH, Menard C, Russo SJ. Depression and Social Defeat Stress Are Associated with Inhibitory Synaptic Changes in the Nucleus Accumbens. *J Neurosci* 2020; **40**: 6228-6233 [PMID: 32561672 DOI: 10.1523/JNEUROSCI.2568-19.2020]

182   **Li ZL**, Wang Y, Zou HW, Jing XY, Liu YJ, Li LF. GABA(B) receptors within the lateral habenula modulate stress resilience and vulnerability in mice. *Physiol Behav* 2021; **230**: 113311 [PMID: 33412189 DOI: 10.1016/j.physbeh.2021.113311]

183   **Liu GX**, Cai GQ, Cai YQ, Sheng ZJ, Jiang J, Mei Z, Wang ZG, Guo L, Fei J. Reduced anxiety and depression-like behaviors in mice lacking GABA transporter subtype 1. *Neuropsychopharmacology* 2007; **32**: 1531-1539 [PMID: 17164814 DOI: 10.1038/sj.npp.1301281]

184   **Gong X**, Shao Y, Li B, Chen L, Wang C, Chen Y. γ-aminobutyric acid transporter-1 is involved in anxiety-like behaviors and cognitive function in knockout mice. *Exp Ther Med* 2015; **10**: 653-658 [PMID: 26622370 DOI: 10.3892/etm.2015.2577]

185   **O'Leary OF**, Felice D, Galimberti S, Savignac HM, Bravo JA, Crowley T, El Yacoubi M, Vaugeois JM, Gassmann M, Bettler B, Dinan TG, Cryan JF. GABAB(1) receptor subunit isoforms differentially regulate stress resilience. *Proc Natl Acad Sci U S A* 2014; **111**: 15232-15237 [PMID: 25288769 DOI: 10.1073/pnas.1404090111]

186   **Cao JL**, Covington HE 3rd, Friedman AK, Wilkinson MB, Walsh JJ, Cooper DC, Nestler EJ, Han MH. Mesolimbic dopamine neurons in the brain reward circuit mediate susceptibility to social defeat and antidepressant action. *J Neurosci* 2010; **30**: 16453-16458 [PMID: 21147984 DOI: 10.1523/JNEUROSCI.3177-10.2010]

187   **Friedman AK**, Walsh JJ, Juarez B, Ku SM, Chaudhury D, Wang J, Li X, Dietz DM, Pan N, Vialou VF, Neve RL, Yue Z, Han MH. Enhancing depression mechanisms in midbrain dopamine neurons achieves homeostatic resilience. *Science* 2014; **344**: 313-319 [PMID: 24744379]

188   **Chaudhury D**, Walsh JJ, Friedman AK, Juarez B, Ku SM, Koo JW, Ferguson D, Tsai HC, Pomeranz L, Christoffel DJ, Nectow AR, Ekstrand M, Domingos A, Mazei-Robison MS, Mouzon E, Lobo MK, Neve RL, Friedman JM, Russo SJ, Deisseroth K, Nestler EJ, Han MH. Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. *Nature* 2013; **493**: 532-536 [PMID: 23235832 DOI: 10.1038/nature11713]

189   **Zhang J**, He ZX, Qu YS, Li LF, Wang LM, Yuan W, Hou WJ, Zhu YQ, Cai WQ, Zhang XN, Guo QQ, An SC, Jia R, Tai FD. Different baseline physical activity predicts susceptibility and resilience to chronic social defeat stress in mice: Involvement of dopamine neurons. *Eur Neuropsychopharmacol* 2021; **45**: 15-28 [PMID: 33730683 DOI: 10.1016/j.euroneuro.2021.02.011]

190   **Francis TC**, Chandra R, Friend DM, Finkel E, Dayrit G, Miranda J, Brooks JM, Iñiguez SD, O'Donnell P, Kravitz A, Lobo MK. Nucleus accumbens medium spiny neuron subtypes mediate depression-related outcomes to social defeat stress. *Biol Psychiatry* 2015; **77**: 212-222 [PMID: 25173629 DOI: 10.1016/j.biopsych.2014.07.021]

191   **Francis TC**, Gaynor A, Chandra R, Fox ME, Lobo MK. The Selective RhoA Inhibitor Rhosin Promotes Stress Resiliency Through Enhancing D1-Medium Spiny Neuron Plasticity and Reducing Hyperexcitability. *Biol Psychiatry* 2019; **85**: 1001-1010 [PMID: 30955841 DOI: 10.1016/j.biopsych.2019.02.007]

192   **Hamilton PJ**, Burek DJ, Lombroso SI, Neve RL, Robison AJ, Nestler EJ, Heller EA. Cell-Type-Specific Epigenetic Editing at the Fosb Gene Controls Susceptibility to Social Defeat Stress. *Neuropsychopharmacology* 2018; **43**: 272-284 [PMID: 28462942 DOI: 10.1038/npp.2017.88]

193   **Khibnik LA**, Beaumont M, Doyle M, Heshmati M, Slesinger PA, Nestler EJ, Russo SJ. Stress and Cocaine Trigger Divergent and Cell Type-Specific Regulation of Synaptic Transmission at Single Spines in Nucleus Accumbens. *Biol Psychiatry* 2016; **79**: 898-905 [PMID: 26164802 DOI: 10.1016/j.biopsych.2015.05.022]

194   **Muir J**, Lorsch ZS, Ramakrishnan C, Deisseroth K, Nestler EJ, Calipari ES, Bagot RC. In Vivo

Fiber Photometry Reveals Signature of Future Stress Susceptibility in Nucleus Accumbens. *Neuropsychopharmacology* 2018; **43**: 255-263 [PMID: 28589967 DOI: 10.1038/npp.2017.122]

195   **Shinohara R**, Taniguchi M, Ehrlich AT, Yokogawa K, Deguchi Y, Cherasse Y, Lazarus M, Urade Y, Ogawa A, Kitaoka S, Sawa A, Narumiya S, Furuyashiki T. Dopamine D1 receptor subtype mediates acute stress-induced dendritic growth in excitatory neurons of the medial prefrontal cortex and contributes to suppression of stress susceptibility in mice. *Mol Psychiatry* 2018; **23**: 1717-1730 [PMID: 28924188 DOI: 10.1038/mp.2017.177]

196   **Bagalkot TR**, Jin HM, Prabhu VV, Muna SS, Cui Y, Yadav BK, Chae HJ, Chung YC. Chronic social defeat stress increases dopamine D2 receptor dimerization in the prefrontal cortex of adult mice. *Neuroscience* 2015; **311**: 444-452 [PMID: 26484605 DOI: 10.1016/j.neuroscience.2015.10.024]

197   **Xu K**, He Y, Chen X, Tian Y, Cheng K, Zhang L, Wang Y, Yang D, Wang H, Wu Z, Li Y, Lan T, Dong Z, Xie P. Validation of the targeted metabolomic pathway in the hippocampus and comparative analysis with the prefrontal cortex of social defeat model mice. *J Neurochem* 2019; **149**: 799-810 [PMID: 30520040 DOI: 10.1111/jnc.14641]

198   **Ano Y**, Kitaoka S, Ohya R, Kondo K, Furuyashiki T. Hop Bitter Acids Increase Hippocampal Dopaminergic Activity in a Mouse Model of Social Defeat Stress. *Int J Mol Sci* 2020; **21** [PMID: 33348553 DOI: 10.3390/ijms21249612]

199   **Yin YQ**, Zhang C, Wang JX, Hou J, Yang X, Qin J. Chronic caffeine treatment enhances the resilience to social defeat stress in mice. *Food Funct* 2015; **6**: 479-491 [PMID: 25474697 DOI: 10.1039/c4fo00702f]

200   **Isingrini E**, Perret L, Rainer Q, Amilhon B, Guma E, Tanti A, Martin G, Robinson J, Moquin L, Marti F, Mechawar N, Williams S, Gratton A, Giros B. Resilience to chronic stress is mediated by noradrenergic regulation of dopamine neurons. *Nat Neurosci* 2016; **19**: 560-563 [PMID: 26878672 DOI: 10.1038/nn.4245]

201   **Zhang H**, Chaudhury D, Nectow AR, Friedman AK, Zhang S, Juarez B, Liu H, Pfau ML, Aleyasin H, Jiang C, Crumiller M, Calipari ES, Ku SM, Morel C, Tzavaras N, Montgomery SE, He M, Salton SR, Russo SJ, Nestler EJ, Friedman JM, Cao JL, Han MH. α_1- and β_3-Adrenergic Receptor-Mediated Mesolimbic Homeostatic Plasticity Confers Resilience to Social Stress in Susceptible Mice. *Biol Psychiatry* 2019; **85**: 226-236 [PMID: 30336931 DOI: 10.1016/j.biopsych.2018.08.020]

202   **Bruchas MR**, Schindler AG, Shankar H, Messinger DI, Miyatake M, Land BB, Lemos JC, Hagan CE, Neumaier JF, Quintana A, Palmiter RD, Chavkin C. Selective p38α MAPK deletion in serotonergic neurons produces stress resilience in models of depression and addiction. *Neuron* 2011; **71**: 498-511 [PMID: 21835346 DOI: 10.1016/j.neuron.2011.06.011]

203   **Xie L**, Chen J, Ding YM, Gui XW, Wu LX, Tian S, Wu W. MicroRNA-26a-2 maintains stress resiliency and antidepressant efficacy by targeting the serotonergic autoreceptor HTR1A. *Biochem Biophys Res Commun* 2019; **511**: 440-446 [PMID: 30808545 DOI: 10.1016/j.bbrc.2019.02.078]

204   **Prakash N**, Stark CJ, Keisler MN, Luo L, Der-Avakian A, Dulcis D. Serotonergic Plasticity in the Dorsal Raphe Nucleus Characterizes Susceptibility and Resilience to Anhedonia. *J Neurosci* 2020; **40**: 569-584 [PMID: 31792153 DOI: 10.1523/JNEUROSCI.1802-19.2019]

205   **Mineur YS**, Obayemi A, Wigestrand MB, Fote GM, Calarco CA, Li AM, Picciotto MR. Cholinergic signaling in the hippocampus regulates social stress resilience and anxiety- and depression-like behavior. *Proc Natl Acad Sci U S A* 2013; **110**: 3573-3578 [PMID: 23401542 DOI: 10.1073/pnas.1219731110]

206   **Mineur YS**, Fote GM, Blakeman S, Cahuzac EL, Newbold SA, Picciotto MR. Multiple Nicotinic Acetylcholine Receptor Subtypes in the Mouse Amygdala Regulate Affective Behaviors and Response to Social Stress. *Neuropsychopharmacology* 2016; **41**: 1579-1587 [PMID: 26471256 DOI: 10.1038/npp.2015.316]

207   **Rosa SG**, Pesarico AP, Nogueira CW. m-Trifluoromethyl-diphenyl diselenide promotes resilience to social avoidance induced by social defeat stress in mice: Contribution of opioid receptors and MAPKs. *Prog Neuropsychopharmacol Biol Psychiatry* 2018; **82**: 123-135 [PMID: 29174974 DOI: 10.1016/j.pnpbp.2017.11.021]

208   **Bérubé P**, Laforest S, Bhatnagar S, Drolet G. Enkephalin and dynorphin mRNA expression are associated with resilience or vulnerability to chronic social defeat stress. *Physiol Behav* 2013; **122**: 237-245 [PMID: 23665402 DOI: 10.1016/j.physbeh.2013.04.009]

209   **Browne CA**, Falcon E, Robinson SA, Berton O, Lucki I. Reversal of Stress-Induced Social Interaction Deficits by Buprenorphine. *Int J Neuropsychopharmacol* 2018; **21**: 164-174 [PMID: 29020387 DOI: 10.1093/ijnp/pyx079]

210   **Henry MS**, Bisht K, Vernoux N, Gendron L, Torres-Berrio A, Drolet G, Tremblay MÈ. Delta Opioid Receptor Signaling Promotes Resilience to Stress Under the Repeated Social Defeat Paradigm in Mice. *Front Mol Neurosci* 2018; **11**: 100 [PMID: 29681795 DOI: 10.3389/fnmol.2018.00100]

211   **Nam H**, Chandra R, Francis TC, Dias C, Cheer JF, Lobo MK. Reduced nucleus accumbens enkephalins underlie vulnerability to social defeat stress. *Neuropsychopharmacology* 2019; **44**: 1876-1885 [PMID: 31132785 DOI: 10.1038/s41386-019-0422-8]

212   **Briand LA**, Hilario M, Dow HC, Brodkin ES, Blendy JA, Berton O. Mouse model of OPRM1 (A118G) polymorphism increases sociability and dominance and confers resilience to social defeat. *J Neurosci* 2015; **35**: 3582-3590 [PMID: 25716856 DOI: 10.1523/JNEUROSCI.4685-14.2015]

213   **Wu G**, Feder A, Wegener G, Bailey C, Saxena S, Charney D, Mathé AA. Central functions of

neuropeptide Y in mood and anxiety disorders. *Expert Opin Ther Targets* 2011; **15**: 1317-1331 [PMID: 21995655 DOI: 10.1517/14728222.2011.628314]

214 **Schmeltzer SN**, Herman JP, Sah R. Neuropeptide Y (NPY) and posttraumatic stress disorder (PTSD): A translational update. *Exp Neurol* 2016; **284**: 196-210 [PMID: 27377319 DOI: 10.1016/j.expneurol.2016.06.020]

215 **He Y**, Li W, Tian Y, Chen X, Cheng K, Xu K, Li C, Wang H, Qu C, Wang C, Li P, Chen H, Xie P. iTRAQ-based proteomics suggests LRP6, NPY and NPY2R perturbation in the hippocampus involved in CSDS may induce resilience and susceptibility. *Life Sci* 2018; **211**: 102-117 [PMID: 30201296 DOI: 10.1016/j.lfs.2018.09.016]

216 **Lacey T**, Sweeting J, Kingston R, Smith M, Markham CM. Neuropeptide Y impairs the acquisition of conditioned defeat in Syrian hamsters. *Neurosci Lett* 2019; **690**: 214-218 [PMID: 30312751 DOI: 10.1016/j.neulet.2018.09.049]

217 **Alviña K**, Jodeiri Farshbaf M, Mondal AK. Long term effects of stress on hippocampal function: Emphasis on early life stress paradigms and potential involvement of neuropeptide Y. *J Neurosci Res* 2021; **99**: 57-66 [PMID: 32162350 DOI: 10.1002/jnr.24614]

218 **Kagerer SM**, Jöhren O. Interactions of orexins/hypocretins with adrenocortical functions. *Acta Physiol (Oxf)* 2010; **198**: 361-371 [PMID: 19719797 DOI: 10.1111/j.1748-1716.2009.02034.x]

219 **Srinivasan S**, Shariff M, Bartlett SE. The role of the glucocorticoids in developing resilience to stress and addiction. *Front Psychiatry* 2013; **4**: 68 [PMID: 23914175 DOI: 10.3389/fpsyt.2013.00068]

220 **Chung HS**, Kim JG, Kim JW, Kim HW, Yoon BJ. Orexin administration to mice that underwent chronic stress produces bimodal effects on emotion-related behaviors. *Regul Pept* 2014; **194-195**: 16-22 [PMID: 25450574 DOI: 10.1016/j.regpep.2014.11.003]

221 **Arendt DH**, Hassell J, Li H, Achua JK, Guarnieri DJ, Dileone RJ, Ronan PJ, Summers CH. Anxiolytic function of the orexin 2/hypocretin A receptor in the basolateral amygdala. *Psychoneuroendocrinology* 2014; **40**: 17-26 [PMID: 24485472 DOI: 10.1016/j.psyneuen.2013.10.010]

222 **Grafe LA**, Eacret D, Dobkin J, Bhatnagar S. Reduced Orexin System Function Contributes to Resilience to Repeated Social Stress. *eNeuro* 2018; **5** [PMID: 29662948 DOI: 10.1523/ENEURO.0273-17.2018]

223 **Staton CD**, Yaeger JDW, Khalid D, Haroun F, Fernandez BS, Fernandez JS, Summers BK, Summers TR, Sathyanesan M, Newton SS, Summers CH. Orexin 2 receptor stimulation enhances resilience, while orexin 2 inhibition promotes susceptibility, to social stress, anxiety and depression. *Neuropharmacology* 2018; **143**: 79-94 [PMID: 30240784 DOI: 10.1016/j.neuropharm.2018.09.016]

224 **Summers CH**, Yaeger JDW, Staton CD, Arendt DH, Summers TR. Orexin/hypocretin receptor modulation of anxiolytic and antidepressive responses during social stress and decision-making: Potential for therapy. *Brain Res* 2020; **1731**: 146085 [PMID: 30590027 DOI: 10.1016/j.brainres.2018.12.036]

225 **Pesarico AP**, Rosa SG, Martini F, Goulart TA, Zeni G, Nogueira CW. Brain-derived neurotrophic factor signaling plays a role in resilience to stress promoted by isoquinoline in defeated mice. *J Psychiatr Res* 2017; **94**: 78-87 [PMID: 28688339 DOI: 10.1016/j.jpsychires.2017.06.012]

226 **Iñiguez SD**, Vialou V, Warren BL, Cao JL, Alcantara LF, Davis LC, Manojlovic Z, Neve RL, Russo SJ, Han MH, Nestler EJ, Bolaños-Guzmán CA. Extracellular signal-regulated kinase-2 within the ventral tegmental area regulates responses to stress. *J Neurosci* 2010; **30**: 7652-7663 [PMID: 20519540 DOI: 10.1523/JNEUROSCI.0951-10.2010]

227 **Castrén E**, Rantamäki T. The role of BDNF and its receptors in depression and antidepressant drug action: Reactivation of developmental plasticity. *Dev Neurobiol* 2010; **70**: 289-297 [PMID: 20186711 DOI: 10.1002/dneu.20758]

228 **Li Y**, Luikart BW, Birnbaum S, Chen J, Kwon CH, Kernie SG, Bassel-Duby R, Parada LF. TrkB regulates hippocampal neurogenesis and governs sensitivity to antidepressive treatment. *Neuron* 2008; **59**: 399-412 [PMID: 18701066 DOI: 10.1016/j.neuron.2008.06.023]

229 **Autry AE**, Monteggia LM. Brain-derived neurotrophic factor and neuropsychiatric disorders. *Pharmacol Rev* 2012; **64**: 238-258 [PMID: 22407616 DOI: 10.1124/pr.111.005108]

230 **Pagliusi MOF Jr**, Bonet IJM, Dias EV, Vieira AS, Tambeli CH, Parada CA, Sartori CR. Social defeat stress induces hyperalgesia and increases truncated BDNF isoforms in the nucleus accumbens regardless of the depressive-like behavior induction in mice. *Eur J Neurosci* 2018 [PMID: 29885271 DOI: 10.1111/ejn.13994]

231 **Mallei A**, Ieraci A, Popoli M. Chronic social defeat stress differentially regulates the expression of *BDNF* transcripts and epigenetic modifying enzymes in susceptible and resilient mice. *World J Biol Psychiatry* 2019; **20**: 555-566 [PMID: 30058429 DOI: 10.1080/15622975.2018.1500029]

232 **Yao W**, Lin S, Su J, Cao Q, Chen Y, Chen J, Zhang Z, Hashimoto K, Qi Q, Zhang JC. Activation of BDNF by transcription factor Nrf2 contributes to antidepressant-like actions in rodents. *Transl Psychiatry* 2021; **11**: 140 [PMID: 33627628 DOI: 10.1038/s41398-021-01261-6]

233 **Taliaz D**, Loya A, Gersner R, Haramati S, Chen A, Zangen A. Resilience to chronic stress is mediated by hippocampal brain-derived neurotrophic factor. *J Neurosci* 2011; **31**: 4475-4483 [PMID: 21430148 DOI: 10.1523/JNEUROSCI.5725-10.2011]

234 **Nasrallah P**, Haidar EA, Stephan JS, El Hayek L, Karnib N, Khalifeh M, Barmo N, Jabre V, Houbeika R, Ghanem A, Nasser J, Zeeni N, Bassil M, Sleiman SF. Branched-chain amino acids mediate resilience to chronic social defeat stress by activating BDNF/TRKB signaling. *Neurobiol*

Stress 2019; **11**: 100170 [PMID: 31193350 DOI: 10.1016/j.ynstr.2019.100170]

235 **Lagace DC**, Donovan MH, DeCarolis NA, Farnbauch LA, Malhotra S, Berton O, Nestler EJ, Krishnan V, Eisch AJ. Adult hippocampal neurogenesis is functionally important for stress-induced social avoidance. *Proc Natl Acad Sci U S A* 2010; **107**: 4436-4441 [PMID: 20176946 DOI: 10.1073/pnas.0910072107]

236 **Duclot F**, Kabbaj M. Individual differences in novelty seeking predict subsequent vulnerability to social defeat through a differential epigenetic regulation of brain-derived neurotrophic factor expression. *J Neurosci* 2013; **33**: 11048-11060 [PMID: 23825410 DOI: 10.1523/JNEUROSCI.0199-13.2013]

237 **Khalifeh M**, Hobeika R, El Hayek L, Saad J, Eid F, El-Khoury R, Ghayad LM, Jabre V, Nasrallah P, Barmo N, Stephan JS, Khnayzer R, Khalil C, Sleiman SF. Nicotine induces resilience to chronic social defeat stress in a mouse model of water pipe tobacco exposure by activating BDNF signaling. *Behav Brain Res* 2020; **382**: 112499 [PMID: 31978493 DOI: 10.1016/j.bbr.2020.112499]

238 **Han QQ**, Yang L, Huang HJ, Wang YL, Yu R, Wang J, Pilot A, Wu GC, Liu Q, Yu J. Differential GR Expression and Translocation in the Hippocampus Mediates Susceptibility vs. Resilience to Chronic Social Defeat Stress. *Front Neurosci* 2017; **11**: 287 [PMID: 28588443 DOI: 10.3389/fnins.2017.00287]

239 **Wang W**, Liu L, Yang X, Gao H, Tang QK, Yin LY, Yin XY, Hao JR, Geng DQ, Gao C. Ketamine improved depressive-like behaviors *via* hippocampal glucocorticoid receptor in chronic stress induced- susceptible mice. *Behav Brain Res* 2019; **364**: 75-84 [PMID: 30753876 DOI: 10.1016/j.bbr.2019.01.057]

240 **Dedic N**, Kühne C, Gomes KS, Hartmann J, Ressler KJ, Schmidt MV, Deussing JM. Deletion of CRH From GABAergic Forebrain Neurons Promotes Stress Resilience and Dampens Stress-Induced Changes in Neuronal Activity. *Front Neurosci* 2019; **13**: 986 [PMID: 31619956 DOI: 10.3389/fnins.2019.00986]

241 **Chen P**, Lou S, Huang ZH, Wang Z, Shan QH, Wang Y, Yang Y, Li X, Gong H, Jin Y, Zhang Z, Zhou JN. Prefrontal Cortex Corticotropin-Releasing Factor Neurons Control Behavioral Style Selection under Challenging Situations. *Neuron* 2020; **106**: 301-315.e7 [PMID: 32101698 DOI: 10.1016/j.neuron.2020.01.033]

242 **Nestler EJ**, Waxman SG. Resilience to Stress and Resilience to Pain: Lessons from Molecular Neurobiology and Genetics. *Trends Mol Med* 2020; **26**: 924-935 [PMID: 32976800 DOI: 10.1016/j.molmed.2020.03.007]

243 **Dudek KA**, Kaufmann FN, Lavoie O, Menard C. Central and peripheral stress-induced epigenetic mechanisms of resilience. *Curr Opin Psychiatry* 2021; **34**: 1-9 [PMID: 33141775 DOI: 10.1097/YCO.0000000000000664]

244 **Wilkinson MB**, Xiao G, Kumar A, LaPlant Q, Renthal W, Sikder D, Kodadek TJ, Nestler EJ. Imipramine treatment and resiliency exhibit similar chromatin regulation in the mouse nucleus accumbens in depression models. *J Neurosci* 2009; **29**: 7820-7832 [PMID: 19535594 DOI: 10.1523/JNEUROSCI.0932-09.2009]

245 **Kenworthy CA**, Sengupta A, Luz SM, Ver Hoeve ES, Meda K, Bhatnagar S, Abel T. Social defeat induces changes in histone acetylation and expression of histone modifying enzymes in the ventral hippocampus, prefrontal cortex, and dorsal raphe nucleus. *Neuroscience* 2014; **264**: 88-98 [PMID: 23370319 DOI: 10.1016/j.neuroscience.2013.01.024]

246 **Covington HE 3rd**, Maze I, Sun H, Bomze HM, DeMaio KD, Wu EY, Dietz DM, Lobo MK, Ghose S, Mouzon E, Neve RL, Tamminga CA, Nestler EJ. A role for repressive histone methylation in cocaine-induced vulnerability to stress. *Neuron* 2011; **71**: 656-670 [PMID: 21867882 DOI: 10.1016/j.neuron.2011.06.007]

247 **Espallergues J**, Teegarden SL, Veerakumar A, Boulden J, Challis C, Jochems J, Chan M, Petersen T, Deneris E, Matthias P, Hahn CG, Lucki I, Beck SG, Berton O. HDAC6 regulates glucocorticoid receptor signaling in serotonin pathways with critical impact on stress resilience. *J Neurosci* 2012; **32**: 4400-4416 [PMID: 22457490 DOI: 10.1523/JNEUROSCI.5634-11.2012]

248 **Jochems J**, Teegarden SL, Chen Y, Boulden J, Challis C, Ben-Dor GA, Kim SF, Berton O. Enhancement of stress resilience through histone deacetylase 6-mediated regulation of glucocorticoid receptor chaperone dynamics. *Biol Psychiatry* 2015; **77**: 345-355 [PMID: 25442004 DOI: 10.1016/j.biopsych.2014.07.036]

249 **Ambrée O**, Ruland C, Scheu S, Arolt V, Alferink J. Alterations of the Innate Immune System in Susceptibility and Resilience After Social Defeat Stress. *Front Behav Neurosci* 2018; **12**: 141 [PMID: 30057531 DOI: 10.3389/fnbeh.2018.00141]

250 **Hodes GE**, Pfau ML, Leboeuf M, Golden SA, Christoffel DJ, Bregman D, Rebusi N, Heshmati M, Aleyasin H, Warren BL, Lebonté B, Horn S, Lapidus KA, Stelzhammer V, Wong EH, Bahn S, Krishnan V, Bolaños-Guzman CA, Murrough JW, Merad M, Russo SJ. Individual differences in the peripheral immune system promote resilience *vs* susceptibility to social stress. *Proc Natl Acad Sci U S A* 2014; **111**: 16136-16141 [PMID: 25331895 DOI: 10.1073/pnas.1415191111]

251 **Finnell JE**, Lombard CM, Melson MN, Singh NP, Nagarkatti M, Nagarkatti P, Fadel JR, Wood CS, Wood SK. The protective effects of resveratrol on social stress-induced cytokine release and depressive-like behavior. *Brain Behav Immun* 2017; **59**: 147-157 [PMID: 27592314 DOI: 10.1016/j.bbi.2016.08.019]

252 **Nasca C**, Menard C, Hodes G, Bigio B, Pena C, Lorsch Z, Zelli D, Ferris A, Kana V, Purushothaman I, Dobbin J, Nassim M, DeAngelis P, Merad M, Rasgon N, Meaney M, Nestler EJ, McEwen BS, Russo SJ. Multidimensional Predictors of Susceptibility and Resilience to Social

Defeat Stress. *Biol Psychiatry* 2019; **86**: 483-491 [PMID: 31466563 DOI: 10.1016/j.biopsych.2019.06.030]

253   **Pearson-Leary J**, Zhao C, Bittinger K, Eacret D, Luz S, Vigderman AS, Dayanim G, Bhatnagar S. The gut microbiome regulates the increases in depressive-type behaviors and in inflammatory processes in the ventral hippocampus of stress vulnerable rats. *Mol Psychiatry* 2020; **25**: 1068-1079 [PMID: 30833676 DOI: 10.1038/s41380-019-0380-x]

254   **Pfau ML**, Menard C, Cathomas F, Desland F, Kana V, Chan KL, Shimo Y, LeClair K, Flanigan ME, Aleyasin H, Walker DM, Bouchard S, Mack M, Hodes GE, Merad MM, Russo SJ. Role of Monocyte-Derived MicroRNA106b   25 in Resilience to Social Stress. *Biol Psychiatry* 2019; **86**: 474-482 [PMID: 31101319 DOI: 10.1016/j.biopsych.2019.02.023]

255   **Szyszkowicz JK**, Wong A, Anisman H, Merali Z, Audet MC. Implications of the gut microbiota in vulnerability to the social avoidance effects of chronic social defeat in male mice. *Brain Behav Immun* 2017; **66**: 45-55 [PMID: 28629758 DOI: 10.1016/j.bbi.2017.06.009]

256   **Aguilar MA**, Cannella N, Ferragud A, Spanagel R. Editorial: Neurobehavioural Mechanisms of Resilience and Vulnerability in Addictive Disorders. *Front Behav Neurosci* 2020; **14**: 644495 [PMID: 33551770 DOI: 10.3389/fnbeh.2020.644495]

257   **Manvich DF**, Stowe TA, Godfrey JR, Weinshenker D. A Method for Psychosocial Stress-Induced Reinstatement of Cocaine Seeking in Rats. *Biol Psychiatry* 2016; **79**: 940-946 [PMID: 26257242 DOI: 10.1016/j.biopsych.2015.07.002]

258   **Ellis AS**, Fosnocht AQ, Lucerne KE, Briand LA. Disruption of GluA2 phosphorylation potentiates stress responsivity. *Behav Brain Res* 2017; **333**: 83-89 [PMID: 28668281 DOI: 10.1016/j.bbr.2017.06.046]

259   **Guerrero-Bautista R**, Do Couto BR, Hidalgo JM, Cárceles-Moreno FJ, Molina G, Laorden ML, Núñez C, Milanés MV. Modulation of stress- and cocaine prime-induced reinstatement of conditioned place preference after memory extinction through dopamine D3 receptor. *Prog Neuropsychopharmacol Biol Psychiatry* 2019; **92**: 308-320 [PMID: 30707990 DOI: 10.1016/j.pnpbp.2019.01.017]

260   **Fallon IP**, Tanner MK, Greenwood BN, Baratta MV. Sex differences in resilience: Experiential factors and their mechanisms. *Eur J Neurosci* 2020; **52**: 2530-2547 [PMID: 31800125 DOI: 10.1111/ejn.14639]

261   **Hodes GE**, Epperson CN. Sex Differences in Vulnerability and Resilience to Stress Across the Life Span. *Biol Psychiatry* 2019; **86**: 421-432 [PMID: 31221426 DOI: 10.1016/j.biopsych.2019.04.028]

262   **Conrad CD**, Grote KA, Hobbs RJ, Ferayorni A. Sex differences in spatial and non-spatial Y-maze performance after chronic stress. *Neurobiol Learn Mem* 2003; **79**: 32-40 [PMID: 12482677 DOI: 10.1016/s1074-7427(02)00018-7]

263   **Galea LA**, McEwen BS, Tanapat P, Deak T, Spencer RL, Dhabhar FS. Sex differences in dendritic atrophy of CA3 pyramidal neurons in response to chronic restraint stress. *Neuroscience* 1997; **81**: 689-697 [PMID: 9316021 DOI: 10.1016/s0306-4522(97)00233-9]

264   **Bowman RE**, Beck KD, Luine VN. Chronic stress effects on memory: sex differences in performance and monoaminergic activity. *Horm Behav* 2003; **43**: 48-59 [PMID: 12614634 DOI: 10.1016/s0018-506x(02)00022-3]

265   **Wood GE**, Shors TJ. Stress facilitates classical conditioning in males, but impairs classical conditioning in females through activational effects of ovarian hormones. *Proc Natl Acad Sci U S A* 1998; **95**: 4066-4071 [PMID: 9520494 DOI: 10.1073/pnas.95.7.4066]

266   **Wood GE**, Beylin AV, Shors TJ. The contribution of adrenal and reproductive hormones to the opposing effects of stress on trace conditioning in males *vs* females. *Behav Neurosci* 2001; **115**: 175-187 [PMID: 11256441 DOI: 10.1037/0735-7044.115.1.175]

267   **Wellman CL**, Bangasser DA, Bollinger JL, Coutellier L, Logrip ML, Moench KM, Urban KR. Sex Differences in Risk and Resilience: Stress Effects on the Neural Substrates of Emotion and Motivation. *J Neurosci* 2018; **38**: 9423-9432 [PMID: 30381434 DOI: 10.1523/JNEUROSCI.1673-18.2018]

268   **Okine T**, Shepard R, Lemanski E, Coutellier L. Sex Differences in the Sustained Effects of Ketamine on Resilience to Chronic Stress. *Front Behav Neurosci* 2020; **14**: 581360 [PMID: 33192367 DOI: 10.3389/fnbeh.2020.581360]

269   **Vassilev P**, Pantoja-Urban AH, Giroux M, Nouel D, Hernandez G, Orsini T, Flores C. Unique effects of social defeat stress in adolescent male mice on the Netrin-1/DCC pathway, prefrontal cortex dopamine and cognition (Social stress in adolescent vs. adult male mice). *eNeuro* 2021 [PMID: 33619036 DOI: 10.1523/ENEURO.0045-21.2021]

270   **Bath KG**, Russo SJ, Pleil KE, Wohleb ES, Duman RS, Radley JJ. Circuit and synaptic mechanisms of repeated stress: Perspectives from differing contexts, duration, and development. *Neurobiol Stress* 2017; **7**: 137-151 [PMID: 29276735 DOI: 10.1016/j.ynstr.2017.05.001]

271   **Douglas AJ**, Brunton PJ, Bosch OJ, Russell JA, Neumann ID. Neuroendocrine responses to stress in mice: hyporesponsiveness in pregnancy and parturition. *Endocrinology* 2003; **144**: 5268-5276 [PMID: 12960085 DOI: 10.1210/en.2003-0461]

272   **Bitencourt RM**, Takahashi RN. Cannabidiol as a Therapeutic Alternative for Post-traumatic Stress Disorder: From Bench Research to Confirmation in Human Trials. *Front Neurosci* 2018; **12**: 502 [PMID: 30087591 DOI: 10.3389/fnins.2018.00502]

273   **Calpe-López C**, García-Pardo MP, Aguilar MA. Cannabidiol Treatment Might Promote Resilience to Cocaine and Methamphetamine Use Disorders: A Review of Possible Mechanisms. *Molecules*

2019; **24** [PMID: 31315244 DOI: 10.3390/molecules24142583]

274   **Ledesma JC**, Manzanedo C, Aguilar MA. Cannabidiol prevents several of the behavioral alterations related to cocaine addiction in mice. *Prog Neuropsychopharmacol Biol Psychiatry* 2021; **111**: 110390 [PMID: 34157334 DOI: 10.1016/j.pnpbp.2021.110390]

275   **Nona CN**, Hendershot CS, Le Foll B. Effects of cannabidiol on alcohol-related outcomes: A review of preclinical and human research. *Exp Clin Psychopharmacol* 2019; **27**: 359-369 [PMID: 31120285 DOI: 10.1037/pha0000272]

276   **Kumar A**, Chanana P. Role of Nitric Oxide in Stress-Induced Anxiety: From Pathophysiology to Therapeutic Target. *Vitam Horm* 2017; **103**: 147-167 [PMID: 28061969 DOI: 10.1016/bs.vh.2016.09.004]

277   **Liddie S**, Balda MA, Itzhak Y. Nitric oxide (NO) signaling as a potential therapeutic modality against psychostimulants. *Curr Pharm Des* 2013; **19**: 7092-7102 [PMID: 23574445 DOI: 10.2174/13816128194013209144527]

278   **Boutrel B**, Kenny PJ, Specio SE, Martin-Fardon R, Markou A, Koob GF, de Lecea L. Role for hypocretin in mediating stress-induced reinstatement of cocaine-seeking behavior. *Proc Natl Acad Sci U S A* 2005; **102**: 19168-19173 [PMID: 16357203 DOI: 10.1073/pnas.0507480102]

279   **Yoshida K**, Drew MR, Kono A, Mimura M, Takata N, Tanaka KF. Chronic social defeat stress impairs goal-directed behavior through dysregulation of ventral hippocampal activity in male mice. *Neuropsychopharmacology* 2021; **46**: 1606-1616 [PMID: 33692477 DOI: 10.1038/s41386-021-00990-y]

280   **Atesyakar N**, Canbeyli R, Unal G. Low cognitive competence as a vulnerability factor for behavioral despair in rats. *Behav Processes* 2020; **174**: 104103 [PMID: 32165180 DOI: 10.1016/j.beproc.2020.104103]

281   **Averill LA**, Averill CL, Kelmendi B, Abdallah CG, Southwick SM. Stress Response Modulation Underlying the Psychobiology of Resilience. *Curr Psychiatry Rep* 2018; **20**: 27 [PMID: 29594808 DOI: 10.1007/s11920-018-0887-x]

282   **Baratta MV**, Maier SF. New tools for understanding coping and resilience. *Neurosci Lett* 2019; **693**: 54-57 [PMID: 28963058 DOI: 10.1016/j.neulet.2017.09.049]

283   **Ersche KD**, Meng C, Ziauddeen H, Stochl J, Williams GB, Bullmore ET, Robbins TW. Brain networks underlying vulnerability and resilience to drug addiction. *Proc Natl Acad Sci U S A* 2020; **117**: 15253-15261 [PMID: 32541059 DOI: 10.1073/pnas.2002509117]

284   **Osório C**, Probert T, Jones E, Young AH, Robbins I. Adapting to Stress: Understanding the Neurobiology of Resilience. *Behav Med* 2017; **43**: 307-322 [PMID: 27100966 DOI: 10.1080/08964289.2016.1170661]

285   **Albrecht A**, Redavide E, Regev-Tsur S, Stork O, Richter-Levin G. Hippocampal GABAergic interneurons and their co-localized neuropeptides in stress vulnerability and resilience. *Neurosci Biobehav Rev* 2021; **122**: 229-244 [PMID: 33188820 DOI: 10.1016/j.neubiorev.2020.11.002]

286   **Stainton A**, Chisholm K, Kaiser N, Rosen M, Upthegrove R, Ruhrmann S, Wood SJ. Resilience as a multimodal dynamic process. *Early Interv Psychiatry* 2019; **13**: 725-732 [PMID: 30126047 DOI: 10.1111/eip.12726]

287   **García-Pardo MP**, Miñarro J, Llansola M, Felipo V, Aguilar MA. Role of NMDA and AMPA glutamatergic receptors in the effects of social defeat on the rewarding properties of MDMA in mice. *Eur J Neurosci* 2019; **50**: 2623-2634 [PMID: 30276890 DOI: 10.1111/ejn.14190]

REVIEW

Depression among caregivers of patients with dementia: Associative factors and management approaches

Si-Sheng Huang

ORCID number: Si-Sheng Huang
0000-0001-7333-3525.

Si-Sheng Huang, Division of Geriatric Psychiatry, Department of Psychiatry, Changhua
Christian Hospital, Changhua 500, Taiwan

Corresponding author: Si-Sheng Huang, MD, Attending Doctor, Director, Division of Geriatric
Psychiatry, Department of Psychiatry, Changhua Christian Hospital, No. 135, Nanhsiao Street,
Changhua 500, Taiwan. 97278@cch.org.tw

Abstract

As elderly people increasingly come to represent a higher proportion of the
world's population, various forms of dementia are becoming a significant chronic
disease burden. The World Health Organization emphasizes dementia care as a
public health priority and calls for more support for family caregivers who
commonly play a significant, central role in dementia care. Taking care of
someone with dementia is a long-term responsibility that can be stressful and may
lead to depression among family caregivers. Depression and related behavioral
and cognitive changes among caregivers could in turn affect the status and
prognosis of the dementia patient. This review article explores depression in
dementia caregivers and summarizes proposed mechanisms, associated factors,
management and research findings, and proposes future research directions.

Key Words: Dementia; Depression; Caregiver; Caregiver burden; Activities of daily living;
Functional status

Core Tip: The prevalence of depression among caregivers of patients with dementia is
higher than that of the general population. The cause of depression in caregivers is
complicated and thought to be related to the patients, caregivers and cultural
backgrounds. Multifaceted treatment for depression is regarded as the current
mainstream clinical intervention. In some areas, supplementation with smart
technology for interventions to alleviate the burden and depression of caregivers could
be considered. There are also some ideas and directions for future research included in
the conclusion section of this review.

Citation: Huang SS. Depression among caregivers of patients with dementia: Associative factors

INTRODUCTION

Depression is a common and serious health condition that is different from usual mood fluctuations and short-lived emotional responses to challenges in everyday life. It can cause the affected person to suffer greatly and function poorly at work, at school and within the family. According to the World Health Organization, over 264 million people globally suffer from major depressive disorder, which is one of the leading causes of disability worldwide[1]. The prevalence of depression among dementia caregivers is even higher than that of the general population[2]. Because patients with dementia suffer from impairment in cognitive functioning and activities of daily living (bathing, eating, *etc.*), the caregiver's quality of care to his or her patient or family member is central, and the caregiver is usually with the patient for several hours per day (or resides in the same house). Many studies have shown that the behavioral and psychological symptoms of dementia (BPSD) mutually affect the caregiver's skills and are also reflexively influenced by the caregiver, so the caregiver's own physical and mental health is extremely important. The topics of depression and the burden of caregivers of dementia patients are popular in clinical research. One of the significant reasons is that interventions for caregiver burden and depression are still a great challenge and an unmet need in clinical practice.

Depression can cause a variety of psychological and physical problems and raise the risk of caregiver suicide[2]. It compromises caregivers' physical health[3], reduces caregivers' quality of life[4], and has been shown to cause caregivers to place patients with dementia in an institutional care facility more rapidly[5,6]. Depression in caregivers can also influence dementia patients' cognitive status and has been associated with more rapid cognitive decline in the dementia patients studied[7].

Caregiver depression is producing a growing impact on existing medical care and insurance systems. Guterman *et al*[8] suggest that caregiver depression shows a significant association with increased emergency department use. They report that medical systems should specifically address patient- and caregiver-centered dementia care and suggest that improved health outcomes and lower costs for this high-risk population could be achieved.

Many studies have investigated the factors associated with dementia caregiver depression and explored various interventions to address it. The work presented in this review falls into several categories, including prevalence, mechanism, associated factors, management, and research trends of depression in caregivers of patients with dementia.

DEFINITION FOR BURDEN AND DEPRESSION IN CAREGIVERS

The author defined a family caregiver as an adult who directly provides observation, encouragement, assistance, or care that substitutes for a patient's efforts related to the activities of elderly patients with dementia. Such activities may include assisting the dementia patient to complete housework cleaning or maintenance, managing economic affairs, facilitating and supervising activities outside the home, and the broad supervision and management of safety, legal, and medically related matters.

Caregiver burden
The author can summarize 4 characteristics on the formation and the source of caregiver burden: (1) Direct care work, assistance in daily activities for patients and implementation of medical care; (2) The gap between the caregiver's expectations and the reality; (3) Breaking the personal routine of the caregiver; and (4) The feelings of taking on the responsibility of the caregiving role.

The caregiver burden has subjective and objective dimensions. The subjective burden refers to the stress and anxiety that the caregiver feels about his or her own situation and the feeling of being manipulated by the care recipient. Objective distress refers to the interference and change of the caregiver's life habits and household caused by care work[9]. In addition to the above concepts, in clinical outpatient

services, caregivers often ask for help and have distress due to the BPSD[10,11].

Caregiver depression

Depression (melancholia) is an emotional response to chronic frustration and disappointment. In psychopathology, it is an affective and emotional disorder[12]. The etiologies for melancholia can be divided into reactive or endogenous types. In general, the mildest form of depressive mood is difficult to distinguish from the experience of disappointment and loss. It is a common, recurrent, and impairing condi -tion that can lead to future suicide attempts, interpersonal problems, unemployment, and psychosocial dysfunctions.

Approximately 80% of dementia patients are being cared for by their families in the community. It was found that patients spent an average of 6.5 years being cared for at home before they were sent to a nursing institution[13]. It takes an average of 4 to 8 h a day to care for elderly individuals with dementia. Fuh *et al*[14] reported that 56.6% of dementia caregivers care for patients for more than 8 h a day. In the early stage of dementia, family members assist patients with higher and more complex daily life functions, such as assistance in dealing with money or with medication problems. However, as the patient's disease progresses, part of the caregiver's care gradually changes to assisting with self-care, such as bathing, dressing, and eating. The safety of the patient becomes the focus, and the problem of urine or stool incontinence gradually develops. At the same time, the caregiver must also deal with the patient's behavioral disturbances. In the process of caring, caregivers have to face the gradual disappearance and changes of the personality of his or her loved one, and witness the process of degeneration, suffering, distress and facing death. In addition to the direct distress of caring for patients, caregivers also deal with family conflicts, financial problems, and employment problems and adapt themselves to the role of caregiving. Furthermore, family caregivers also play a role in the medical care process of patients, including providing the patient's illness history, describing symptoms, and assisting in medical care[13].

EPIDEMIOLOGY OF CAREGIVER DEPRESSION

Many studies have investigated the quality of life of dementia caregivers and found that they experienced high levels of grief, ambivalence, and other psychological ailments[15]. Major depressive symptomatology was most common, reported by more than 50% of caregivers[16,17]. A meta-analysis study revealed that depression occurs in at least 1 in 3 caregivers of persons with dementia[18,19]. Some previous studies have also reported high rates of caregiver depression, approximately 30%–83%[20].

CLINICAL MECHANISMS OF DEPRESSION IN CAREGIVERS OF DEMEN-TIA PATIENTS

High prevalence rates of caregiver depression may be explained by several factors. Many mechanisms and models have been developed and tested, and the evolution in understanding depression in those who provide care to family members with dementia is introduced in this section.

Stress process model

The stress process model[21] proposes that caregiver demographics (such as age, sex, employment status, and relationship to the patient) are associated with and actively affect each part of the stress process and types of stress, including subjective stressors, objective stressors, the perception of those stressors, and outcomes such as caregiver burden and depression.

The stress process model assumes that various factors influence stress and coping reactions. Some factors are naturally protective bodily resources that decrease the negative effects of stress. Other associated factors may increase the effects of stress and render the individual more vulnerable to stress. The model suggests that caregiver outcomes are often influenced by subjective and objective stressors, role strains, and psychological strains and are balanced with mediating influences such as coping strategies and social support resources such as family, friends, and other social groups. Other caregiver distress studies identified similar variables present in the stress process model[22]. Caregivers' mental health outcomes depend not only on objective

factors such as the BPSD and number of caregiving hours worked, but also on the caregivers' subjective appraisals of the individuals with dementia or the accompanying situations[23]. Many caregivers misunderstand that problematic behaviors are under dementia patients' control. Caregivers making this assumption are more likely to be depressed than those who attribute the BPSD to the disease itself and accept them[23]. On the other hand, caregivers with a sense of purpose, more closeness with the patients, and higher competencies may more easily find positive rewards in this challenging situation[24,25]. Previous studies have indicated that caregiver outcomes, including a sense of self-efficacy in controlling upsetting thoughts about the patient, rather than mechanistically dealing with problematic behaviors or obtaining respite, are highly associated with improved caregiver outcomes[26-29].

Core stress and coping model

Previous studies[30] suggest a common core model for explaining the formation of caregiver distress. In this core model, BPSD are seen as basic stressors for informal caregivers, the caregivers' personal perceptions of burden as key mediators are incorporated, and it is suggested that higher levels of caregiver burden are positively associated with worse caregiver outcomes.

Sociocultural stress and coping model

Aranda and Knight[31] suggest that culture and ethnicity play important roles in the stress and coping processes of caregivers to elderly individuals. Cultural and ethnic factors may even be associated with specific health disorders and disabilities and explain variations in caregivers' appraisals of potential stressors. Knight and Sayegh [32] suggest a revised model (Figure 1) that takes cultural values into more robust consideration. They suggest that familism as a cultural value adds multidimensional effects and that values regarding social or familial obligations show more influence than family solidarity. Knight and Sayegh[32] further point out that the effects of cultural values and ethnicity on stress and coping processes are found to relate more to social support and coping styles than to caregiver burden. In summary, cultural values are, at best, indirectly related to the mental health of caregivers, which in turn affects the social and family support of dementia caregivers and further affects the way they respond to dementia patient(s) in their care. The authors suggest that these factors are at least indirectly associated with the mental health of caregivers.

Systemic family framework model

The psychological and dynamic dimensions within a family are thought to affect caregiver stress perceptions and coping processes. Acceptance of aversive experiences and a commitment to personal values by the caregiver are proven to be associated with challenges and experiences, including sadness and grief. Although there is usually one member of the family that assumes most caregiving responsibility, the caregiving process impacts the whole family.

Mitrani et al[33] applied structural family theory[34] in studying the role of family functioning in caregiver stress and coping processes. They indicated that family functioning partially mediates the relationship between objective burden and caregiver distress in the stress process model (Figure 2). Mitrani et al[33] suggested that caregiver distress appraisal may be mitigated by any intervention that is best targeted at correcting problematic family interactions and preserving protective family patterns. Family interventions may enhance the participation of dementia patients in family activities, resolution of disagreements, and expressions of emotionality and further decrease expressed negative responses to the patient.

Activity restriction model

The Activity Restriction Model[35] suggests that the stresses of caregiving discourage one's ability to engage in social and recreational activities, and this restriction is expected to contribute to depression. Mausbach et al[36] examined the activity restriction model in the context of dementia caregiver research. Their results suggest that activity restriction significantly mediated the relationship of the caregiving role and depression. On the other hand, they also found that depression acts as a key mediating factor of the caregiving role and activity restrictions. These findings support the use of social and recreational activities of dementia caregivers as opportunities for useful depression-improving behavioral interventions. Moreover, the caregiver's participation in pleasurable activities (i.e., behavioral activation) could be promoted with behavioral and cognitive-behavioral approaches[37]. These results raise the importance and application of the activity restriction model in explaining and treating
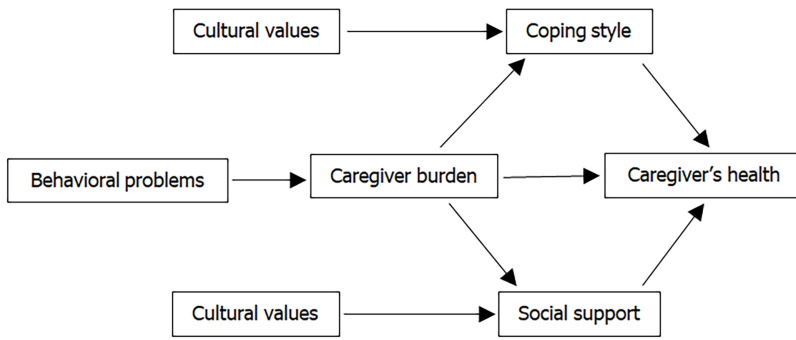
Figure 1 The sociocultural stress and coping model is based on the core stress and coping model and further takes cultural values into consideration.
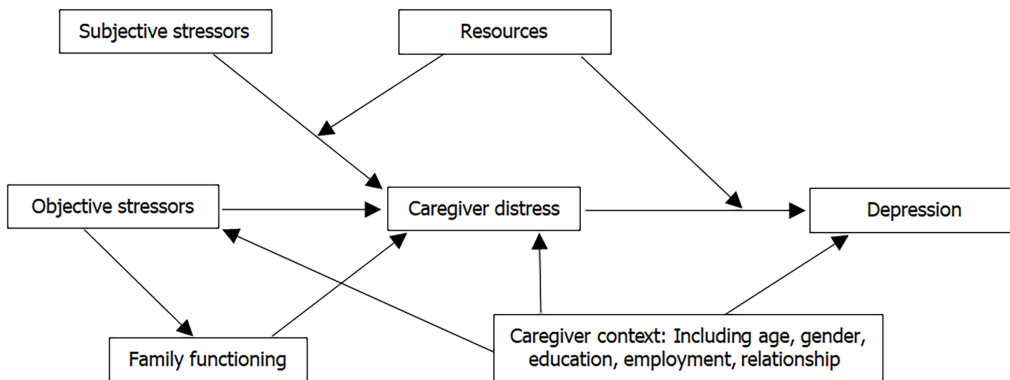
Figure 2 Systemic family framework model is based on the stress process model and the family functioning is taken into consideration.

caregiver depression.

Suffering-compassion model

Previous studies suggest that caregivers' perceived suffering of the dementia patients was significantly associated with caregiver depression[38]. The Suffering-Compassion Model demonstrates the relations among the dementia patient's suffering, and the caregiver's perceived suffering, intrusive thoughts, and compassion. The contribution of caregivers' perceived suffering to caregiver depression is, however, mediated by their own personal intrusive thoughts. At the same time, caregiver compassion appears to moderate the relations of the caregiver's perceived suffering and intrusive thoughts. If the caregiver had higher compassion, he or she was more likely to experience greater intrusive thoughts. It should be noted that the physical suffering of dementia patients may be more easily recognized than their psychological suffering [39]. This could therefore cyclically mediate caregiver perception, reaction, emotion, *etc.*

In summary, the author merged the above 6 common models for explaining caregiver depression, as shown in Figure 3.

FACTORS ASSOCIATED WITH CAREGIVER DEPRESSION

It is important to explore all factors that may be relevant to the development of dementia caregiver depression. By understanding the relevant factors, treatment may be designed to improve caregivers' mental health.

As dementia diseases progress, an individual's forethought, planning, organizing, and execution of instrumental and basic activities of daily living (ADL) deteriorate and ultimately require oversight, assistance, and then performance on behalf of the patient. Without caregiver assistance, a large proportion of patients with dementia would need nursing home care earlier in the disease process, and the costs of long-term care would increase. Depression is one of the most important issues for caregivers because it is related to poor quality of life, functional decline, and even mortality. Caregiver
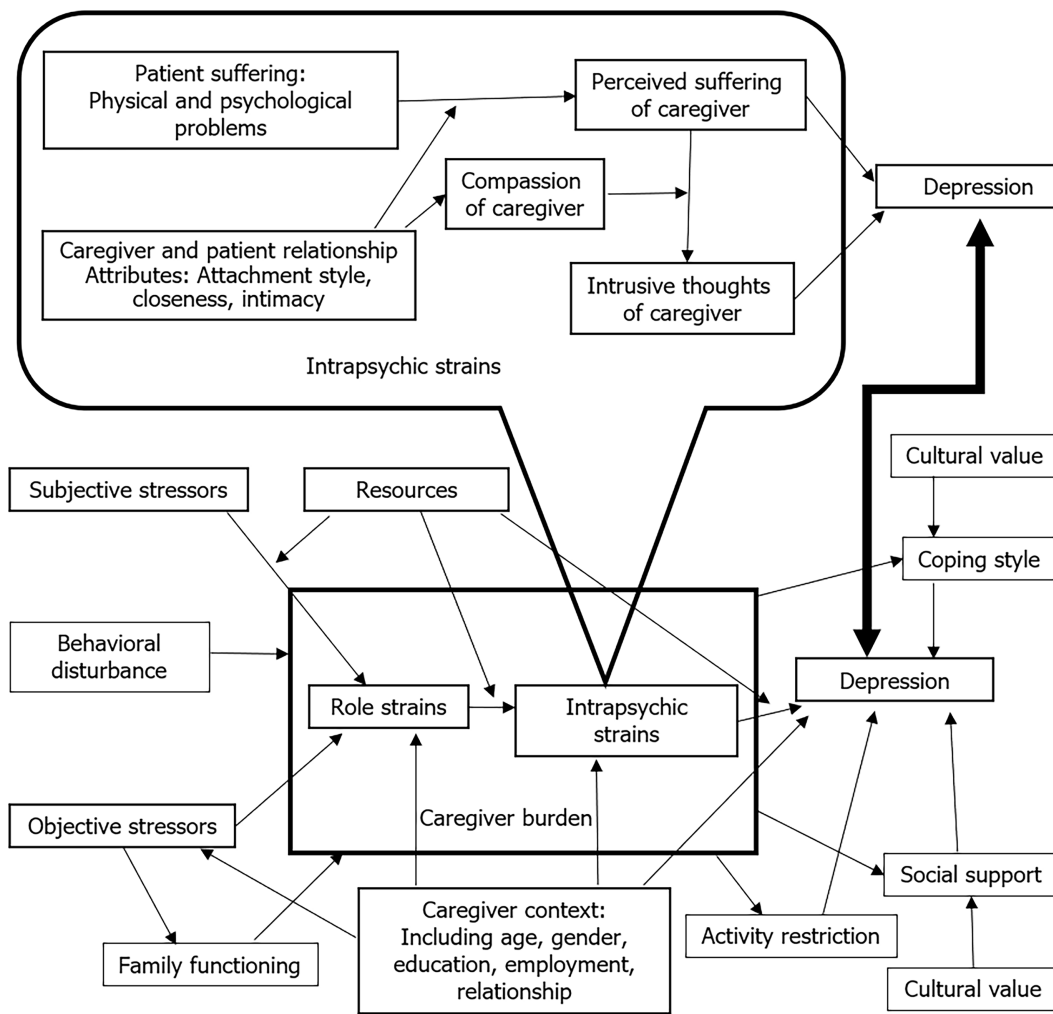
Figure 3 A conceptual model includes the factors related to the caregiver depression. The figure is based on the stress process model and combined with core stress and coping model, sociocultural stress and coping model, systemic family framework model, activity restriction model, and suffering-compassion model.

depression is thought to be a consequence of care due to a complex interplay of factors that comprises dimensions of the patient, caregiver, and cultural background.

Characteristics of patients with dementia

Previous studies associated caregiver depression with being younger, having White or Hispanic ethnicity (compared to black ethnicity), having a lower educational level, and caring for a patient with ADL dependence[40,41], and behavioral disturbances[41,42]. There is significant evidence that BPSD influence depression in caregivers and may be more influential than the severity of cognitive deficits seen or perceived in the patient [43,44]. Different dementia types are also associated with caregiver depression. Liu *et al*[45] reported that the severity of patients' BPSD and caregivers' perceived stress contributed to the increased caregiver burden. Caregivers for patients with fronto-temporal lobar degeneration and dementia with Lewy bodies are likely to have more caregiver burdens than those who care for patients with Alzheimer's disease.

Apart from cognitive and functional impairment, BPSD affect a large proportion of patients with dementia at some point in their disease course. Behavioral disturbances are highly challenging for patients with dementia, their caregivers, and their physicians, as some BPSD are difficult to manage and associated with a greater caregiver burden, higher risk for nursing home placement, prolonged hospitalization, and reduced quality of life. Huang *et al*[46] suggested that agitation, aggression, anxiety, nighttime behavior disturbances, irritability, and hallucinations are the five leading BPSD that are significantly related to caregiver depression. Choi *et al*[47] suggested that different BPSD clusters have a differential impact on caregivers' mental health. Care providers should first distinguish between rejection of care, aggression, and agitation in patients with dementia and then manage those problematic behaviors

to decrease the risk of caregiver depression.

Some studies have found anosognosia in patients with dementia to be related to caregiver burden and depression[48-50]. Anosognosia is characterized by the phenomenon of obvious unawareness, misinterpretation, or total denial of an illness. It is a common symptom of dementia[51]. One explanation is that a patient's higher level of anosognosia results in a higher burden and depression of the caregiver. Anosognosia would increase caregivers' social isolation and tension related to obtaining and receiving patient care[50]. Another possible explanation could be that the depression of the caregiver may distort the perceived health status of the dementia patient and possibly cause a more negative assessment of caregiver-rated dementia problems[52].

Other than the patients' demographics, the subjective feelings of the dementia patients may also be an important topic to be studied, such as the patient's sensation of suffering. In a longitudinal analysis[53], increases in patients' suffering were associated with higher caregiver depression. Several studies suggest that measurable manifestations of suffering comprise (1) Physical symptoms such as chronic or acute pain, nausea, and dyspnea; (2) Psychological symptoms such as depressive sympto-matology and anxiety; and (3) Spiritual well-being including inner harmony, meaning of life, and the extent to which people find comfort and strength in religious beliefs[54-56].

Characteristics of the caregivers

For dementia caregivers, factors associated with depression risk include having a low income, spending more hours caregiving (40 to 79 h/wk compared to less than 40 h/wk)[40], being female[41], having a spousal relationship[40,57], living with the patient[41,44,58], having poorer health status[44,58], and having a higher caregiver distress sensation[44,58,59]. It has been reported that approximately 80% of caregivers have some form of sleep disturbance. Poor sleep is independently associated with greater depressive symptoms[60].

Robinowitz et al[61] suggested that self-efficacy may be an important factor for recognizing caregiver depression risk. Measurements of self-efficacy in caregivers for dealing with memory decline and behavioral disturbances may be valuable to providers who may care for either or both dementia patients and caregivers. Caregiver self-efficacy relates to their conviction about his or her adaptive ability and skills to manage caregiving problems that may arise. Greater self-efficacy has been associated with better psychological and physical health outcomes in dementia caregivers, including decreased depression and anxiety[62].

It has also been suggested that social support and perceived caregiving competency are significant protective factors for caregiver depression[47].

The commitment to the caregiving role, leisure, and work was associated with the formation of guilt feelings. A higher commitment to the caregiving role has been reported to contribute to lower levels of guilt[63]. Higher levels of guilty feelings are related to lower levels of commitment to the caregiving role and to leisure and higher commitment to work. Feelings of guilt may have resulted in caregivers' distress and depression[64].

Impact of cultural issues and values

In some regions and cultures around the globe, symptoms of dementia may be regarded as normal aging or even as a consequence of previous wrongdoing. It has also been reported that some South Asian regions tend to consider dementia an outcome of family conflict or impaired family support. On the other hand, African Americans, due in part to religious beliefs, are prone to rely more on prayer and reconstruction of difficult circumstances during challenging times. Dementia is also thought to be influenced by negative spiritual forces. Cultural factors may influence the conceptualization and help-seeking behaviors of patients with dementia and the caregivers that control their access to care. Indeed, cultural factors affect caregiver responses to the cognitive and noncognitive symptoms of dementia and the consequences of adherence or nonadherence to treatment recommendations[65].

Understanding caregiver stress has become an emerging, relevant cultural value [66]. Based on the sociocultural stress and coping model[32], Losada et al[66] explained the association between cultural values and caregiving distress. Traditional beliefs about family obligations, such as the values systems of Asian and Latino/Hispanic regions, may result in psychological strain from a greater than average emphasis on the caregiving role and the encouragement to overlook one's own needs and feelings. When caregivers feel stress about performing duties and their personal needs are ignored, avoidant coping styles may therefore arise. Avoidant coping strategies may be the mediating factor between familial obligations and cultural values toward

caregiver depression[67].

Youn *et al*[68] suggested that Korean and Korean American caregivers had higher levels of familism and burden than white American caregivers. It is indicated that first-generation employed caregivers appear to have less flexibility and accommodations in their work environments and are more likely to leave their positions when performing caregiving roles than second-generation caregivers. Challenges in utilizing health care systems and language barriers are also higher within the groups of first-generation caregivers[69].

Factors associated with higher rates of dementia caregiver depression, as seen in the literature review, are listed in Table 1.

MANAGEMENT FOR CAREGIVER DEPRESSION

Regarding dementia patients, there are few effective interventions to slow and stop the progression of cognitive impairment. However, there are many interventions designed to treat BPSD and therefore alleviate caregiver burden. Multicomponent nonpharmacological treatments, including caregiver education and support, problem solving training, and assistance in comprehending and managing specific behavioral problems, have been suggested to be effective in treating behavioral disturbances and increasing the quality of life of patients with dementia and their caregivers[70].

Numerous studies have been designed to improve depression in dementia family caregivers. We summarized types of caregiver interventions that have been classified by psychoeducation[71-77], leisure and physical activity[37,78-80], counseling[81-90], cognitive-behavioral approaches[91-94], mindfulness-based interventions[95], and psychological and social support[96-99], as shown in Table 2. We also observed and highlighted interventions utilizing telephone and technologies to deliver nonface-to-face management below.

Various interventions and key clinical content elements identified in the literature review are listed below in Table 2.

Psychoeducation

In this intervention, caregivers are educated on suitable skills to deal with caregiving requirements and stress using structured content and are often performed by small groups, including time for practice. The topics in these sessions usually comprise knowledge of dementia, learning to reserve time for self, enhancement of communication and interaction with family members, skills for managing BPSD, and related community services. More specialized topics, such as emotional management, thought and behavioral modification, and pleasant activity scheduling, may also be involved in some studies.

Leisure and physical activity

Daily pleasant experiences can create balance between "self-life" and caring for patients and help caregivers to maintain positive points of view while serving in the caregiving role. Leisure or physical activities may also serve to transform the caregivers' negative experiences[37]. It is challenging to incorporate activities in the daily lives of caregivers for dementia patients because of their heavy workloads. Moreover, stressed individuals may diminish the skills to engage in positive interactions. The behavioral theory of depression interprets depression as a result of a series of negative reinforcements. Multiple factors create a downward spiral toward the further disruption of a healthy lifestyle and its biological rhythms and social activities, resulting in more severe depressive symptoms.

Counseling

Individual and family counseling is provided by trained providers to help caregivers manage stress and crises. This intervention is performed face to face or through telephone calls.

Psychotherapy and cognitive behavioral approaches

Psychotherapy and cognitive behavioral approaches are performed by trained health care providers to help caregivers manage stress and to treat distress and depression. These interventions are often used for caregivers with clinical depression or other significant mental health problems. They can be performed in individual or group circumstances.

Table 1 Factors associated with increased depression in caregivers of patients with dementia in the literature

Dimension	Less modifiable factors	More modifiable factors
Patient	Younger age, white and Hispanic ethnicity, less educational level, type of dementia (frontotemporal lobar degeneration and dementia with Lewy bodies)	More activities of daily living dependence, behavioral disturbances, higher levels of anosognosia, more physical and psychological suffering
Caregiver	Low income, more hours spent caregiving, female sex, spousal relationship, living with the patient, poorer health status	Higher distress sensations, sleep disturbances, lower self-efficacy, lower levels of commitment to the caregiving role, guilty feelings
Cultural	Familism, family obligation, language barriers	Misunderstandings, coping style, less flexibility and accommodations in their work environments

Table 2 Types of intervention for dementia caregiver depression in the studies

Type of intervention	Content of program
Psychoeducation	Information about dementia and the different stages of dementia severity[71-73], understanding and managing behavioral problems[71,73-76], problem-solving techniques[73], coping strategies for emotional problems[73-75], communication skills[71,73-75], crisis management[73], resource information[73], targeting pain and distress (mood problems, lack of engagement in activities)[74,75,77]
Leisure and physical activity	Education on how to monitor time spent in leisure activities[78,79], identification of enjoyable leisure activities[78,79], prioritizing activities[79], scheduling/participating in leisure activities[79], fostering physical activity[78], individualized goal setting[78], behavioral modification skill training, behavioral activation[37,80], increasing pleasant activities[37,79]
Counseling	Care consultation[81-90], managing dementia symptoms[81,82,84,85,87,88], accessing community support services[81,82,86], telephone-based use of logbooks[83], information about dementia and legal issues and resources for social support[83,86]
Cognitive behavioral approaches	Cognitive reappraisal[91], controlling upsetting thoughts[27], enhancing self-efficacy[27,28], cognitive restructuring[92], assertive skills[92], relaxation[92], acceptance of aversive internal events and circumstances[92], choosing meaningful courses of action[92], telephone-based identification and expression of painful thoughts and emotions[93], managing painful emotions[93], accepting thoughts and emotions[93], redefinition of the relationship[92], reactivation of resources[93], adaptation to bereavement[93,94]
Mindfulness-based interventions	A range of practices with a focus on stress reduction, such as gentle mindful movement (awareness of the body), a body scan (to nurture awareness of the body region by region), and meditation (awareness of the breath)[95]
Psychological and social support	Providing information on formal social support[96,97], mutual sharing of emotions[96-98], creating an appropriate social network and home environment for the caregiver[96], support group participation[96], family role and strength rebuilding[99]

Mindfulness-based interventions

In this treatment model, caregivers are trained in mindfulness and meditation strategies with the basic purpose of concentrating on the present experience nonjudgmentally. Thoughts, emotions, and behaviors are observed without being judged as good or bad with a final aim of relieving suffering. Mindfulness-based interventions are based on acceptance, receptiveness of the current situation, and establishing a balanced coexistence with personal feelings and thoughts, instead of attempting change from the beginning. Mindfulness-based stress reduction is a widely used program that involves practices with a focus on stress reduction, including gentle mindful movement (awareness of the body), a body scan (to foster awareness of the body), and meditation (awareness of the breath)[100]. Dementia not only affects the person who suffers from it but also has an impact on the patients' caregivers. Caregivers of dementia patients are groups that experience mindfulness problems[101] and symptoms of stress and depression.

Psychological and social support

The support group is characterized by a type of mutual helping that comprises a group of people to share experiences and deal with common problems. Studies have shown that support groups can be valuable resources to the families of dementia patients, and include care information and psychological support[99]. Several studies show that caregiver support groups are able to help individuals relieve the distress of caregiving and decrease depressive symptoms[102].

We divided factors associated with caregiver depression into three dimensions: patient, caregiver, and cultural background according to the literature and matched them with the treatment plan for each factor. The appropriate treatment content corresponding to each factor is listed for reference in Table 3. However, this table needs more clinical research for validation.

Table 3 Interventions and modifications for caregiver depression in reviewed literature, classified and matched according to the associated factors and dimensions

Patient with dementia

Address physical care domain

Psychoeducation

Counseling

Environmental modification

Access to community resources

Relief pain

Address psychological domain

Psychoeducation

Cognitive Behavioral approaches

Strategies to treat and compensate cognitive deficits

Reality and insight enhancements

Address behavioral and psychological symptoms

Psychoeducation

Counseling

Pharmacological treatments

Caregiver

Address distress sensation

Leisure and physical activity

Counseling

Mindfulness-Based Interventions

Psychological and social support

Address self-efficacy

Counseling

Cognitive Behavioral approaches

Communication skills

Behavioral management skills

Problem-solving techniques

Crisis management

Training on nursing care

Address commitment to caregiving role

Counseling

Psychological and social support

Address guilty feelings

Leisure and physical activity

Counseling

Cognitive Behavioral approaches

Psychological and social support

Address sleep problems

Leisure and physical activity

Cognitive Behavioral approaches

Address coping strategies	Mindfulness-Based Interventions	
	Psychoeducation	
	Leisure and physical activity	
	Counseling	
	Psychological and social support	
	Coping with loss and grief	
Address accommodations in work environment		
	Counseling	
	Psychological and social support	

Key factors (listed in Table 1) considered include: (1) For patients: Activities of daily living dependence, behavioral disturbances, higher levels of anosognosia, physical, and psychological suffering; (2) For caregivers: Higher caregiver distress sensations, sleep disturbances, lower self-efficacy, lower levels of commitment to the caregiving role, guilty feelings; and (3) For cultural background: Coping style, less flexibility, and accommodations in their work environments.

DELIVERY OF TREATMENT FOR CAREGIVER DEPRESSION

Because of dementia caregiving duties or conflicts with other schedules, face-to-face interventions for caregivers are not practical in certain situations. Family caregivers may also have difficulties leaving the patient to participate in intervention activities in certain places. Furthermore, interventions for caregivers are possibly not available or difficult to participate in many communities around the world, such as rural or underdeveloped communities. Nonface-to-face interventions may also be practical in the current clinical environment with the coronavirus disease 2019 pandemic.

Telephone-based intervention
As dementia progresses, caregivers may become isolated and need a prolonged period of time to meet caregiving demands. This condition can make it difficult for them to leave their homes to seek support and resources through face-to-face interventions. To overcome these barriers, telephone-based interventions targeted to increase accessibility for caregivers are recommended. Telephone-based interventions have been demonstrated to promote the physical and mental health of caregivers[86,87]. Furthermore, telephone-based intervention is an alternative for caregivers for whom certain services are not available locally[89].

Telephone coaching also has the advantage of offering individualized recommendations for the caregiver. This is not always possible in a group setting, such as a large educational group. In some crisis situations, caregivers wanted to meet face-to-face with their instructors for suggestions. Interventions combining telephone and video have been introduced and performed[103].

Technology-driven interventions
Interventions for depression using eHealth or Connected Health (CH) largely employ information and communication technologies for caregivers. These evaluations, interventions, and treatments are performed *via* the internet[104]. For instance, these interventions can be provided in the form of an online course on the computer. Healthcare providers can also utilize smartphone or tablet applications designed to provide newer information and psychological support from peers as well as professionals. The care model is assisted by technology, and all the associated disciplines involved in patient care can be communicated through a health portal that offers beneficial information between formal and informal caregivers. Additionally, some programs for technology-driven interventions use technologies such as body-worn and monitoring devices. Health care professionals can help informal caregivers monitor dementia patients' health status using these devices. The devices can provide an event alert (such as a fall or other emergency event) and facilitate communication. Technology-driven models could provide a handy and lower cost intervention compared to traditional home care, supply a family caregiver with social interaction and emotional support and facilitate information exchange with other caregivers and professionals. It could also ameliorate the decision-making process for matters about

patient care[105]. The literature also suggests that dementia caregiver burden and stress could be reduced through technology-driven interventions[106]. At the same time, the self-efficacy and quality of life of caregivers will be improved by this type of intervention[105].

A study performed in Ireland[107,108] used a Connected Health Sustaining Home Stay Model for caring for patients with dementia and their caregivers. The purpose of the study was to (1) Assess the effectiveness of the platform in supporting caregivers at home; (2) Study the potential improvement of patients with dementia and their family caregivers' mental and physical health; and (3) Investigate the platform's usability and user experience. Another example is the system named the A Technology Platform for the Assisted Living of Dementia Elderly Individuals and their Carers[109]. It is a digital platform designed to offer support to the informal caregiver.

Case management

Patient-centered care planning is essential for case management. It includes identification and outreach, comprehensive individualized assessments, care planning, care coordination, service provisions, monitoring, evaluation and fulfilling individualized needs[110].

Due to the complexity of the symptoms of dementia, the model using a multidisciplinary approach and integrated working is beneficial in care for dementia patients. Case managers, nurses, psychiatrists, pharmacists, psychologists, occupational therapists, and social workers are all involved in decision making and supporting the caregivers living with people with dementia[111].

CONCLUSION

Overall, the prevalence of depression among dementia caregivers is higher than that seen in the general population. A structured way to study and verify associated factors and etiologies for caregivers' depression is based on the stress coping model, which may then be expanded by adding relevant important variables. The activity restriction model in the mechanism of caregiver depression also provides an important theoretical basis for interventions and management, such as behavioral activation, leisure, and physical activities. There are many interventions used to manage caregiver depression in the literature, but after further reviewing the intervention methods, it was found that most recommended treatment plans incorporated multicomponent interventions.

The following points provide some perspective and a few suggestions to address currently unmet gaps in treatment adequacy for depression in caregivers of patients with dementia.

Understanding the clinical mechanisms of depression requires investigating psychosocial, physiological, and biological contributions. Is there a difference between depression in caregivers of dementia patients and the general population in imaging studies or in brain neuroendocrine studies? These questions need further exploration.

Most of the current research utilized psychosocial approaches. What should be further studied is whether there will be a meaningful improvement if the caregiver's depression is also given pharmacological treatment such as antidepressants. Is there a difference in antidepressant efficacy between dementia caregivers and the general population? For individual depression symptoms, are there differences in the treatment response of these two groups?

Additionally, many current clinical studies available for review were based on cross-sectional research designs. The behavioral symptoms and daily life functions of dementia deteriorate over time. More long-term follow-up studies are needed to track whether the depressive symptoms of caregivers also change over time.

Dementia is known to occur in many different forms, each having different symptoms and disease courses. For instance, patients with vascular dementia have more obvious physical disabilities and often experience stepwise cognitive declines following each clinically diagnosed stroke event. Cognitive functioning in those with Alzheimer's disease degrades slowly, from instrumental ADL to the most basic ADL. Different types of dementia may very well have different impacts on the moods and daily lives of their caregivers.

Many clinical studies assessed the depression of caregivers by using self-rated scales or scales asking about subjective feelings as the main outcome. One such instrument is the Center for Epidemiologic Studies Depression Scale[112], whose reliability and validity have been proven. Maintaining reliability and validity is best assured by

objective evaluation by trained researchers. Two scales also recommended as appropriate evaluation tools are the Hamilton Depression Rating Scale[113] and the Montgomery–Asberg Depression Rating Scale[114].

The clinical problems of patients with dementia are individual and unique. The author believes that the formulation and implementation of individualized treatment plans are an important component of addressing dementia caregiver depression. Therefore, the case management model for people with dementia and their caregivers needs promotion and the opportunity to evolve to meet these populations' needs.

REFERENCES

1   **GBD 2017 Disease and Injury Incidence and Prevalence Collaborators**. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392**: 1789-1858 [PMID: 30496104 DOI: 10.1016/S0140-6736(18)32279-7]

2   **Chamberlain L**, Anderson C, Knifton C, Madden G. Suicide risk in informal carers of people living with dementia. *Nurs Older People* 2018; **30**: 20-25 [PMID: 29869482 DOI: 10.7748/nop.2018.e1035]

3   **Greaney ML**, Kunicki ZJ, Drohan MM, Ward-Ritacco CL, Riebe D, Cohen SA. Self-reported changes in physical activity, sedentary behavior, and screen time among informal caregivers during the COVID-19 pandemic. *BMC Public Health* 2021; **21**: 1292 [PMID: 34215246 DOI: 10.1186/s12889-021-11294-7]

4   **Montgomery W**, Goren A, Kahle-Wrobleski K, Nakamura T, Ueda K. Alzheimer's disease severity and its association with patient and caregiver quality of life in Japan: results of a community-based survey. *BMC Geriatr* 2018; **18**: 141 [PMID: 29898679 DOI: 10.1186/s12877-018-0831-2]

5   **Coehlo DP**, Hooker K, Bowman S. Institutional placement of persons with dementia: what predicts occurrence and timing? *J Fam Nurs* 2007; **13**: 253-277 [PMID: 17452605 DOI: 10.1177/1074840707300947]

6   **Macfarlane S**, Atee M, Morris T, Whiting D, Healy M, Alford M, Cunningham C. Evaluating the Clinical Impact of National Dementia Behaviour Support Programs on Neuropsychiatric Outcomes in Australia. *Front Psychiatry* 2021; **12**: 652254 [PMID: 33927656 DOI: 10.3389/fpsyt.2021.652254]

7   **Norton MC**, Clark C, Fauth EB, Piercy KW, Pfister R, Green RC, Corcoran CD, Rabins PV, Lyketsos CG, Tschanz JT. Caregiver personality predicts rate of cognitive decline in a community sample of persons with Alzheimer's disease. The Cache County Dementia Progression Study. *Int Psychogeriatr* 2013; **25**: 1629-1637 [PMID: 23830578 DOI: 10.1017/S1041610213001105]

8   **Guterman EL**, Allen IE, Josephson SA, Merrilees JJ, Dulaney S, Chiong W, Lee K, Bonasera SJ, Miller BL, Possin KL. Association between caregiver depression and emergency department use among patients with dementia. *JAMA Neurol* 2019; **76**: 1166-1173 [PMID: 31282955 DOI: 10.1001/jamaneurol.2019.1820]

9   **Etters L**, Goodall D, Harrison BE. Caregiver burden among dementia patient caregivers: a review of the literature. *J Am Acad Nurse Pract* 2008; **20**: 423-428 [PMID: 18786017 DOI: 10.1111/j.1745-7599.2008.00342.x]

10   **Matsumoto N**, Ikeda M, Fukuhara R, Shinagawa S, Ishikawa T, Mori T, Toyota Y, Matsumoto T, Adachi H, Hirono N, Tanabe H. Caregiver burden associated with behavioral and psychological symptoms of dementia in elderly people in the local community. *Dement Geriatr Cogn Disord* 2007; **23**: 219-224 [PMID: 17299264 DOI: 10.1159/000099472]

11   **Meiland FJ**, Kat MG, van Tilburg W, Jonker C, Dröes RM. The emotional impact of psychiatric symptoms in dementia on partner caregivers: do caregiver, patient, and situation characteristics make a difference? *Alzheimer Dis Assoc Disord* 2005; **19**: 195-201 [PMID: 16327346 DOI: 10.1097/01.wad.0000189035.25277.02]

12   **Oyebode F**. Sims' symptoms in the mind: textbook of descriptive psychopathology. 5th ed. Philadelphia: Saunders, 2015

13   **Haley WE**. The family caregiver's role in Alzheimer's disease. *Neurology* 1997; **48**: S25-S29 [PMID: 9153157 DOI: 10.1212/wnl.48.5_suppl_6.25s]

14   **Fuh JL**, Wang SJ, Liu HC, Wang HC. The caregiving burden scale among Chinese caregivers of Alzheimer patients. *Dement Geriatr Cogn Disord* 1999; **10**: 186-191 [PMID: 10325445 DOI: 10.1159/000017118]

15   **Skaalvik MW**, Norberg A, Normann K, Fjelltun AM, Asplund K. The experience of self and threats to sense of self among relatives caring for people with Alzheimer's disease. *Dementia (London)* 2016; **15**: 467-480 [PMID: 24535820 DOI: 10.1177/1471301214523438]

16   **García-Alberca JM**, Lara JP, Berthier ML. Anxiety and depression in caregivers are associated with patient and caregiver characteristics in Alzheimer's disease. *Int J Psychiatry Med* 2011; **41**: 57-69 [PMID: 21495522 DOI: 10.2190/PM.41.1.f]

17   **Liu S**, Li C, Shi Z, Wang X, Zhou Y, Liu S, Liu J, Yu T, Ji Y. Caregiver burden and prevalence of depression, anxiety and sleep disturbances in Alzheimer's disease caregivers in China. *J Clin Nurs* 2017; **26**: 1291-1300 [PMID: 27681477 DOI: 10.1111/jocn.13601]

18   **Sallim AB**, Sayampanathan AA, Cuttilan A, Ho R. Prevalence of mental health disorders among caregivers of patients with Alzheimer disease. *J Am Med Dir Assoc* 2015; **16**: 1034-1041 [PMID: 26593303 DOI: 10.1016/j.jamda.2015.09.007]

19   **Ying J**, Yap P, Gandhi M, Liew TM. Validity and utility of the Center for Epidemiological Studies Depression Scale for detecting depression in family caregivers of persons with dementia. *Dement Geriatr Cogn Disord* 2019; **47**: 323-334 [PMID: 31307034 DOI: 10.1159/000500940]

20   **Huang SS**, Lee MC, Liao YC, Wang WF, Lai TJ. Caregiver burden associated with behavioral and psychological symptoms of dementia (BPSD) in Taiwanese elderly. *Arch Gerontol Geriatr* 2012; **55**: 55-59 [PMID: 21601931 DOI: 10.1016/j.archger.2011.04.009]

21   **Pearlin LI**, Mullan JT, Semple SJ, Skaff MM. Caregiving and the stress process: an overview of concepts and their measures. *Gerontologist* 1990; **30**: 583-594 [PMID: 2276631 DOI: 10.1093/geront/30.5.583]

22   **Haley WE**, Roth DL, Coleton MI, Ford GR, West CA, Collins RP, Isobe TL. Appraisal, coping, and social support as mediators of well-being in black and white family caregivers of patients with Alzheimer's disease. *J Consult Clin Psychol* 1996; **64**: 121-129 [PMID: 8907091 DOI: 10.1037//0022-006x.64.1.121]

23   **Polenick CA**, Struble LM, Stanislawski B, Turnwald M, Broderick B, Gitlin LN, Kales HC. "The Filter is Kind of Broken": Family Caregivers' Attributions About Behavioral and Psychological Symptoms of Dementia. *Am J Geriatr Psychiatry* 2018; **26**: 548-556 [PMID: 29373300 DOI: 10.1016/j.jagp.2017.12.004]

24   **Fuju T**, Yamagami T, Yamaguchi H, Yamazaki T. Development of the Dementia Caregiver Positive Feeling Scale 21-item version (DCPFS-21) in Japan to recognise positive feelings about caregiving for people with dementia. *Psychogeriatrics* 2021; **21**: 650-658 [PMID: 34056808 DOI: 10.1111/psyg.12727]

25   **Yu DSF**, Cheng ST, Wang J. Unravelling positive aspects of caregiving in dementia: An integrative review of research literature. *Int J Nurs Stud* 2018; **79**: 1-26 [PMID: 29128685 DOI: 10.1016/j.ijnurstu.2017.10.008]

26   **Hepburn KW**, Tornatore J, Center B, Ostwald SW. Dementia family caregiver training: affecting beliefs about caregiving and caregiver outcomes. *J Am Geriatr Soc* 2001; **49**: 450-457 [PMID: 11347790 DOI: 10.1046/j.1532-5415.2001.49090.x]

27   **Cheng ST**, Fung HH, Chan WC, Lam LC. Short-Term Effects of a gain-focused reappraisal intervention for dementia caregivers: a double-blind cluster-randomized controlled trial. *Am J Geriatr Psychiatry* 2016; **24**: 740-750 [PMID: 27401052 DOI: 10.1016/j.jagp.2016.04.012]

28   **Cheng ST**, Mak EPM, Fung HH, Kwok T, Lee DTF, Lam LCW. Benefit-finding and effect on caregiver depression: a double-blind randomized controlled trial. *J Consult Clin Psychol* 2017; **85**: 521-529 [PMID: 28287803 DOI: 10.1037/ccp0000176]

29   **Au A**, Li S, Lee K, Leung P, Pan PC, Thompson L, Gallagher-Thompson D. The Coping with Caregiving Group Program for Chinese caregivers of patients with Alzheimer's disease in Hong Kong. *Patient Educ Couns* 2010; **78**: 256-260 [PMID: 19619974 DOI: 10.1016/j.pec.2009.06.005]

30   **Kim JH**, Knight BG, Longmire CV. The role of familism in stress and coping processes among African American and White dementia caregivers: effects on mental and physical health. *Health Psychol* 2007; **26**: 564-576 [PMID: 17845108 DOI: 10.1037/0278-6133.26.5.564]

31   **Aranda MP**, Knight BG. The influence of ethnicity and culture on the caregiver stress and coping process: a sociocultural review and analysis. *Gerontologist* 1997; **37**: 342-354 [PMID: 9203758 DOI: 10.1093/geront/37.3.342]

32   **Knight BG**, Sayegh P. Cultural values and caregiving: the updated sociocultural stress and coping model. *J Gerontol B Psychol Sci Soc Sci* 2010; **65B**: 5-13 [PMID: 19934166 DOI: 10.1093/geronb/gbp096]

33   **Mitrani VB**, Lewis JE, Feaster DJ, Czaja SJ, Eisdorfer C, Schulz R, Szapocznik J. The role of family functioning in the stress process of dementia caregivers: a structural family framework. *Gerontologist* 2006; **46**: 97-105 [PMID: 16452289 DOI: 10.1093/geront/46.1.97]

34   **Minuchin S**.   Families and family therapy. Cambridge, MA: Harvard University Press, 1974

35   **Williamson GM**, Shaffer DR.   The activity restriction model of depressed affect: Antecedents and consequences of restricted normal activities. In: Williamson GM, Shaffer DR, Parmelee PA, editors. Physical Illness and Depression in Older Adults: A Handbook of Theory, Research, and Practice. New York: Kluwer Academic/Plenum, 2000: 173–200

36   **Mausbach BT**, Patterson TL, Grant I. Is depression in Alzheimer's caregivers really due to activity restriction? *J Behav Ther Exp Psychiatry* 2008; **39**: 459-466 [PMID: 18294613 DOI: 10.1016/j.jbtep.2007.12.001]

37   **Au A**, Gallagher-Thompson D, Wong MK, Leung J, Chan WC, Chan CC, Lu HJ, Lai MK, Chan K. Behavioral activation for dementia caregivers: scheduling pleasant events and enhancing communications. *Clin Interv Aging* 2015; **10**: 611-619 [PMID: 25848237 DOI: 10.2147/CIA.S72348]

38   **Monin JK**, Schulz R, Feeney BC, Cook TB. Attachment insecurity and perceived partner suffering as predictors of personal distress. *J Exp Soc Psychol* 2010; **46**: 1143-1147 [PMID: 21057662 DOI: 10.1016/j.jesp.2010.05.009]

39   **Schulz R**, Savla J, Czaja SJ, Monin J. The role of compassion, suffering, and intrusive thoughts in dementia caregiver depression. *Aging Ment Health* 2017; **21**: 997-1004 [PMID: 27260874 DOI: 10.1080/13607863.2016.1191057]

40 **Covinsky KE**, Newcomer R, Fox P, Wood J, Sands L, Dane K, Yaffe K. Patient and caregiver characteristics associated with depression in caregivers of patients with dementia. *J Gen Intern Med* 2003; **18**: 1006-1014 [PMID: 14687259 DOI: 10.1111/j.1525-1497.2003.30103.x]

41 **Chang CC**, Wang WF, Li YY, Chen YA, Chen YJ, Liao YC, Jhang KM, Wu HH. Using the Apriori algorithm to explore caregivers' depression by the combination of the patients with dementia and their caregivers. *Risk Manag Healthc Policy* 2021; **14**: 2953-2963 [PMID: 34285609 DOI: 10.2147/RMHP.S316361]

42 **Hiyoshi-Taniguchi K**, Becker CB, Kinoshita A. What behavioral and psychological symptoms of dementia affect caregiver burnout? *Clin Gerontol* 2018; **41**: 249-254 [PMID: 29252121 DOI: 10.1080/07317115.2017.1398797]

43 **Donaldson C**, Tarrier N, Burns A. The impact of the symptoms of dementia on caregivers. *Br J Psychiatry* 1997; **170**: 62-68 [PMID: 9068778 DOI: 10.1192/bjp.170.1.62]

44 **Omranifard V**, Haghighizadeh E, Akouchekian S. Depression in main caregivers of dementia patients: prevalence and predictors. *Adv Biomed Res* 2018; **7**: 34 [PMID: 29531932 DOI: 10.4103/2277-9175.225924]

45 **Liu S**, Liu J, Wang XD, Shi Z, Zhou Y, Li J, Yu T, Ji Y. Caregiver burden, sleep quality, depression, and anxiety in dementia caregivers: a comparison of frontotemporal lobar degeneration, dementia with Lewy bodies, and Alzheimer's disease. *Int Psychogeriatr* 2018; **30**: 1131-1138 [PMID: 29223171 DOI: 10.1017/S1041610217002630]

46 **Huang SS**, Liao YC, Wang WF. Association between caregiver depression and individual behavioral and psychological symptoms of dementia in Taiwanese patients. *Asia Pac Psychiatry* 2015; **7**: 251-259 [PMID: 25704825 DOI: 10.1111/appy.12175]

47 **Choi SSW**, Budhathoki C, Gitlin LN. Impact of three dementia-related behaviors on caregiver depression: The role of rejection of care, aggression, and agitation. *Int J Geriatr Psychiatry* 2019; **34**: 966-973 [PMID: 30897238 DOI: 10.1002/gps.5097]

48 **Alexander CM**, Martyr A, Savage SA, Morris RG, Clare L. Measuring awareness in people with dementia: results of a systematic scoping review. *J Geriatr Psychiatry Neurol* 2021; **34**: 335-348 [PMID: 32400259 DOI: 10.1177/0891988720924717]

49 **Hallam B**, Chan J, Gonzalez Costafreda S, Bhome R, Huntley J. What are the neural correlates of meta-cognition and anosognosia in Alzheimer's disease? *Neurobiol Aging* 2020; **94**: 250-264 [PMID: 32679396 DOI: 10.1016/j.neurobiolaging.2020.06.011]

50 **Bertrand E**, Azar M, Rizvi B, Brickman AM, Huey ED, Habeck C, Landeira-Fernandez J, Mograbi DC, Cosentino S. Cortical thickness and metacognition in cognitively diverse older adults. *Neuropsychology* 2018; **32**: 700-710 [PMID: 29878837 DOI: 10.1037/neu0000458]

51 **Migliorelli R**, Tesón A, Sabe L, Petracca G, Petracchi M, Leiguarda R, Starkstein SE. Anosognosia in Alzheimer's disease: a study of associated factors. *J Neuropsychiatry Clin Neurosci* 1995; **7**: 338-344 [PMID: 7580194 DOI: 10.1176/jnp.7.3.338]

52 **Perales J**, Turró-Garriga O, Gascón-Bayarri J, Reñé-Ramírez R, Conde-Sala JL. The longitudinal association between a discrepancy measure of anosognosia in patients with dementia, caregiver burden and depression. *J Alzheimers Dis* 2016; **53**: 1133-1143 [PMID: 27258415 DOI: 10.3233/JAD-160065]

53 **Schulz R**, McGinnis KA, Zhang S, Martire LM, Hebert RS, Beach SR, Zdaniuk B, Czaja SJ, Belle SH. Dementia patient suffering and caregiver depression. *Alzheimer Dis Assoc Disord* 2008; **22**: 170-176 [PMID: 18525290 DOI: 10.1097/WAD.0b013e31816653cc]

54 **Cassell EJ**. Diagnosing suffering: a perspective. *Ann Intern Med* 1999; **131**: 531-534 [PMID: 10507963 DOI: 10.7326/0003-4819-131-7-199910050-00009]

55 **Black HK**. Gender, religion, and the experience of suffering: a case study. *J Relig Health* 2013; **52**: 1108-1119 [PMID: 22033671 DOI: 10.1007/s10943-011-9544-y]

56 **Rodgers BL**, Cowles KV. A conceptual foundation for human suffering in nursing care and research. *J Adv Nurs* 1997; **25**: 1048-1053 [PMID: 9147211 DOI: 10.1046/j.1365-2648.1997.19970251048.x]

57 **Chen C**, Thunell J, Zissimopoulos J. Changes in physical and mental health of Black, Hispanic, and White caregivers and non-caregivers associated with onset of spousal dementia. *Alzheimers Dement (N Y)* 2020; **6**: e12082 [PMID: 33163612 DOI: 10.1002/trc2.12082]

58 **Beeson R**, Horton-Deutsch S, Farran C, Neundorfer M. Loneliness and depression in caregivers of persons with Alzheimer's disease or related disorders. *Issues Ment Health Nurs* 2000; **21**: 779-806 [PMID: 11854982 DOI: 10.1080/016128400750044279]

59 **Takahashi M**, Tanaka K, Miyaoka H. Depression and associated factors of informal caregivers versus professional caregivers of demented patients. *Psychiatry Clin Neurosci* 2005; **59**: 473-480 [PMID: 16048454 DOI: 10.1111/j.1440-1819.2005.01401.x]

60 **Beaudreau SA**, Spira AP, Gray HL, Depp CA, Long J, Rothkopf M, Gallagher-Thompson D. The relationship between objectively measured sleep disturbance and dementia family caregiver distress and burden. *J Geriatr Psychiatry Neurol* 2008; **21**: 159-165 [PMID: 18503035 DOI: 10.1177/0891988708316857]

61 **Rabinowitz YG**, Mausbach BT, Gallagher-Thompson D. Self-efficacy as a moderator of the relationship between care recipient memory and behavioral problems and caregiver depression in female dementia caregivers. *Alzheimer Dis Assoc Disord* 2009; **23**: 389-394 [PMID: 19935146 DOI: 10.1097/WAD.0b013e3181b6f74d]

62 **Steffen AM**, McKibbin C, Zeiss AM, Gallagher-Thompson D, Bandura A. The revised scale for

caregiving self-efficacy: reliability and validity studies. *J Gerontol B Psychol Sci Soc Sci* 2002; **57**: P74-P86 [PMID: 11773226 DOI: 10.1093/geronb/57.1.p74]

63   **Gallego-Alberto L**, Losada A, Márquez-González M, Romero-Moreno R, Vara C. Commitment to personal values and guilt feelings in dementia caregivers. *Int Psychogeriatr* 2017; **29**: 57-65 [PMID: 27609481 DOI: 10.1017/S1041610216001393]

64   **Merrilees J**. The impact of dementia on family caregivers: what is research teaching us? *Curr Neurol Neurosci Rep* 2016; **16**: 88 [PMID: 27541750 DOI: 10.1007/s11910-016-0692-z]

65   **Pachana NA**, Gallagher-Thompson D. The importance of attention to cultural factors in the approach to dementia care services for older persons. *Clin Gerontol* 2018; **41**: 181-183 [PMID: 29482470 DOI: 10.1080/07317115.2018.1438875]

66   **Losada A**, Marquez-Gonzalez M, Knight BG, Yanguas J, Sayegh P, Romero-Moreno R. Psychosocial factors and caregivers' distress: effects of familism and dysfunctional thoughts. *Aging Ment Health* 2010; **14**: 193-202 [PMID: 20336551 DOI: 10.1080/13607860903167838]

67   **Sayegh P**, Knight BG. The effects of familism and cultural justification on the mental and physical health of family caregivers. *J Gerontol B Psychol Sci Soc Sci* 2011; **66**: 3-14 [PMID: 20797972 DOI: 10.1093/geronb/gbq061]

68   **Youn G**, Knight BG, Jeong HS, Benton D. Differences in familism values and caregiving outcomes among Korean, Korean American, and White American dementia caregivers. *Psychol Aging* 1999; **14**: 355-364 [PMID: 10509692 DOI: 10.1037//0882-7974.14.3.355]

69   **Liu LW**, McDaniel SA. Family caregiving for immigrant seniors living with heart disease and stroke: Chinese Canadian perspective. *Health Care Women Int* 2015; **36**: 1327-1345 [PMID: 25985230 DOI: 10.1080/07399332.2015.1038346]

70   **Gitlin LN**, Winter L, Dennis MP, Hodgson N, Hauck WW. Targeting and managing behavioral symptoms in individuals with dementia: a randomized trial of a nonpharmacological intervention. *J Am Geriatr Soc* 2010; **58**: 1465-1474 [PMID: 20662955 DOI: 10.1111/j.1532-5415.2010.02971.x]

71   **Blom MM**, Zarit SH, Groot Zwaaftink RB, Cuijpers P, Pot AM. Effectiveness of an Internet intervention for family caregivers of people with dementia: results of a randomized controlled trial. *PLoS One* 2015; **10**: e0116622 [PMID: 25679228 DOI: 10.1371/journal.pone.0116622]

72   **Kurz A**, Wagenpfeil S, Hallauer J, Schneider-Schelte H, Jansen S; AENEAS Study. Evaluation of a brief educational program for dementia carers: the AENEAS study. *Int J Geriatr Psychiatry* 2010; **25**: 861-869 [PMID: 19946869 DOI: 10.1002/gps.2428]

73   **Villars H**, Cantet C, de Peretti E, Perrin A, Soto-Martin M, Gardette V. Impact of an educational programme on Alzheimer's disease patients' quality of life: results of the randomized controlled trial THERAD. *Alzheimers Res Ther* 2021; **13**: 152 [PMID: 34511121 DOI: 10.1186/s13195-021-00896-3]

74   **Kunik ME**, Snow AL, Wilson N, Amspoker AB, Sansgiry S, Morgan RO, Ying J, Hersch G, Stanley MA. Teaching caregivers of persons with dementia to address pain. *Am J Geriatr Psychiatry* 2017; **25**: 144-154 [PMID: 27743840 DOI: 10.1016/j.jagp.2016.04.009]

75   **Villars H**, Dupuy C, Perrin A, Vellas B, Nourhashemi F. Impact of a therapeutic educational program on quality of life in Alzheimer's disease: results of a pilot study. *J Alzheimers Dis* 2015; **43**: 167-176 [PMID: 25079807 DOI: 10.3233/JAD-141179]

76   **Söylemez BA**, Küçükgüçlü Ö, Buckwalter KC. Application of the Progressively Lowered Stress Threshold Model with community-based caregivers: a randomized controlled trial. *J Gerontol Nurs* 2016; **42**: 44-54 [PMID: 27064606 DOI: 10.3928/00989134-20160406-01]

77   **Parker D**, Mills S, Abbey J. Effectiveness of interventions that assist caregivers to support people with dementia living in the community: a systematic review. *Int J Evid Based Healthc* 2008; **6**: 137-172 [PMID: 21631819 DOI: 10.1111/j.1744-1609.2008.00090.x]

78   **Connell CM**, Janevic MR. Effects of a telephone-based exercise intervention for dementia caregiving wives: a randomized controlled trial. *J Appl Gerontol* 2009; **28**: 171-194 [PMID: 21709757 DOI: 10.1177/0733464808326951]

79   **Gitlin LN**, Arthur P, Piersol C, Hessels V, Wu SS, Dai Y, Mann WC. Targeting behavioral symptoms and functional decline in dementia: a randomized clinical trial. *J Am Geriatr Soc* 2018; **66**: 339-345 [PMID: 29192967 DOI: 10.1111/jgs.15194]

80   **Moore RC**, Chattillion EA, Ceglowski J, Ho J, von Känel R, Mills PJ, Ziegler MG, Patterson TL, Grant I, Mausbach BT. A randomized clinical trial of Behavioral Activation (BA) therapy for improving psychological and physical health in dementia caregivers: results of the Pleasant Events Program (PEP). *Behav Res Ther* 2013; **51**: 623-632 [PMID: 23916631 DOI: 10.1016/j.brat.2013.07.005]

81   **Steffen AM**, Gant JR. A telehealth behavioral coaching intervention for neurocognitive disorder family carers. *Int J Geriatr Psychiatry* 2016; **31**: 195-203 [PMID: 26077904 DOI: 10.1002/gps.4312]

82   **Holmes SB**, Adler D. Dementia care: critical interactions among primary care physicians, patients and caregivers. *Prim Care* 2005; **32**: 671-682, vi [PMID: 16140122 DOI: 10.1016/j.pop.2005.07.001]

83   **Joling KJ**, van Marwijk HW, Smit F, van der Horst HE, Scheltens P, van de Ven PM, Mittelman MS, van Hout HP. Does a family meetings intervention prevent depression and anxiety in family caregivers of dementia patients? *PLoS One* 2012; **7**: e30936 [PMID: 22303473 DOI: 10.1371/journal.pone.0030936]

84   **Phung KT**, Waldorff FB, Buss DV, Eckermann A, Keiding N, Rishøj S, Siersma V, Sørensen J,

Søgaard R, Sørensen LV, Vogel A, Waldemar G. A three-year follow-up on the efficacy of psychosocial interventions for patients with mild dementia and their caregivers: the multicentre, rater-blinded, randomised Danish Alzheimer Intervention Study (DAISY). *BMJ Open* 2013; **3**: e003584 [PMID: 24270834 DOI: 10.1136/bmjopen-2013-003584]

85   **Kuo LM**, Huang HL, Liang J, Kwok YT, Hsu WC, Su PL, Shyu YL. A randomized controlled trial of a home-based training programme to decrease depression in family caregivers of persons with dementia. *J Adv Nurs* 2017; **73**: 585-598 [PMID: 27653753 DOI: 10.1111/jan.13157]

86   **Kuo LM**, Huang HL, Liang J, Kwok YT, Hsu WC, Liu CY, Shyu YL. Trajectories of health-related quality of life among family caregivers of individuals with dementia: A home-based caregiver-training program matters. *Geriatr Nurs* 2017; **38**: 124-132 [PMID: 27720499 DOI: 10.1016/j.gerinurse.2016.08.017]

87   **Jackson D**, Roberts G, Wu ML, Ford R, Doyle C. A systematic review of the effect of telephone, internet or combined support for carers of people living with Alzheimer's, vascular or mixed dementia in the community. *Arch Gerontol Geriatr* 2016; **66**: 218-236 [PMID: 27372903 DOI: 10.1016/j.archger.2016.06.013]

88   **Tremont G**, Davis JD, Bishop DS, Fortinsky RH. Telephone-delivered psychosocial intervention reduces burden in dementia caregivers. *Dementia (London)* 2008; **7**: 503-520 [PMID: 20228893 DOI: 10.1177/1471301208096632]

89   **González-Fraile E**, Ballesteros J, Rueda JR, Santos-Zorrozúa B, Solà I, McCleery J. Remotely delivered information, training and support for informal caregivers of people with dementia. *Cochrane Database Syst Rev* 2021; **1**: CD006440 [PMID: 33417236 DOI: 10.1002/14651858.CD006440.pub3]

90   **Tremont G**, Davis JD, Papandonatos GD, Ott BR, Fortinsky RH, Gozalo P, Yue MS, Bryant K, Grover C, Bishop DS. Psychosocial telephone intervention for dementia caregivers: A randomized, controlled trial. *Alzheimers Dement* 2015; **11**: 541-548 [PMID: 25074341 DOI: 10.1016/j.jalz.2014.05.1752]

91   **Au A**, Yip HM, Lai S, Ngai S, Cheng ST, Losada A, Thompson L, Gallagher-Thompson D. Telephone-based behavioral activation intervention for dementia family caregivers: Outcomes and mediation effect of a randomized controlled trial. *Patient Educ Couns* 2019; **102**: 2049-2059 [PMID: 31279613 DOI: 10.1016/j.pec.2019.06.009]

92   **Losada A**, Márquez-González M, Romero-Moreno R, Mausbach BT, López J, Fernández-Fernández V, Nogales-González C. Cognitive-behavioral therapy (CBT) versus acceptance and commitment therapy (ACT) for dementia family caregivers with significant depressive symptoms: Results of a randomized clinical trial. *J Consult Clin Psychol* 2015; **83**: 760-772 [PMID: 26075381 DOI: 10.1037/ccp0000028]

93   **Meichsner F**, Schinköthe D, Wilz G. Managing loss and change: grief interventions for dementia caregivers in a CBT-based trial. *Am J Alzheimers Dis Other Demen* 2016; **31**: 231-240 [PMID: 26311735 DOI: 10.1177/1533317515602085]

94   **Lopez L**, Vázquez FL, Torres ÁJ, Otero P, Blanco V, Díaz O, Páramo M. Long-term effects of a cognitive behavioral conference call intervention on depression in non-professional caregivers. *Int J Environ Res Public Health* 2020; **17** [PMID: 33187116 DOI: 10.3390/ijerph17228329]

95   **Kor PPK**, Liu JYW, Chien WT. Effects of a modified mindfulness-based cognitive therapy for family caregivers of people with dementia: A pilot randomized controlled trial. *Int J Nurs Stud* 2019; **98**: 107-117 [PMID: 30922609 DOI: 10.1016/j.ijnurstu.2019.02.020]

96   **Chien WT**, Lee IY. Randomized controlled trial of a dementia care programme for families of home-resided older people with dementia. *J Adv Nurs* 2011; **67**: 774-787 [PMID: 21198803 DOI: 10.1111/j.1365-2648.2010.05537.x]

97   **Chu H**, Yang CY, Liao YH, Chang LI, Chen CH, Lin CC, Chou KR. The effects of a support group on dementia caregivers' burden and depression. *J Aging Health* 2011; **23**: 228-241 [PMID: 20847363 DOI: 10.1177/0898264310381522]

98   **Dröes RM**, van Rijn A, Rus E, Dacier S, Meiland F. Utilization, effect, and benefit of the individualized Meeting Centers Support Program for people with dementia and caregivers. *Clin Interv Aging* 2019; **14**: 1527-1553 [PMID: 31692559 DOI: 10.2147/CIA.S212852]

99   **Fung WY**, Chien WT. The effectiveness of a mutual support group for family caregivers of a relative with dementia. *Arch Psychiatr Nurs* 2002; **16**: 134-144 [PMID: 12037799 DOI: 10.1053/apnu.2002.32951]

100   **Kabat-Zinn J**. An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results. *Gen Hosp Psychiatry* 1982; **4**: 33-47 [PMID: 7042457 DOI: 10.1016/0163-8343(82)90026-3]

101   **Danucalov MA**, Kozasa EH, Afonso RF, Galduroz JC, Leite JR. Yoga and compassion meditation program improve quality of life and self-compassion in family caregivers of Alzheimer's disease patients: A randomized controlled trial. *Geriatr Gerontol Int* 2017; **17**: 85-91 [PMID: 26685923 DOI: 10.1111/ggi.12675]

102   **Kaasalainen S**, Craig D, Wells D. Impact of the Caring for Aging Relatives Group program: an evaluation. *Public Health Nurs* 2000; **17**: 169-177 [PMID: 10840286 DOI: 10.1046/j.1525-1446.2000.00169.x]

103   **Graven LJ**, Glueckauf RL, Regal RA, Merbitz NK, Lustria MLA, James BA. Telehealth Interventions for Family Caregivers of Persons with Chronic Health Conditions: A Systematic Review of Randomized Controlled Trials. *Int J Telemed Appl* 2021; **2021**: 3518050 [PMID:

34093704 DOI: 10.1155/2021/3518050]

104   **Christie HL**, Bartels SL, Boots LMM, Tange HJ, Verhey FJJ, de Vugt ME. A systematic review on the implementation of eHealth interventions for informal caregivers of people with dementia. *Internet Interv* 2018; **13**: 51-59 [PMID: 30206519 DOI: 10.1016/j.invent.2018.07.002]

105   **Godwin KM**, Mills WL, Anderson JA, Kunik ME. Technology-driven interventions for caregivers of persons with dementia: a systematic review. *Am J Alzheimers Dis Other Demen* 2013; **28**: 216-222 [PMID: 23528881 DOI: 10.1177/1533317513481091]

106   **Bossen AL**, Kim H, Williams KN, Steinhoff AE, Strieker M. Emerging roles for telemedicine and smart technologies in dementia care. *Smart Homecare Technol Telehealth* 2015; **3**: 49-57 [PMID: 26636049 DOI: 10.2147/SHTT.S59500]

107   **Guisado-Fernandez E**, Blake C, Mackey L, Silva PA, Power D, O'Shea D, Caulfield B. A smart health platform for measuring health and well-being improvement in people with dementia and their informal caregivers: usability study. *JMIR Aging* 2020; **3**: e15600 [PMID: 32706650 DOI: 10.2196/15600]

108   **Guisado-Fernandez E**, Caulfield B, Silva PA, Mackey L, Singleton D, Leahy D, Dossot S, Power D, O'Shea D, Blake C. Development of a caregivers' support platform (Connected Health Sustaining Home Stay in Dementia): protocol for a longitudinal observational mixed methods study. *JMIR Res Protoc* 2019; **8**: 13280 [PMID: 31464187 DOI: 10.2196/13280]

109   **Torkamani M**, McDonald L, Saez Aguayo I, Kanios C, Katsanou MN, Madeley L, Limousin PD, Lees AJ, Haritou M, Jahanshahi M; ALADDIN Collaborative Group. A randomized controlled pilot study to evaluate a technology platform for the assisted living of people with dementia and their carers. *J Alzheimers Dis* 2014; **41**: 515-523 [PMID: 24643137 DOI: 10.3233/JAD-132156]

110   **Sandberg M**, Jakobsson U, Midlöv P, Kristensson J. Case management for frail older people - a qualitative study of receivers' and providers' experiences of a complex intervention. *BMC Health Serv Res* 2014; **14**: 14 [PMID: 24410755 DOI: 10.1186/1472-6963-14-14]

111   **Grand JH**, Caspar S, Macdonald SW. Clinical features and multidisciplinary approaches to dementia care. *J Multidiscip Healthc* 2011; **4**: 125-147 [PMID: 21655340 DOI: 10.2147/JMDH.S17773]

112   **Carleton RN**, Thibodeau MA, Teale MJ, Welch PG, Abrams MP, Robinson T, Asmundson GJ. The center for epidemiologic studies depression scale: a review with a theoretical and empirical examination of item content and factor structure. *PLoS One* 2013; **8**: e58067 [PMID: 23469262 DOI: 10.1371/journal.pone.0058067]

113   **Zimmerman M**, Martinez JH, Young D, Chelminski I, Dalrymple K. Severity classification on the Hamilton Depression Rating Scale. *J Affect Disord* 2013; **150**: 384-388 [PMID: 23759278 DOI: 10.1016/j.jad.2013.04.028]

114   **Montgomery SA**, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979; **134**: 382-389 [PMID: 444788 DOI: 10.1192/bjp.134.4.382]

REVIEW

Brain-derived neurotrophic factor and inflammation in depression: Pathogenic partners in crime?

Grace A Porter, Jason C O'Connor

Grace A Porter, Department of Pharmacology, UT Health San Antonio, San Antonio, TX 78229, United States

Jason C O'Connor, Department of Pharmacology, University of Texas Health San Antonio, San Antonio, TX 78229, United States

Jason C O'Connor, Audie L. Murphy VA Hospital, South Texas Veterans Health System, San Antonio, TX 78229, United States

Corresponding author: Jason C O'Connor, PhD, Associate Professor, Department of Pharmacology, University of Texas Health San Antonio, 216B Medical Building MC-7764, 7703 Floyd Curl Drive, San Antonio, TX 78229, United States. oconnorj@uthscsa.edu

Abstract

Major depressive disorder is a debilitating disorder affecting millions of people each year. Brain-derived neurotrophic factor (BDNF) and inflammation are two prominent biologic risk factors in the pathogenesis of depression that have received considerable attention. Many clinical and animal studies have highlighted associations between low levels of BDNF or high levels of inflammatory markers and the development of behavioral symptoms of depression. However, less is known about potential interaction between BDNF and inflammation, particularly within the central nervous system. Emerging evidence suggests that there is bidirectional regulation between these factors with important implications for the development of depressive symptoms and antidepressant response. Elevated levels of inflammatory mediators have been shown to reduce expression of BDNF, and BDNF may play an important negative regulatory role on inflammation within the brain. Understanding this interaction more fully within the context of neuropsychiatric disease is important for both developing a fuller understanding of biological pathogenesis of depression and for identifying novel therapeutic opportunities. Here we review these two prominent risk factors for depression with a particular focus on pathogenic implications of their interaction.

Key Words: Brain-derived neurotrophic factor; Microglia; Neuroinflammation; Growth factors; Depression

Core Tip: Low levels of brain-derived neurotrophic factor (BDNF) and high inflammation have both been implicated as risk factors in the pathogenesis of major depressive disorder. Here we review the role BDNF and inflammation play in the etiology of depression and the interaction between them. Recent evidence suggests a bidirectional connection between these two risk factors: inflammation reduces BDNF expression, and BDNF may have a negative regulatory role in resolving neuroinflammation. Understanding of this interaction in the context of neuropsychiatric disease is important for a fuller understanding of biological pathogenesis of depression and for identifying novel therapeutic opportunities.

INTRODUCTION

Research has made important advances in recent decades towards the understanding and treatment of major depressive disorder, a debilitating disorder with a heterogeneous range of symptoms. Despite these advancements, depression remains a leading cause of disability with an estimated 264 million individuals worldwide affected by the disorder[1]. In the United States, the economic burden of major depressive disorder is an estimated 210.5 billion dollar[2] with substantial lost productivity and diminished quality of life for affected patients and their families. Recent interest has turned to biomarker and genetic analysis to predict those who may be vulnerable to developing depression and to understand the etiology of patients' existing diagnosis in order to better prevent and treat this debilitating disorder. Two notable biological risk factors for depression are of particular interest: A deficiency in brain-derived neurotrophic factor (BDNF) and inflammation. In this review, we will highlight the mechanisms by which these factors are known to contribute to the development of depression and summarize emerging evidence suggesting that interactions between these two factors within the brain are important in the pathogenesis of depression.

BRAIN DERIVED NEUROTROPHIC FACTOR

BDNF, a member of the neurotrophin family of growth factors, has been well-studied for its role in the pathogenesis of major depressive disorder and antidepressant efficacy. BDNF is a small protein expressed by the *bdnf* gene on chromosome 11 in humans[3]. Transcription of the *bdnf* gene is controlled by nine distinct promoters. The *bdnf* gene contains up to 11 exons; exons II, III, IV, and VII are brain-specific[4]. BDNF is first synthesized as the precursor pre-proBDNF in the endoplasmic reticulum. The pre- domain is cleaved off and proBDNF is transported to the Golgi apparatus. ProBDNF may be secreted in the precursor form or proteolytically cleaved intracellularly or extracellularly to form mature BDNF (mBDNF)[5,6]. Both pro- and mature forms of the BDNF protein are neuroactive, though the activity of proBDNF and mBDNF have largely opposite effects. ProBDNF binds and activates the pan-neurotrophin receptor p75[NTR], a member of the tumor necrosis factor receptor family, promoting apoptosis[7]. mBDNF binds with high affinity to the tyrosine kinase receptor tropomycin receptor kinase B (TrkB).

When mature BDNF, or neurotrophins with lesser affinity for TrkB including neurotrophin-4 and neurotrophin-3, bind to the extracellular domain of TrkB, the intracellular domains of the receptor dimerize and autophosphorylate one of three tyrosine residues. Phosphorylation at each residue initiates a distinct signaling cascade: Ras-PI3K-Akt, Ras-MAP kinase-Erk, or phospholipase Cγ[8]. These signaling cascades activate transcription factors such as CREB, resulting in cell proliferation, cell survival, synaptogenesis, and memory formation (Figure 1).
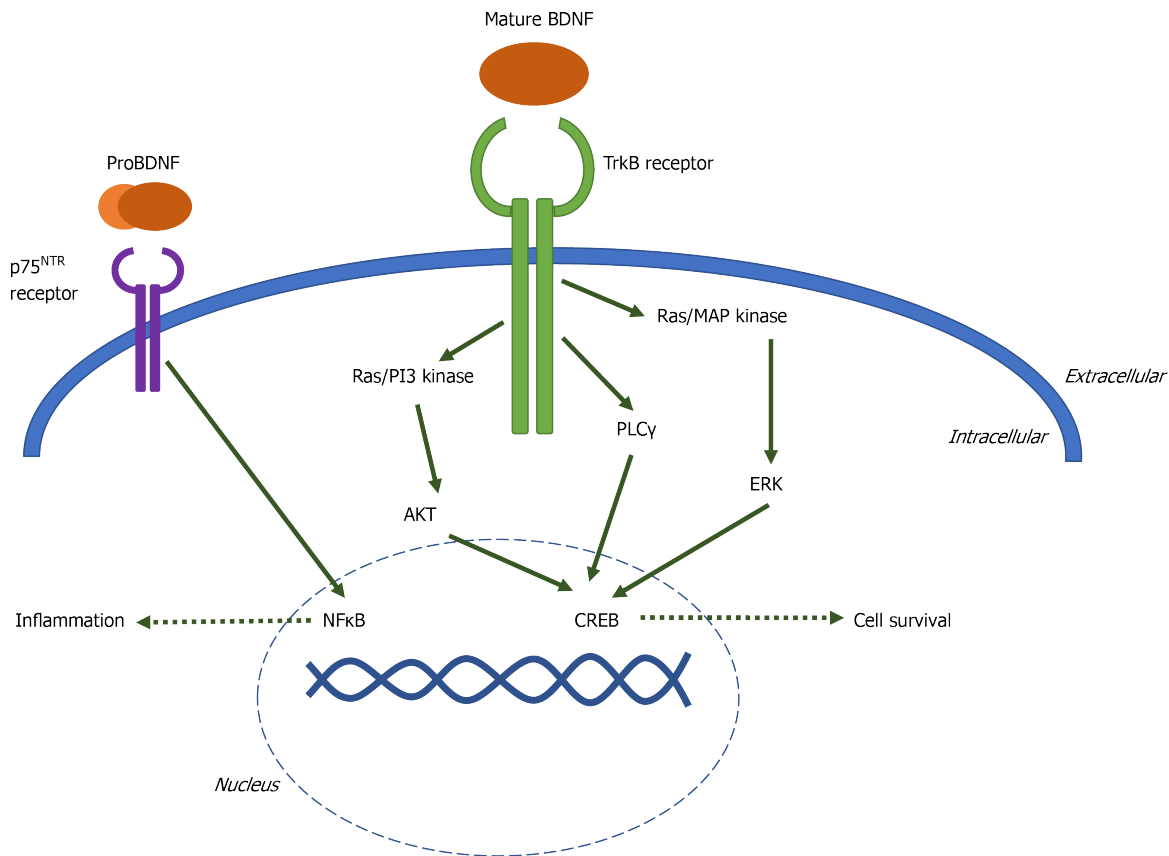
Figure 1 Brain-derived neurotrophic factor signaling cascade diagram. When TrkB is activated by binding mature brain-derived neurotrophic factor (BDNF), the intracellular domains of the receptor dimerize and autophosphorylate one of three tyrosine residues. Phosphorylation at each residue initiates a distinct signaling cascade: Ras-PI3K-Akt, Ras-MAP kinase-Erk, or phospholipase Cγ. These signaling cascades activate transcription factor CREB, resulting in cell proliferation, cell survival, synaptogenesis, and memory formation. ProBDNF binds to pan-neurotrophin receptor P75NTR. P75NTR signaling activates transcription factor NFκB, leading to inflammation and apoptosis. BDNF: Brain-derived neurotrophic factor.

BDNF and TrkB are expressed both peripherally and within the central nervous system. In the periphery, BDNF has been detected in the heart and spleen[9], expressed by myoblasts[10], dorsal root ganglion cells[11], vascular endothelial cells [12], leukocytes[13] and is stored in platelets[14]. In the brain, BDNF is expressed by neurons, astrocytes[15], and microglia[16]. BDNF is highly expressed in the hippocampus and is found in lower concentrations in the cerebral cortex and brainstem[17]. TrkB is expressed in neurons, microglia, and astrocytes throughout the brain[18,19].

A number of factors may modulate BDNF expression or function. Prenatal, early life, social, and unpredictable stress are all associated with reduced BDNF expression or protein levels[20]. Exercise increases BDNF expression[21] and environmental enrichment protects against the effects of stress and early life inflammation on BDNF expression[22,23]. BDNF levels may also decline with age[24,25] and low BDNF levels are associated with age-related neurodegenerative disorders such as Alzheimer's and Parkinson's disease[26,27]. However, some studies suggest BDNF expression does not change with age[28,29].

While a number of genetic factors may contribute to a reduction of BDNF expression or function[30-33], the val66met mutation has garnered considerable attention due to its relevance in psychiatric conditions like bi-polar disorder and suicidality[34,35]. The single nucleotide polymorphism (SNP; rs6265) at nucleotide 196 (G/A) occurs on the 5' pro-BDNF sequence, producing a valine to methionine substitution within codon 66. This SNP does not appear to alter BDNF expression or biological activity, but impairs translocation and activity-dependent secretion[36], thus reducing BDNF- TrkB signaling. The val66met SNP is also associated with reduced serum BDNF protein levels in the periphery[37].

BDNF IN DEPRESSION

The negative correlation between BDNF levels and symptoms of depression have been well established; researchers have been interested in BDNF as a biomarker for depression for decades[38-40]. Clinical data has often demonstrated that patients suffering from major depression disorder are more likely to have alterations in their BDNF-TrkB signaling activity. Numerous studies have found that depressed or suicidal patients have lower BDNF levels than healthy controls[41-48]. Keller *et al*[30] found that suicide victims were more likely to have DNA methylation in the *BDNF* promotor/exon IV compared to control subjects, suggesting a link between epigenetic down-regulation of BDNF and suicidal behavior. Further, psychosocial stress, a known precursor to depression and anxiety, reduces BDNF levels[20].

Genetic analysis reveals several polymorphisms that are associated with susceptibility to developing depression or suicide, such as rs12273363, rs7124442, rs10767664, rs962369, rs908867[31,33]. Of these polymorphisms, the rs6265 SNP known as val66met has been most extensively studied in psychiatric conditions. Some studies suggest that individuals carrying the val66met polymorphism are more vulnerable to developing depression[37,49-52], suicidality[53,54], or to be nonresponsive to antidepressant treatment[55]. However, others dispute this association[55-60]. The val66met polymorphism has been linked to depression in breast cancer patients/survivors[61, 62], but also appears to be protective against chemotherapy-associated cognitive impairments in breast cancer patients[63]. The mixed findings pertaining to association between the val66met SNP and psychiatric disorders suggest that the mutation alone is likely not sufficient to cause pathology. Rather it is a risk factor that interacts with other genetic or environmental factors to contribute to pathogenesis of depression or depressive symptoms.

Clinical studies investigating BDNF have been limited to measuring BDNF in the blood or cerebral spinal fluid, direct measurement of mRNA or protein in the brain being only available in post-mortem tissue samples. However, BDNF does cross the blood-brain barrier (BBB)[64], and Karege *et al*[65] found that brain and serum levels of BDNF are positively correlated in rats. For this reason, measuring peripheral BDNF levels are a feasible indicator of central BDNF expression. Moreover, there is a negative correlation between serum BDNF stored in platelets and depression in humans[66]. BDNF release from platelets may be impaired in depressed patients[67] while antidepressants increase BDNF release from platelets[68], suggesting platelet-derived BDNF is a contributing factor to the interaction between peripheral BDNF levels and depression.

Recent preclinical studies revealed that mice heterozygous for the BDNF allele, which reduces BDNF levels within the brain by about half[69], are susceptible to depressive-like phenotypes after a challenge such as mild stress or acute inflammation [70,71,201]. Direct infusion of BDNF into the rodent brain[72,73] and periphery[74] is protective against the behavioral consequences of stress in the forced swim test and learned helplessness models of depressive-like despair behavior. Further, manipulation of the BDNF-TrkB signaling activity through TrkB agonist 7,8-dihydroxyflavone (DHF)[75] reduces depressive-like behavioral changes induced by social defeat stress [76] and acute inflammation[77]. Many antidepressant treatments increase levels of circulating BDNF[46,68,78-84]. In the brain, anti-depressant treatment induces BDNF mRNA expression in neurons[85], astrocytes[86-88], and microglia[88]. Up-regulation of BDNF may be necessary for the anti-depressant response[89-93].

INFLAMMATION IN THE PERIPHERY AND THE BRAIN

As suggested above, dysregulation in the BDNF-TrkB system may not be a pathological factor that acts alone, rather perturbation within this neurotrophic factor expression/signaling may engender a foundation of vulnerability to subsequent insults to increase the risk of depression or lead to pathology (Figure 2). Inflammation is one risk factor that may well fit this profile.

The ancient Roman encyclopedist Celcus defined inflammation by the presence of "rubor, calor, dolor, tumor", or redness, heat, pain, and swelling. Modern scientists have a deeper understanding of inflammation as a consequence of the innate immune system's activation in response to an irritant or loss of homeostatic control due to factors such as stress, obesity, and aging. Acute inflammation occurs when a tissue injury, pathogen, or noxious stimuli is detected. Leukocytes travel to the impacted region to remove the stimuli and repair damage. Chronic inflammation is a persistent
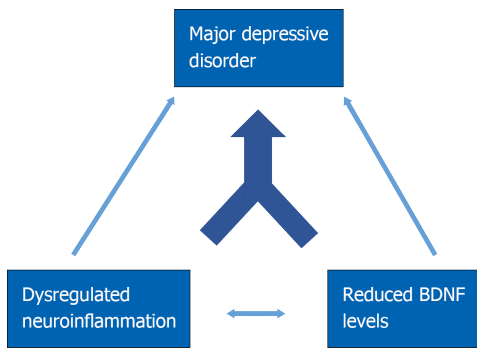
Figure 2 Hypothesis diagram. Brain-derived neurotrophic factor (BDNF) deficiency and elevated or chronic neuroinflammation independently confer vulnerability to development of major depressive disorder. BDNF plays a negative regulatory role in resolving neuroinflammation, and high inflammation reduces BDNF expression. BDNF: Brain-derived neurotrophic factor. BDNF: Brain-derived neurotrophic factor.

and maladaptive response that can be caused by many factors, such as chronic somatic diseases, advancing age, obesity, smoking, and high fat diets. In addition to contributing directly to risk of depression, chronic inflammation may lead to chronic illnesses such as allergies, arthritis, and autoimmune disease that also have high comorbidity with depression.

Invading pathogens or signals released by damaged cells are detected by toll-like receptors (TLR) in the plasma membrane of innate immune cells. TLRs are classified as pattern recognition receptors (PRRs). PRRs recognize and bind pathogen-associated molecular patterns (PAMPs)[94], such as lipopolysaccharide (LPS) on the gram-negative bacterial cell wall, or damage-associated molecular patterns (DAMPs) in a pathogen-independent process known as "sterile inflammation". Activation of TLRs initiate an intracellular signaling cascade, activating the transcription factor NFκB, causing up-regulation of pro-inflammatory mediators including cytokines, chemokines, cellular adhesion molecules[95], and downstream induction of reactive oxygen species[96]. Of these mediators, macrophage-derived TNFα, IL-1β, IL-6, and IL-10 have received extensive attention due their roles in regulating the immune system and their effects on the body[97].

Inflammation as a function of the immune response is necessary to protect the life of the organism. Recently, intentional induction of inflammation has been wielded as a promising tool against cancer as immunotherapy[98]. However, numerous studies have shown prolonged and elevated immune activation has significant impacts on physiological, metabolic, and neural/behavioral processes. The effects of peripheral inflammation or immune challenge do not remain in the periphery; inflammatory conditions impact the CNS through several possible mechanisms. The BBB created by the tight junctions of brain endothelium restricts diffusion of pathogens and non-select solutes from the blood into the brain. Peripheral inflammation may disrupt this boundary, increasing the permeability of the BBB and allowing infiltration by circulating monocytes, cytokines, and other substances[99,100]. Cytokines and monocytes attracted by the expression of chemokines such as monocyte chemoat-tractant protein 1 will travel to the brain and enter through leaky regions of the BBB or through active transport systems. Peripheral cytokines, PAMPs, and DAMPs can also impact brain homeostasis by signaling through the vagus nerve[101] or by signaling through PRRs on the BBB endothelial cells[102,103]. These inflammatory signaling pathways across the BBB initiate the neuroinflammatory response within the brain.

Numerous animal studies have demonstrated that microglia, the resident immune cell in the brain, adopt an "activated" phenotype following peripheral inflammation induced by LPS and live or heat-killed pathogens[100]. In their resting state, microglia are "ramified" with small somas and long highly branched processes. Once microglia detect an immune challenge, their morphology shifts toward an "amoeboid" shape with enlarged soma and shorter, thicker processes. Microglia are the primary source for brain-borne cytokines and other inflammatory mediators.

In addition to producing cytokines, inflammatory microglia also synthesize metabolites of the tryptophan-kynurenine pathway associated with oxidative stress. Tryptophan is converted to kynurenine by the enzyme indolamine-2,3 dioxygenase. Kynurenine metabolism then splits into distinct branches: Kyurenic acid, a metabolite with NMDA receptor antagonist activity, is produced in astrocytes by the enzyme kynurenine aminotransferase, while the enzyme kynurenine monooxygenase (KMO) produces 3-hydroxykynurenine (3-HK) in microglia (Figure 3). 3-HK is further
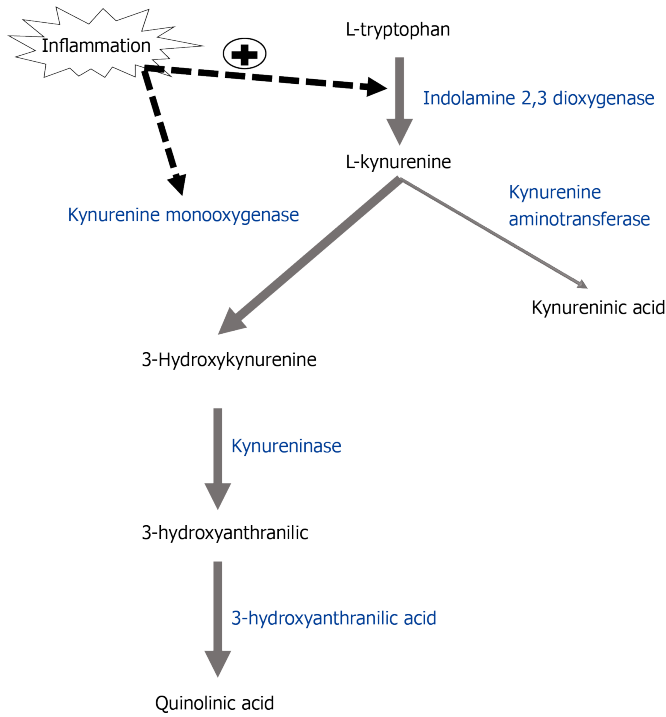
Figure 3 Inflammation shifts kynurenine metabolism pathway towards oxidative stress-associated metabolites. The enzyme indolamine-2,3-dioxygenase (IDO) converts tryptophan to kynurenine. Kynurenine aminotransferase converts kynurenine to kynureninic acid in astrocytes while kynurenine monooxygenase (KMO) metabolizes kynurenine to 3-hyroxykynurenine (3-HK) in microglia. 3-HK is metabolized by kynureninase to 3-hydroxyanthranilic acid and 3-hydroxyanthranilic acid dioxygenase to quinolinic acid. Inflammation up-regulates the enzymes IDO and KMO, resulting in increased levels of KMO-dependent metabolites associated with oxidative stress and depression. IDO: Indolamine-2,3-dioxygenase; KAT: Kynurenine aminotransferase; KMO: Kynurenine monooxygenase; 3-HK: 3-hyroxykynurenine; KYNU: Kynureninase; HAAO: 3-hydroxyanthranilic acid dioxygenase; QA: Quinolinic acid.

metabolized by the enzyme 3-hydroxyanthranilate 3,4-dioxygenase (HAAO) into the neuroactive NMDA receptor agonist quinolinic acid (QA). 3-HK and QA are also free radical inducers and are necessary for the development of inflammation-induced development of depressive-like phenotypes[104], described below.

NEUROINFLAMMATION IN DEPRESSION

Symptoms of typical "sickness behaviors" which cease upon recovery – fatigue, loss of appetite, pain sensitivity, anhedonia, cognitive deficits, social withdrawal – have significant overlap with symptoms of major depressive disorder[105]. In fact, a subset of patients with chronic inflammatory diseases will suffer from longer-lasting symptoms of depression[106]. Individuals suffering from depression but who are otherwise medically healthy often have higher baseline levels of circulating pro-inflammatory mediators, particularly TNFα and IL-6[82,107-110]. Some anti-depressant treatments may reduce neuroinflammation[111,112], but most studies suggest that conventional antidepressants have reduced efficacy in depressed patients who have high inflammation. Conversely, while direct TNFα inhibition was ineffective as an anti-depressant in treatment resistant depression patients with low-moderate CRP levels, it was quite effective in treatment resistant patients with high inflammation[113]. This finding underscores the notion that anti-depressant treatment decisions and efficacy may be improved by integrating understanding of a patient's inflammatory status. At the cellular/molecular level, post-mortem studies indicate that microglia density in the dorsolateral prefrontal cortex, anterior cingulate cortex, and mediodorsal thalamus[114,115], expression levels of IL-1β, IL-6, and TNFα in the prefrontal cortex[116,117] and blood[118], and production of QA in the ACC[119] is significantly higher in suicide victims compared to non-suicide controls. Further, anti-depressants with secondary anti-inflammatory properties are more effective in treatment-resistant patients with high baseline levels of inflammatory markers IL-6 and C-reactive protein[120]. These studies suggest a strong association between inflammation and the development of depression.

Inflammation on its own may be sufficient to promote the development of depressive symptoms. Subsets of patients report feelings of depression following cytokine treatment for hepatitis or cancer[121,122]. Experimental treatment with endotoxin[123] or *Salmonella typhi* vaccine in healthy subjects similarly induced symptoms of depression and anxiety alongside acute inflammation[124] and increased kynurenine pathway metabolism. Numerous rodent studies have likewise demonstrated that inflammation can induce depressive-like phenotypes[125].

Inflammation can arise from multiple sources and events. In humans and rodents, acute and chronic stress is known to promote activation of the innate immune system [126,127] and induce microglial activation[115,128]. Psychological stress, a frequent trigger for depression and suicidality in humans, is commonly modeled in rodents using acute or chronic stressors such as social defeat, restraint, or home cage disruption. You *et al*[129] found that rats exposed to chronic mild stress have elevated central and peripheral pro-inflammatory cytokines, reduced neurogenesis in the hippocampus, and display anhedonia-like behavior as measured by the sucrose preference test. Hodes *et al*[109] found that mice with higher baseline levels of circulating IL-6 are more susceptible to developing depressive-like behavioral phenotypes after chronic social stress; IL-6$^{-/-}$ mice were resilient to the effects of social stress. Aging similarly increases vulnerability to neuroinflammation and subsequent depressive-like behaviors. Peripheral LPS treatment promotes a more robust inflammatory responses and sickness behavior in aged mice compared to young adults[130,131]. Culley *et al*[132] found that LPS increases pro-inflammatory cytokine expression in the prefrontal cortex and impairments in prefrontal cortex-dependent cognition in aged rats. Inflammation associated with obesity[133] and alcohol consumption[134] have similarly been shown to induce depressive symptoms and behaviors in humans and animals.

Researchers have extensively studied depressive-like behavioral changes induced by peripheral immune challenge in rodents[125]. The viral mimetic Poly:IC, attenuated bacterial strain Bacillus Calmette-Guerin (BCG), and LPS are common models used to induce chronic or acute innate immune activation in animal models. Poly:IC increases expression of IL-1β, TNFα, and CD11b and elevates kynurenine levels in the rat brain, followed by a reduction in saccharin preference up to 72 h after treatment[135]. BCG inoculation induces chronic inflammation, up-regulates TNFα, INFy, and the tryptophan-kynurenine enzymes IDO and HAAO, and drives despair-like behavior measured by immobility in forced swim test and tail suspension test one week after infection[136,137]. LPS treatment models acute inflammation: Pro-inflammatory cytokine up-regulation and sickness behaviors resolve within 24 h after administration. Once motor activity and food intake is restored at 24 h, mice continue to display anhedonia-like, despair-like, and anxiety-like behavior[131,138,139]. Anti-inflammatory compounds ameliorate the depressive-like behaviors after LPS[138,140-144]. Moreover, many of these effects appear to be dependent on neurotoxic kynurenine metabolism. Inhibition of, or targeted deletion of, the gene for the rate-limiting enzyme IDO prevents development of LPS- and BCG-induced depressive-like behaviors, despite the elevation of pro-inflammatory cytokines[136,145,146]. KMO$^{-/-}$ and HAAO$^{-/-}$ mice are likewise are protected against many of the depressive-like behavioral effects of LPS, while direct administration of 3-HK provokes immobility in the tail suspension test and hippocampal-dependent cognitive impairment in the y-maze without an increase in pro-inflammatory cytokines[147], suggesting a causative role of downstream metabolites 3-HK and QA.

However, of the total human population that is exposed to high levels of inflammation, only a relatively small subset goes on to develop symptoms of major depressive disorder. For this reason, researchers have lately turned to investigating the environmental and genetic risk factors that contribute to a patient's vulnerability to developing depression. Recent research has revealed a role for BDNF in modulating the effects of neuroinflammation in a psychiatric context. A deficiency in BDNF may prime the system to develop neuropsychiatric symptoms in a maladaptive response to neuroinflammation-induced sickness behavior (Figure 2).

PATHOGENIC TUG OF WAR?

Mounting evidence has revealed negative correlations between BDNF and neuroinflammation, particularly in psychiatric populations[148,149]. Depression is frequently comorbid with chronic inflammatory conditions, and BDNF deficiency has been identified as a risk factor. Breast cancer survivors are more likely to suffer from inflam-

mation-associated depression if they carry the Met allele in the val66met SNP[62]. BDNF expression is reduced in animals models and patients with rheumatoid arthritis, a disease characterized by chronic inflammation, and associated with major depressive disorders[150]. In Hepatitis C patients undergoing IFNα therapy, elevated cytokine levels are predictive of lower BDNF levels, and both BDNF and cytokine expression are associated with depressive symptoms[151]. Uint *et al*[152] found that elevated levels of both IL-1β and BDNF were predictive of treatment-resistant depression, but posited that this relationship may be due to the patients' long-term use of anti-depressant medications buoying their BDNF levels. Treating rats with viral mimetic Poly:IC increases expression of IL-1β, TNFα, IL-6, and CD11b and decreases BDNF and TrkB in the frontal cortex and hippocampus and reduces saccharin preference (anhedonia-like behavior)[135].

Numerous anti-inflammatory treatments have shown promising effects in alleviating depressive-like symptoms and increasing BDNF. Clinically, zinc monotherapy decreases depressive symptoms and increases BDNF in obese subjects[153]. In pre-clinical studies, insulin-like growth factor-1[81] and drugs such as resveratrol[140, 154], imipramine[89,144], doxycycline[144], fluoxetine[155], etazolate[156], chaihu-shugan-san[157], dihydromyricetin[158], minocycline[159], ketamine[160], and caffeine [161] all inhibit inflammation, increase BDNF, and improve depressive-like behavioral phenotypes.

BDNF activity likewise appears to impact stress or inflammation-induced depression. Mice with genetically reduced baseline levels of BDNF (BDNF^{+/-} mice) develop an exaggerated neuroinflammatory and anhedonia-like response to peripheral LPS challenge compared to wild-type controls[201] and increased despair-like behavior in the forced swim test after acute mild stress[71]. Both the TrkB agonist DHF and the TrkB antagonist ANA-12 are anti-depressant in mice treated with LPS, likely due to opposing effects of BDNF-TrkB activity between the hippocampus and nucleus accumbens[77]. INFα therapy patients with the Val66Met polymorphism display symptoms of suicidal ideation and depression compared to those with the Val allele[162]. Mice with the humanized val66met polymorphism (Val/Met mice) are more sensitive to LPS-induced depressive-like behaviors than Val/Val mice and exhibit microglia with an already primed morphology (unpublished data).

Additionally, investigating the interaction between BDNF-TrkB system and inflammation may be relevant for addressing the sex differences in the presentation of depression. Women report experiencing depression at up to twice the rate of men. BDNF is expressed differentially in various regions of the CNS between males and females and environmental conditions modulate BDNF expression differentially between males and females, although circulating levels of peripheral BDNF appear consistent between sexes[163]. Female BDNF conditional KO mice display more depressive-like behaviors and attenuated anti-depressant response than male BDNF conditional KO mice[164]. Women may also be more vulnerable to developing inflammation-induced depression. Females tend to have higher baseline levels of inflammation than males[165] and have a larger pro-inflammatory and depressive response to endotoxin exposure[166]. In the brain, while male microglia appear to be more reactive early in life than female microglia, female microglia may be reactive and inflammatory later in life, when neuropsychiatric disorders tend to manifest[167]. Estrogen may also play a role: Rodent models of estrogen deficiency results in increased depressive-like behaviors, pro-inflammatory cytokine expression, and increased levels of kynurenine pathway enzyme IDO in the hippocampus[168]. There is also evidence that estrogen regulates expression of BDNF and that the estrogen receptor may be necessary for the protective effects of TrkB activation[163]. These findings suggest the relationship between BDNF, inflammation, and sex warrants further investigation.

BDNF AND NEUROINFLAMMATION: BI-DIRECTIONAL MODULATION

Mounting evidence suggests that the connection between BDNF expression and neuroinflammation regulation is bi-directional in nature (Figure 2). Interestingly, Gomes *et al*[169] found *in vitro* that microglia acutely increase extracellular secretion of BDNF in response to LPS, leading to reduced intracellular levels of BDNF. Cultured human monocyte cells constitutively secrete BDNF, and BDNF secretion is increased when monocytes are stimulated by TNFα or IL-6, although no change in BDNF mRNA was detected[170]. Astrocytes likewise express BDNF when stimulated by TNFα[15] and increase expression of BDNF, TNFα, and IL-6 after LPS treatment[171]. BDNF

regulates proliferation and survival of microglia[172]. This acutely elevated BDNF secretion may be necessary for microglia proliferation and activation after immune challenge[173].

Alternatively, increased BDNF secretion may be a means of inhibitory feedback, as BDNF dampens microglial activation. In spinal cord injury, locally applied BDNF reduces microglial density and inhibits free radical production around injury site [174]. Exogenous BDNF infusion dampens microglial activation by LPS in the substantia nigra in aged mice[175]. In a mouse model of Type I diabetes, overexpressing BDNF in the hippocampus suppressed microglial activation and expression of TNFα and IL-6 induced by hyperglycemia[176]. Further, hypermethylation of BDNF is associated with higher levels of serum IL-6 in patients with acute coronary syndrome[177]. Exogenous BDNF administration significantly decreases TNFα and increases expression of the anti-inflammatory cytokine IL-10 in rodent models of stroke, multiple sclerosis, and pneumococcal meningitis[178-181]. Along this line, BDNF^{+/-} mice have reduced expression of IL-10 and kynurenic acid levels while 3-HK is increased in the brain compared to wild-type controls following chronic mild stress [182]. After LPS treatment, BDNF^{+/-} mice have increased expression of pro-inflammatory cytokines IL-1β and TNFα and elevated levels of kynurenine and QA[201]. Reduced BDNF after viral mimetic poly:IC treatment is likewise accompanied by a shift in the tryptophan/kynurenine ratio[135]. *In vitro* studies in BV2 microglia by Park *et al*[183] have demonstrated that TrkB activation by the agonist DHF inhibits production of nitric oxide, TNFα, and IL-1β, and translocation and transcriptional activity of NFκB. These data suggest a role for BDNF-TrkB activity in modulating and resolving the neuroinflammatory response to immune challenge with implications for the development of the depressive-like behavioral phenotypes (Figure 4).

While BDNF secretion may be acutely increased after immune challenge, long-term BDNF expression is hindered in an inflammatory environment. Patients undergoing INFα treatment have significantly reduced BDNF levels[151,162], and Lotrich *et al*[162] found this effect was largest in those with the Val66Met genotype. In rodents, BDNF mRNA is significantly reduced after peripheral injection of LPS in the hippocampus [184,185], substantia nigra[186], and in the whole brain[161]. Similarly, poly I:C also reduces BDNF expression in the brain[135] and E. coli treatment down-regulated BDNF and reduced levels of phosphorylated TrkB receptors in the hippocampus of aged animals[187].

Down-regulation of BDNF may be driven by the pro-inflammatory cytokines IL-1β. *In vitro* experiments have shown that IL-1β treatment inhibits the neuroprotective effects of BDNF through the PI3-K and MAPK pathways and activity of the CREB transcription factor[188]. In rodents, exogenous IL-1β treatment blocks BDNF expression in the hippocampus[189-191], and while BDNF expression was not directly measured, chronic inflammation induced by BCG reduces neurogenesis[192] which is a BDNF-TrkB dependent process and correlate of anti-depressant efficacy.

THERAPEUTIC IMPLICATIONS

BDNF as a treatment target for inflammation-associated depression has its challenges. While BDNF and TrkB ligands do cross the b BBB[64,193], BDNF has opposing effects in different cell types and brain regions. For example, LPS treatment down-regulates BDNF in the hippocampus but up-regulates BDNF in the nucleus accumbens[77]. BDNF and TrkB agonists have anti-depressant-like effects in the hippocampus, but pro-depressive-like effects in the nucleus accumbens; inhibiting TrkB activation is anti-depressant in the nucleus accumbens[77]. Further, peripheral infusion of BDNF induces hyperalgesia[194] which, together with differential regionally-distinct CNS effects, precludes the therapeutic utility of systemic BDNF infusion and flooding the CNS with BDNF or TrkB ligands. However, intranasal ketamine, which was recently approved for anti-depressant use, activates BDNF-TrkB signaling directly in the brain, suggesting that therapeutic strategies that deliver BDNF-TrkB modulators directly to target regions within the CNS could prove efficacious.

Peripheral levels of BDNF and inflammatory markers may be useful as biomarkers for treatment-resistant depression, although this approach also is not without challenge. An ideal biomarker of risk or diagnosis should be reliably sensitive to predicting the disease in an asymptomatic individual and be specific to the disorder in question with little to no overlap with other diseases[195]. While low BDNF and high inflammation markers are frequently measured together in depressed individuals, there are many individuals who meet criteria but report no symptoms of depression,
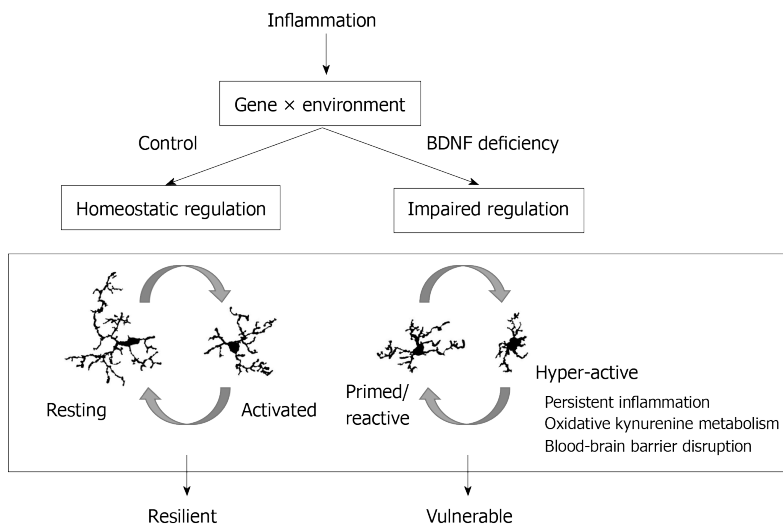
Figure 4 Brain-derived neurotrophic factor deficiency impairs resolution of microglial inflammatory phenotypes. Brain-derived neurotrophic factor (BDNF) levels are altered by genetics and environmental circumstances. Reduced levels of BDNF impair microglia regulation after inflammation. Hyper-active microglia contribute to blood-brain barrier disruption and express higher levels of pro-inflammatory cytokines and kynurenine metabolism pathway enzymes. Individuals with hyper-active microglia are vulnerable to developing symptoms of depression after inflammatory challenge. BDNF: Brain-derived neurotrophic factor.

or become depressed without diverging from average serum levels of each marker. Additionally, low peripheral BDNF and elevated inflammatory markers are reported in other neurodegenerative or neuropsychiatric disorders, including Parkinson's disease, bi-polar disorder, and schizophrenia[196-198]. Epigenetic patterns that disrupt inflammatory homeostasis or functional immunoreactivity of circulating immune cells may provide better prognostic value in predicting vulnerability.

Despite the obstacles, the association between BDNF and inflammation may have utility in deciding treatment options for depressed patients. Patients with inflammation and dysregulation of their BDNF-TrkB system may respond better to anti-depressant drugs with known anti-inflammatory properties, or anti-inflammatory drugs that incidentally have anti-depressant actions, and are able to elevate BDNF levels. Further mechanistic investigations of the interaction between BDNF expression and secretion and pro-inflammatory microglial responses may illuminate potentials targets for novel anti-depressant medication. One emerging approach that has yielded positive results in neurodegenerative disease is to use genetically modified hematopoietic stem cells that express growth factor and traffic specifically to the areas of the brain where pathology occurs[199,200]. While this approach has not yet been tested, it could be viable in cases of severe treatment-resistant depression.

CONCLUSION

Researchers have long recognized BDNF and neuroinflammation as key players in the development of neuropsychiatric conditions, notably major depressive disorder. Recent research has uncovered bi-directional modulation between these two risk factors in the development of depression with promising implications for predicting vulnerability to and treatment of depression. Future studies exploring the mechanisms of BDNF modulation by inflammatory signals, and the anti-inflammatory effects of BDNF in the brain, will provide greater insight into the complex pathogenesis of depression and other neuropsychiatric disorders.

REFERENCES

1   **GBD 2017 Disease and Injury Incidence and Prevalence Collaborators**. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392**: 1789-1858 [PMID: 30496104 DOI: 10.1016/S0140-6736(18)32279-7]
2   **Greenberg PE**, Fournier AA, Sisitsky T, Pike CT, Kessler RC. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psychiatry* 2015; **76**: 155-162

[PMID: 25742202 DOI: 10.4088/JCP.14m09298]

3   **Maisonpierre PC**, Le Beau MM, Espinosa R 3rd, Ip NY, Belluscio L, de la Monte SM, Squinto S, Furth ME, Yancopoulos GD. Human and rat brain-derived neurotrophic factor and neurotrophin-3: gene structures, distributions, and chromosomal localizations. *Genomics* 1991; **10**: 558-568 [PMID: 1889806 DOI: 10.1016/0888-7543(91)90436-I]

4   **Pruunsild P**, Kazantseva A, Aid T, Palm K, Timmusk T. Dissecting the human BDNF locus: bidirectional transcription, complex splicing, and multiple promoters. *Genomics* 2007; **90**: 397-406 [PMID: 17629449 DOI: 10.1016/j.ygeno.2007.05.004]

5   **Mowla SJ**, Farhadi HF, Pareek S, Atwal JK, Morris SJ, Seidah NG, Murphy RA. Biosynthesis and post-translational processing of the precursor to brain-derived neurotrophic factor. *J Biol Chem* 2001; **276**: 12660-12666 [PMID: 11152678 DOI: 10.1074/jbc.M008104200]

6   **Lessmann V**, Brigadski T. Mechanisms, locations, and kinetics of synaptic BDNF secretion: an update. *Neurosci Res* 2009; **65**: 11-22 [PMID: 19523993 DOI: 10.1016/j.neures.2009.06.004]

7   **Teng HK**, Teng KK, Lee R, Wright S, Tevar S, Almeida RD, Kermani P, Torkin R, Chen ZY, Lee FS, Kraemer RT, Nykjaer A, Hempstead BL. ProBDNF induces neuronal apoptosis *via* activation of a receptor complex of p75NTR and sortilin. *J Neurosci* 2005; **25**: 5455-5463 [PMID: 15930396 DOI: 10.1523/JNEUROSCI.5123-04.2005]

8   **Gupta VK**, You Y, Gupta VB, Klistorner A, Graham SL. TrkB receptor signalling: implications in neurodegenerative, psychiatric and proliferative disorders. *Int J Mol Sci* 2013; **14**: 10122-10142 [PMID: 23670594 DOI: 10.3390/ijms140510122]

9   **Yamamoto M**, Sobue G, Yamamoto K, Terao S, Mitsuma T. Expression of mRNAs for neurotrophic factors (NGF, BDNF, NT-3, and GDNF) and their receptors (p75NGFR, trkA, trkB, and trkC) in the adult human peripheral nervous system and nonneural tissues. *Neurochem Res* 1996; **21**: 929-938 [PMID: 8895847 DOI: 10.1007/BF02532343]

10   **Mousavi K**, Jasmin BJ. BDNF is expressed in skeletal muscle satellite cells and inhibits myogenic differentiation. *J Neurosci* 2006; **26**: 5739-5749 [PMID: 16723531 DOI: 10.1523/JNEUROSCI.5398-05.2006]

11   **Cho HJ**, Kim SY, Park MJ, Kim DS, Kim JK, Chu MY. Expression of mRNA for brain-derived neurotrophic factor in the dorsal root ganglion following peripheral inflammation. *Brain Res* 1997; **749**: 358-362 [PMID: 9138740 DOI: 10.1016/S0006-8993(97)00048-6]

12   **Nakahashi T**, Fujimura H, Altar CA, Li J, Kambayashi J, Tandon NN, Sun B. Vascular endothelial cells synthesize and secrete brain-derived neurotrophic factor. *FEBS Lett* 2000; **470**: 113-117 [PMID: 10734218 DOI: 10.1016/S0014-5793(00)01302-8]

13   **Noga O**, Englmann C, Hanf G, Grützkau A, Seybold J, Kunkel G. The production, storage and release of the neurotrophins nerve growth factor, brain-derived neurotrophic factor and neurotrophin-3 by human peripheral eosinophils in allergics and non-allergics. *Clin Exp Allergy* 2003; **33**: 649-654 [PMID: 12752594 DOI: 10.1046/j.1365-2222.2003.01586.x]

14   **Fujimura H**, Altar CA, Chen R, Nakamura T, Nakahashi T, Kambayashi J, Sun B, Tandon NN. Brain-derived neurotrophic factor is stored in human platelets and released by agonist stimulation. *Thromb Haemost* 2002; **87**: 728-734 [PMID: 12008958 DOI: 10.1055/s-0037-1613072]

15   **Saha RN**, Liu X, Pahan K. Up-regulation of BDNF in astrocytes by TNF-alpha: a case for the neuroprotective role of cytokine. *J Neuroimmune Pharmacol* 2006; **1**: 212-222 [PMID: 18040799 DOI: 10.1007/s11481-006-9020-8]

16   **Coull JA**, Beggs S, Boudreau D, Boivin D, Tsuda M, Inoue K, Gravel C, Salter MW, De Koninck Y. BDNF from microglia causes the shift in neuronal anion gradient underlying neuropathic pain. *Nature* 2005; **438**: 1017-1021 [PMID: 16355225 DOI: 10.1038/nature04223]

17   **Ernfors P**, Wetmore C, Olson L, Persson H. Identification of cells in rat brain and peripheral tissues expressing mRNA for members of the nerve growth factor family. *Neuron* 1990; **5**: 511-526 [PMID: 2206535 DOI: 10.1016/0896-6273(90)90090-3]

18   **Frisén J**, Verge VM, Fried K, Risling M, Persson H, Trotter J, Hökfelt T, Lindholm D. Characterization of glial trkB receptors: differential response to injury in the central and peripheral nervous systems. *Proc Natl Acad Sci U S A* 1993; **90**: 4971-4975 [PMID: 8389459 DOI: 10.1073/pnas.90.11.4971]

19   **Nakajima K**, Kikuchi Y, Ikoma E, Honda S, Ishikawa M, Liu Y, Kohsaka S. Neurotrophins regulate the function of cultured microglia. *Glia* 1998; **24**: 272-289 [PMID: 9775979 DOI: 10.1002/(SICI)1098-1136(199811)24:3<272::AID-GLIA2>3.0.CO;2-4]

20   **Bath KG**, Schilit A, Lee FS. Stress effects on BDNF expression: effects of age, sex, and form of stress. *Neuroscience* 2013; **239**: 149-156 [PMID: 23402850 DOI: 10.1016/j.neuroscience.2013.01.074]

21   **Bechara RG**, Kelly ÁM. Exercise improves object recognition memory and induces BDNF expression and cell proliferation in cognitively enriched rats. *Behav Brain Res* 2013; **245**: 96-100 [PMID: 23439217 DOI: 10.1016/j.bbr.2013.02.018]

22   **Dandi E**, Kalamari A, Touloumi O, Lagoudaki R, Nousiopoulou E, Simeonidou C, Spandou E, Tata DA. Beneficial effects of environmental enrichment on behavior, stress reactivity and synaptophysin/BDNF expression in hippocampus following early life stress. *Int J Dev Neurosci* 2018; **67**: 19-32 [PMID: 29545098 DOI: 10.1016/j.ijdevneu.2018.03.003]

23   **Kentner AC**, Khoury A, Lima Queiroz E, MacRae M. Environmental enrichment rescues the effects of early life inflammation on markers of synaptic transmission and plasticity. *Brain Behav Immun* 2016; **57**: 151-160 [PMID: 27002704 DOI: 10.1016/j.bbi.2016.03.013]

24   **Lommatzsch M**, Zingler D, Schuhbaeck K, Schloetcke K, Zingler C, Schuff-Werner P, Virchow JC. The impact of age, weight and gender on BDNF levels in human platelets and plasma. *Neurobiol Aging* 2005; **26**: 115-123 [PMID: 15585351 DOI: 10.1016/J.NEUROBIOLAGING.2004.03.002]

25   **Erickson KI**, Prakash RS, Voss MW, Chaddock L, Heo S, McLaren M, Pence BD, Martin SA, Vieira VJ, Woods JA, McAuley E, Kramer AF. Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume. *J Neurosci* 2010; **30**: 5368-5375 [PMID: 20392958 DOI: 10.1523/JNEUROSCI.6251-09.2010]

26   **Palasz E**, Wysocka A, Gasiorowska A, Chalimoniuk M, Niewiadomski W, Niewiadomska G. BDNF as a Promising Therapeutic Agent in Parkinson's Disease. *Int J Mol Sci* 2020; **21** [PMID: 32050617 DOI: 10.3390/ijms21031170]

27   **Tanila H**. The role of BDNF in Alzheimer's disease. *Neurobiol Dis* 2017; **97**: 114-118 [PMID: 27185594 DOI: 10.1016/j.nbd.2016.05.008]

28   **Ziegenhorn AA**, Schulte-Herbrüggen O, Danker-Hopfe H, Malbranc M, Hartung HD, Anders D, Lang UE, Steinhagen-Thiessen E, Schaub RT, Hellweg R. Serum neurotrophins--a study on the time course and influencing factors in a large old age sample. *Neurobiol Aging* 2007; **28**: 1436-1445 [PMID: 16879899 DOI: 10.1016/j.neurobiolaging.2006.06.011]

29   **Lapchak PA**, Araujo DM, Beck KD, Finch CE, Johnson SA, Hefti F. BDNF and trkB mRNA expression in the hippocampal formation of aging rats. *Neurobiol Aging* 1993; **14**: 121-126 [PMID: 8487914 DOI: 10.1016/0197-4580(93)90087-R]

30   **Keller S**, Sarchiapone M, Zarrilli F, Videtic A, Ferraro A, Carli V, Sacchetti S, Lembo F, Angiolillo A, Jovanovic N, Pisanti F, Tomaiuolo R, Monticelli A, Balazic J, Roy A, Marusic A, Cocozza S, Fusco A, Bruni CB, Castaldo G, Chiariotti L. Increased BDNF promoter methylation in the Wernicke area of suicide subjects. *Arch Gen Psychiatry* 2010; **67**: 258-267 [PMID: 20194826 DOI: 10.1001/archgenpsychiatry.2010.9]

31   **Ropret S**, Zupanc T, Komel R, Videtič Paska A. Single nucleotide polymorphisms in the BDNF gene and suicide in the Slovenian sample. *Neurosci Lett* 2015; **602**: 12-16 [PMID: 26115627 DOI: 10.1016/j.neulet.2015.06.027]

32   **Hing B**, Sathyaputri L, Potash JB. A comprehensive review of genetic and epigenetic mechanisms that regulate BDNF expression and function with relevance to major depressive disorder. *Am J Med Genet B Neuropsychiatr Genet* 2018; **177**: 143-167 [PMID: 29243873 DOI: 10.1002/ajmg.b.32616]

33   **Hing B**, Davidson S, Lear M, Breen G, Quinn J, McGuffin P, MacKenzie A. A polymorphism associated with depressive disorders differentially regulates brain derived neurotrophic factor promoter IV activity. *Biol Psychiatry* 2012; **71**: 618-626 [PMID: 22265241 DOI: 10.1016/j.biopsych.2011.11.030]

34   **Sarchiapone M**, Carli V, Roy A, Iacoviello L, Cuomo C, Latella MC, di Giannantonio M, Janiri L, de Gaetano M, Janal MN. Association of polymorphism (Val66Met) of brain-derived neurotrophic factor with suicide attempts in depressed patients. *Neuropsychobiology* 2008; **57**: 139-145 [PMID: 18600033 DOI: 10.1159/000142361]

35   **Pregelj P**, Nedic G, Paska AV, Zupanc T, Nikolac M, Balažic J, Tomori M, Komel R, Seler DM, Pivac N. The association between brain-derived neurotrophic factor polymorphism (BDNF Val66Met) and suicide. *J Affect Disord* 2011; **128**: 287-290 [PMID: 20667416 DOI: 10.1016/j.jad.2010.07.001]

36   **Egan MF**, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 2003; **112**: 257-269 [PMID: 12553913 DOI: 10.1016/S0092-8674(03)00035-7]

37   **Ozan E**, Okur H, Eker C, Eker OD, Gönül AS, Akarsu N. The effect of depression, BDNF gene val66met polymorphism and gender on serum BDNF levels. *Brain Res Bull* 2010; **81**: 61-65 [PMID: 19589373 DOI: 10.1016/j.brainresbull.2009.06.022]

38   **Hashimoto K**. Brain-derived neurotrophic factor as a biomarker for mood disorders: an historical overview and future directions. *Psychiatry Clin Neurosci* 2010; **64**: 341-357 [PMID: 20653908 DOI: 10.1111/j.1440-1819.2010.02113.x]

39   **Duman RS**, Monteggia LM. A neurotrophic model for stress-related mood disorders. *Biol Psychiatry* 2006; **59**: 1116-1127 [PMID: 16631126 DOI: 10.1016/j.biopsych.2006.02.013]

40   **Chakrapani S**, Eskander N, De Los Santos LA, Omisore BA, Mostafa JA. Neuroplasticity and the Biological Role of Brain Derived Neurotrophic Factor in the Pathophysiology and Management of Depression. *Cureus* 2020; **12**: e11396 [PMID: 33312794 DOI: 10.7759/cureus.11396]

41   **Karege F**, Perret G, Bondolfi G, Schwald M, Bertschy G, Aubry JM. Decreased serum brain-derived neurotrophic factor levels in major depressed patients. *Psychiatry Res* 2002; **109**: 143-148 [PMID: 11927139 DOI: 10.1016/S0165-1781(02)00005-7]

42   **Pandey GN**, Ren X, Rizavi HS, Conley RR, Roberts RC, Dwivedi Y. Brain-derived neurotrophic factor and tyrosine kinase B receptor signalling in post-mortem brain of teenage suicide victims. *Int J Neuropsychopharmacol* 2008; **11**: 1047-1061 [PMID: 18611289 DOI: 10.1017/S1461145708009000]

43   **Chauhan VS**, Khan SA, Kulhari K. Correlation of brain-derived neurotrophic factor with severity of depression and treatment response. *Med J Armed Forces India* 2020 [DOI: 10.1016/j.mjafi.2020.09.014]

44   **Sen S**, Duman R, Sanacora G. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. *Biol Psychiatry* 2008; **64**: 527-532

[PMID: 18571629 DOI: 10.1016/j.biopsych.2008.05.005]

45   **Dwivedi Y**, Rizavi HS, Conley RR, Roberts RC, Tamminga CA, Pandey GN. Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. *Arch Gen Psychiatry* 2003; **60**: 804-815 [PMID: 12912764 DOI: 10.1001/archpsyc.60.8.804]

46   **Aydemir C**, Yalcin ES, Aksaray S, Kisa C, Yildirim SG, Uzbay T, Goka E. Brain-derived neurotrophic factor (BDNF) changes in the serum of depressed women. *Prog Neuropsychopharmacol Biol Psychiatry* 2006; **30**: 1256-1260 [PMID: 16647794 DOI: 10.1016/j.pnpbp.2006.03.025]

47   **Cattaneo A**, Bocchio-Chiavetto L, Zanardini R, Milanesi E, Placentino A, Gennarelli M. Reduced peripheral brain-derived neurotrophic factor mRNA levels are normalized by antidepressant treatment. *Int J Neuropsychopharmacol* 2010; **13**: 103-108 [PMID: 19835669 DOI: 10.1017/S1461145709990812]

48   **Pandey GN**, Dwivedi Y, Rizavi HS, Ren X, Zhang H, Pavuluri MN. Brain-derived neurotrophic factor gene and protein expression in pediatric and adult depressed subjects. *Prog Neuropsychopharmacol Biol Psychiatry* 2010; **34**: 645-651 [PMID: 20227453 DOI: 10.1016/j.pnpbp.2010.03.003]

49   **Bukh JD**, Bock C, Vinberg M, Werge T, Gether U, Vedel Kessing L. Interaction between genetic polymorphisms and stressful life events in first episode depression. *J Affect Disord* 2009; **119**: 107-115 [PMID: 19339052 DOI: 10.1016/j.jad.2009.02.023]

50   **Hwang JP**, Tsai SJ, Hong CJ, Yang CH, Lirng JF, Yang YM. The Val66Met polymorphism of the brain-derived neurotrophic-factor gene is associated with geriatric depression. *Neurobiol Aging* 2006; **27**: 1834-1837 [PMID: 16343697 DOI: 10.1016/j.neurobiolaging.2005.10.013]

51   **Zhao M**, Chen L, Yang J, Han D, Fang D, Qiu X, Yang X, Qiao Z, Ma J, Wang L, Jiang S, Song X, Zhou J, Zhang J, Chen M, Qi D, Yang Y, Pan H. BDNF Val66Met polymorphism, life stress and depression: A meta-analysis of gene-environment interaction. *J Affect Disord* 2018; **227**: 226-235 [PMID: 29102837 DOI: 10.1016/j.jad.2017.10.024]

52   **Lin E**, Hong CJ, Hwang JP, Liou YJ, Yang CH, Cheng D, Tsai SJ. Gene-gene interactions of the brain-derived neurotrophic-factor and neurotrophic tyrosine kinase receptor 2 genes in geriatric depression. *Rejuvenation Res* 2009; **12**: 387-393 [PMID: 20014955 DOI: 10.1089/rej.2009.0871]

53   **Schenkel LC**, Segal J, Becker JA, Manfro GG, Bianchin MM, Leistner-Segal S. The BDNF Val66Met polymorphism is an independent risk factor for high lethality in suicide attempts of depressed patients. *Prog Neuropsychopharmacol Biol Psychiatry* 2010; **34**: 940-944 [PMID: 20433887 DOI: 10.1016/j.pnpbp.2010.04.023]

54   **Kim YK**, Lee HP, Won SD, Park EY, Lee HY, Lee BH, Lee SW, Yoon D, Han C, Kim DJ, Choi SH. Low plasma BDNF is associated with suicidal behavior in major depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2007; **31**: 78-85 [PMID: 16904252 DOI: 10.1016/j.pnpbp.2006.06.024]

55   **Kocabas NA**, Antonijevic I, Faghel C, Forray C, Kasper S, Lecrubier Y, Linotte S, Massat I, Mendlewicz J, Noro M, Montgomery S, Oswald P, Snyder L, Zohar J, Souery D. Brain-derived neurotrophic factor gene polymorphisms: influence on treatment response phenotypes of major depressive disorder. *Int Clin Psychopharmacol* 2011; **26**: 1-10 [PMID: 21188787 DOI: 10.1097/YIC.0b013e32833d18f8]

56   **Gyekis JP**, Yu W, Dong S, Wang H, Qian J, Kota P, Yang J. No association of genetic variants in BDNF with major depression: a meta- and gene-based analysis. *Am J Med Genet B Neuropsychiatr Genet* 2013; **162B**: 61-70 [PMID: 23184535 DOI: 10.1002/ajmg.b.32122]

57   **Herbert J**, Ban M, Brown GW, Harris TO, Ogilvie A, Uher R, Craig TK. Interaction between the BDNF gene Val/66/Met polymorphism and morning cortisol levels as a predictor of depression in adult women. *Br J Psychiatry* 2012; **201**: 313-319 [PMID: 22844024 DOI: 10.1192/bjp.bp.111.107037]

58   **Skibinska M**, Groszewska A, Kapelski P, Rajewska-Rager A, Pawlak J, Dmitrzak-Weglarz M, Szczepankiewicz A, Twarowska-Hauser J. Val66Met functional polymorphism and serum protein level of brain-derived neurotrophic factor (BDNF) in acute episode of schizophrenia and depression. *Pharmacol Rep* 2018; **70**: 55-59 [PMID: 29331787 DOI: 10.1016/j.pharep.2017.08.002]

59   **Ryan KM**, Dunne R, McLoughlin DM. BDNF plasma levels and genotype in depression and the response to electroconvulsive therapy. *Brain Stimul* 2018; **11**: 1123-1131 [PMID: 29802070 DOI: 10.1016/j.brs.2018.05.011]

60   **Froud A**, Murphy J, Cribb L, Ng CH, Sarris J. The relationship between dietary quality, serum brain-derived neurotrophic factor (BDNF) level, and the Val66met polymorphism in predicting depression. *Nutr Neurosci* 2019; **22**: 513-521 [PMID: 29280414 DOI: 10.1080/1028415X.2017.1415281]

61   **Kim JM**, Jang JE, Stewart R, Kim SY, Kim SW, Kang HJ, Shin IS, Park MH, Yoon JH, Yoon JS. Determinants of suicidal ideation in patients with breast cancer. *Psychooncology* 2013; **22**: 2848-2856 [PMID: 23904143 DOI: 10.1002/pon.3367]

62   **Dooley LN**, Ganz PA, Cole SW, Crespi CM, Bower JE. Val66Met BDNF polymorphism as a vulnerability factor for inflammation-associated depressive symptoms in women with breast cancer. *J Affect Disord* 2016; **197**: 43-50 [PMID: 26967918 DOI: 10.1016/j.jad.2016.02.059]

63   **Ng T**, Teo SM, Yeo HL, Shwe M, Gan YX, Cheung YT, Foo KM, Cham MT, Lee JA, Tan YP, Fan G, Yong WS, Preetha M, Loh WJ, Koo SL, Jain A, Lee GE, Wong M, Dent R, Yap YS, Ng R, Khor

CC, Ho HK, Chan A. Brain-derived neurotrophic factor genetic polymorphism (rs6265) is protective against chemotherapy-associated cognitive impairment in patients with early-stage breast cancer. *Neuro Oncol* 2016; **18**: 244-251 [PMID: 26289590 DOI: 10.1093/neuonc/nov162]

64   **Pan W**, Banks WA, Fasold MB, Bluth J, Kastin AJ. Transport of brain-derived neurotrophic factor across the blood-brain barrier. *Neuropharmacology* 1998; **37**: 1553-1561 [PMID: 9886678 DOI: 10.1016/S0028-3908(98)00141-5]

65   **Karege F**, Schwald M, Cisse M. Postnatal developmental profile of brain-derived neurotrophic factor in rat brain and platelets. *Neurosci Lett* 2002; **328**: 261-264 [PMID: 12147321 DOI: 10.1016/S0304-3940(02)00529-3]

66   **Lee BH**, Kim YK. Reduced platelet BDNF level in patients with major depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2009; **33**: 849-853 [PMID: 19371767 DOI: 10.1016/j.pnpbp.2009.04.002]

67   **Karege F**, Bondolfi G, Gervasoni N, Schwald M, Aubry JM, Bertschy G. Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity. *Biol Psychiatry* 2005; **57**: 1068-1072 [PMID: 15860348 DOI: 10.1016/j.biopsych.2005.01.008]

68   **Watanabe K**, Hashimoto E, Ukai W, Ishii T, Yoshinaga T, Ono T, Tateno M, Watanabe I, Shirasaka T, Saito S, Saito T. Effect of antidepressants on brain-derived neurotrophic factor (BDNF) release from platelets in the rats. *Prog Neuropsychopharmacol Biol Psychiatry* 2010; **34**: 1450-1454 [PMID: 20708057 DOI: 10.1016/j.pnpbp.2010.07.036]

69   **Ibarguen-Vargas Y**, Surget A, Vourc'h P, Leman S, Andres CR, Gardier AM, Belzung C. Deficit in BDNF does not increase vulnerability to stress but dampens antidepressant-like effects in the unpredictable chronic mild stress. *Behav Brain Res* 2009; **202**: 245-251 [PMID: 19463708 DOI: 10.1016/j.bbr.2009.03.040]

70   **Duman CH**, Schlesinger L, Kodama M, Russell DS, Duman RS. A role for MAP kinase signaling in behavioral models of depression and antidepressant treatment. *Biol Psychiatry* 2007; **61**: 661-670 [PMID: 16945347 DOI: 10.1016/j.biopsych.2006.05.047]

71   **Advani T**, Koek W, Hensler JG. Gender differences in the enhanced vulnerability of BDNF+/- mice to mild stress. *Int J Neuropsychopharmacol* 2009; **12**: 583-588 [PMID: 19341512 DOI: 10.1017/S1461145709000248]

72   **Shirayama Y**, Chen AC, Nakagawa S, Russell DS, Duman RS. Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. *J Neurosci* 2002; **22**: 3251-3261 [PMID: 11943826 DOI: 10.1523/JNEUROSCI.22-08-03251.2002]

73   **Siuciak JA**, Lewis DR, Wiegand SJ, Lindsay RM. Antidepressant-like effect of brain-derived neurotrophic factor (BDNF). *Pharmacol Biochem Behav* 1997; **56**: 131-137 [PMID: 8981620 DOI: 10.1016/S0091-3057(96)00169-4]

74   **Schmidt HD**, Duman RS. Peripheral BDNF produces antidepressant-like effects in cellular and behavioral models. *Neuropsychopharmacology* 2010; **35**: 2378-2391 [PMID: 20686454 DOI: 10.1038/npp.2010.114]

75   **Jang SW**, Liu X, Yepes M, Shepherd KR, Miller GW, Liu Y, Wilson WD, Xiao G, Blanchi B, Sun YE, Ye K. A selective TrkB agonist with potent neurotrophic activities by 7,8-dihydroxyflavone. *Proc Natl Acad Sci U S A* 2010; **107**: 2687-2692 [PMID: 20133810 DOI: 10.1073/pnas.0913572107]

76   **Zhang JC**, Yao W, Dong C, Yang C, Ren Q, Ma M, Han M, Hashimoto K. Comparison of ketamine, 7,8-dihydroxyflavone, and ANA-12 antidepressant effects in the social defeat stress model of depression. *Psychopharmacology (Berl)* 2015; **232**: 4325-4335 [PMID: 26337614 DOI: 10.1007/s00213-015-4062-3]

77   **Zhang JC**, Wu J, Fujita Y, Yao W, Ren Q, Yang C, Li SX, Shirayama Y, Hashimoto K. Antidepressant effects of TrkB ligands on depression-like behavior and dendritic changes in mice after inflammation. *Int J Neuropsychopharmacol* 2014; **18** [PMID: 25628381 DOI: 10.1093/ijnp/pyu077]

78   **Nibuya M**, Morinobu S, Duman RS. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *J Neurosci* 1995; **15**: 7539-7547 [PMID: 7472505 DOI: 10.1523/JNEUROSCI.15-11-07539.1995]

79   **Russo-Neustadt AA**, Beard RC, Huang YM, Cotman CW. Physical activity and antidepressant treatment potentiate the expression of specific brain-derived neurotrophic factor transcripts in the rat hippocampus. *Neuroscience* 2000; **101**: 305-312 [PMID: 11074154 DOI: 10.1016/S0306-4522(00)00349-3]

80   **Haile CN**, Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Foulkes A, Iqbal S, Mahoney JJ 3rd, De La Garza R 2nd, Charney DS, Newton TF, Mathew SJ. Plasma brain derived neurotrophic factor (BDNF) and response to ketamine in treatment-resistant depression. *Int J Neuropsychopharmacol* 2014; **17**: 331-336 [PMID: 24103211 DOI: 10.1017/S1461145713001119]

81   **Park SE**, Dantzer R, Kelley KW, McCusker RH. Central administration of insulin-like growth factor-I decreases depressive-like behavior and brain cytokine expression in mice. *J Neuroinflammation* 2011; **8**: 12 [PMID: 21306618 DOI: 10.1186/1742-2094-8-12]

82   **Cattaneo A**, Gennarelli M, Uher R, Breen G, Farmer A, Aitchison KJ, Craig IW, Anacker C, Zunsztain PA, McGuffin P, Pariante CM. Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline 'predictors' and longitudinal 'targets'. *Neuropsychopharmacology* 2013; **38**: 377-385 [PMID: 22990943 DOI: 10.1038/npp.2012.191]

83   **Ping G**, Qian W, Song G, Zhaochun S. Valsartan reverses depressive/anxiety-like behavior and induces hippocampal neurogenesis and expression of BDNF protein in unpredictable chronic mild stress mice. *Pharmacol Biochem Behav* 2014; **124**: 5-12 [PMID: 24844704 DOI: 10.1016/j.pbb.2014.05.006]

84   **Chen B**, Dowlatshahi D, MacQueen GM, Wang JF, Young LT. Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. *Biol Psychiatry* 2001; **50**: 260-265 [PMID: 11522260 DOI: 10.1016/S0006-3223(01)01083-6]

85   **Lepack AE**, Bang E, Lee B, Dwyer JM, Duman RS. Fast-acting antidepressants rapidly stimulate ERK signaling and BDNF release in primary neuronal cultures. *Neuropharmacology* 2016; **111**: 242-252 [PMID: 27634096 DOI: 10.1016/j.neuropharm.2016.09.011]

86   **Takano K**, Yamasaki H, Kawabe K, Moriyama M, Nakamura Y. Imipramine induces brain-derived neurotrophic factor mRNA expression in cultured astrocytes. *J Pharmacol Sci* 2012; **120**: 176-186 [PMID: 23076128 DOI: 10.1254/jphs.12039FP]

87   **Allaman I**, Fiumelli H, Magistretti PJ, Martin JL. Fluoxetine regulates the expression of neurotrophic/growth factors and glucose metabolism in astrocytes. *Psychopharmacology (Berl)* 2011; **216**: 75-84 [PMID: 21301813 DOI: 10.1007/s00213-011-2190-y]

88   **Hisaoka-Nakashima K**, Kajitani N, Kaneko M, Shigetou T, Kasai M, Matsumoto C, Yokoe T, Azuma H, Takebayashi M, Morioka N, Nakata Y. Amitriptyline induces brain-derived neurotrophic factor (BDNF) mRNA expression through ERK-dependent modulation of multiple BDNF mRNA variants in primary cultured rat cortical astrocytes and microglia. *Brain Res* 2016; **1634**: 57-67 [PMID: 26764533 DOI: 10.1016/j.brainres.2015.12.057]

89   **Peng CH**, Chiou SH, Chen SJ, Chou YC, Ku HH, Cheng CK, Yen CJ, Tsai TH, Chang YL, Kao CL. Neuroprotection by Imipramine against lipopolysaccharide-induced apoptosis in hippocampus-derived neural stem cells mediated by activation of BDNF and the MAPK pathway. *Eur Neuropsychopharmacol* 2008; **18**: 128-140 [PMID: 17566715 DOI: 10.1016/j.euroneuro.2007.05.002]

90   **Adachi M**, Barrot M, Autry AE, Theobald D, Monteggia LM. Selective loss of brain-derived neurotrophic factor in the dentate gyrus attenuates antidepressant efficacy. *Biol Psychiatry* 2008; **63**: 642-649 [PMID: 17981266 DOI: 10.1016/j.biopsych.2007.09.019]

91   **Adachi M**, Autry AE, Mahgoub M, Suzuki K, Monteggia LM. TrkB Signaling in Dorsal Raphe Nucleus is Essential for Antidepressant Efficacy and Normal Aggression Behavior. *Neuropsychopharmacology* 2017; **42**: 886-894 [PMID: 27634357 DOI: 10.1038/npp.2016.201]

92   **Saarelainen T**, Hendolin P, Lucas G, Koponen E, Sairanen M, MacDonald E, Agerman K, Haapasalo A, Nawa H, Aloyz R, Ernfors P, Castrén E. Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. *J Neurosci* 2003; **23**: 349-357 [PMID: 12514234 DOI: 10.1523/jneurosci.23-01-00349.2003]

93   **Monteggia LM**, Barrot M, Powell CM, Berton O, Galanis V, Gemelli T, Meuth S, Nagy A, Greene RW, Nestler EJ. Essential role of brain-derived neurotrophic factor in adult hippocampal function. *Proc Natl Acad Sci U S A* 2004; **101**: 10827-10832 [PMID: 15249684 DOI: 10.1073/pnas.0402141101]

94   **Jiménez-Dalmaroni MJ**, Gerswhin ME, Adamopoulos IE. The critical role of toll-like receptors-- From microbial recognition to autoimmunity: A comprehensive review. *Autoimmun Rev* 2016; **15**: 1-8 [PMID: 26299984 DOI: 10.1016/j.autrev.2015.08.009]

95   **Shih RH**, Wang CY, Yang CM. NF-kappaB Signaling Pathways in Neurological Inflammation: A Mini Review. *Front Mol Neurosci* 2015; **8**: 77 [PMID: 26733801 DOI: 10.3389/fnmol.2015.00077]

96   **Lingappan K**. NF-κB in Oxidative Stress. *Curr Opin Toxicol* 2018; **7**: 81-86 [PMID: 29862377 DOI: 10.1016/j.cotox.2017.11.002]

97   **Abdulkhaleq LA**, Assi MA, Abdullah R, Zamri-Saad M, Taufiq-Yap YH, Hezmee MNM. The crucial roles of inflammatory mediators in inflammation: A review. *Vet World* 2018; **11**: 627-635 [PMID: 29915501 DOI: 10.14202/vetworld.2018.627-635]

98   **Farkona S**, Diamandis EP, Blasutig IM. Cancer immunotherapy: the beginning of the end of cancer? *BMC Med* 2016; **14**: 73 [PMID: 27151159 DOI: 10.1186/s12916-016-0623-5]

99   **Abbott NJ**. Inflammatory mediators and modulation of blood-brain barrier permeability. *Cell Mol Neurobiol* 2000; **20**: 131-147 [PMID: 10696506 DOI: 10.1023/A:1007074420772]

100   **Hoogland IC**, Houbolt C, van Westerloo DJ, van Gool WA, van de Beek D. Systemic inflammation and microglial activation: systematic review of animal experiments. *J Neuroinflammation* 2015; **12**: 114 [PMID: 26048578 DOI: 10.1186/s12974-015-0332-6]

101   **Zanos TP**, Silverman HA, Levy T, Tsaava T, Battinelli E, Lorraine PW, Ashe JM, Chavan SS, Tracey KJ, Bouton CE. Identification of cytokine-specific sensory neural signals by decoding murine vagus nerve activity. *Proc Natl Acad Sci U S A* 2018; **115**: E4843-E4852 [PMID: 29735654 DOI: 10.1073/pnas.1719083115]

102   **Engblom D**, Ek M, Saha S, Ericsson-Dahlstrand A, Jakobsson PJ, Blomqvist A. Prostaglandins as inflammatory messengers across the blood-brain barrier. *J Mol Med (Berl)* 2002; **80**: 5-15 [PMID: 11862319 DOI: 10.1007/s00109-001-0289-z]

103   **Capuron L**, Miller AH. Immune system to brain signaling: neuropsychopharmacological implications. *Pharmacol Ther* 2011; **130**: 226-238 [PMID: 21334376 DOI: 10.1016/j.pharmthera.2011.01.014]

104   **Parrott JM**, O'Connor JC. Kynurenine 3-Monooxygenase: An Influential Mediator of Neuropathology. *Front Psychiatry* 2015; **6**: 116 [PMID: 26347662 DOI: 10.3389/fpsyt.2015.00116]

105   **Dantzer R**, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* 2008; **9**: 46-56 [PMID: 18073775 DOI: 10.1038/nrn2297]

106   **Evans DL**, Charney DS, Lewis L, Golden RN, Gorman JM, Krishnan KR, Nemeroff CB, Bremner JD, Carney RM, Coyne JC, Delong MR, Frasure-Smith N, Glassman AH, Gold PW, Grant I, Gwyther L, Ironson G, Johnson RL, Kanner AM, Katon WJ, Kaufmann PG, Keefe FJ, Ketter T, Laughren TP, Leserman J, Lyketsos CG, McDonald WM, McEwen BS, Miller AH, Musselman D, O'Connor C, Petitto JM, Pollock BG, Robinson RG, Roose SP, Rowland J, Sheline Y, Sheps DS, Simon G, Spiegel D, Stunkard A, Sunderland T, Tibbits P Jr, Valvo WJ. Mood disorders in the medically ill: scientific review and recommendations. *Biol Psychiatry* 2005; **58**: 175-189 [PMID: 16084838 DOI: 10.1016/j.biopsych.2005.05.001]

107   **Dowlati Y**, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL. A meta-analysis of cytokines in major depression. *Biol Psychiatry* 2010; **67**: 446-457 [PMID: 20015486 DOI: 10.1016/j.biopsych.2009.09.033]

108   **Köhler CA**, Freitas TH, Maes M, de Andrade NQ, Liu CS, Fernandes BS, Stubbs B, Solmi M, Veronese N, Herrmann N, Raison CL, Miller BJ, Lanctôt KL, Carvalho AF. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. *Acta Psychiatr Scand* 2017; **135**: 373-387 [PMID: 28122130 DOI: 10.1111/acps.12698]

109   **Hodes GE**, Pfau ML, Leboeuf M, Golden SA, Christoffel DJ, Bregman D, Rebusi N, Heshmati M, Aleyasin H, Warren BL, Lebonté B, Horn S, Lapidus KA, Stelzhammer V, Wong EH, Bahn S, Krishnan V, Bolaños-Guzman CA, Murrough JW, Merad M, Russo SJ. Individual differences in the peripheral immune system promote resilience *vs* susceptibility to social stress. *Proc Natl Acad Sci U S A* 2014; **111**: 16136-16141 [PMID: 25331895 DOI: 10.1073/pnas.1415191111]

110   **Dahl J**, Ormstad H, Aass HC, Malt UF, Bendz LT, Sandvik L, Brundin L, Andreassen OA. The plasma levels of various cytokines are increased during ongoing depression and are reduced to normal levels after recovery. *Psychoneuroendocrinology* 2014; **45**: 77-86 [PMID: 24845179 DOI: 10.1016/j.psyneuen.2014.03.019]

111   **Hannestad J**, DellaGioia N, Bloch M. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. *Neuropsychopharmacology* 2011; **36**: 2452-2459 [PMID: 21796103 DOI: 10.1038/npp.2011.132]

112   **Ohgi Y**, Futamura T, Kikuchi T, Hashimoto K. Effects of antidepressants on alternations in serum cytokines and depressive-like behavior in mice after lipopolysaccharide administration. *Pharmacol Biochem Behav* 2013; **103**: 853-859 [PMID: 23262300 DOI: 10.1016/j.pbb.2012.12.003]

113   **Raison CL**, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, Haroon E, Miller AH. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry* 2013; **70**: 31-41 [PMID: 22945416 DOI: 10.1001/2013.jamapsychiatry.4]

114   **Steiner J**, Bielau H, Brisch R, Danos P, Ullrich O, Mawrin C, Bernstein HG, Bogerts B. Immunological aspects in the neurobiology of suicide: elevated microglial density in schizophrenia and depression is associated with suicide. *J Psychiatr Res* 2008; **42**: 151-157 [PMID: 17174336 DOI: 10.1016/j.jpsychires.2006.10.013]

115   **Suzuki H**, Ohgidani M, Kuwano N, Chrétien F, Lorin de la Grandmaison G, Onaya M, Tominaga I, Setoyama D, Kang D, Mimura M, Kanba S, Kato TA. Suicide and Microglia: Recent Findings and Future Perspectives Based on Human Studies. *Front Cell Neurosci* 2019; **13**: 31 [PMID: 30814929 DOI: 10.3389/fncel.2019.00031]

116   **Pandey GN**, Rizavi HS, Ren X, Fareed J, Hoppensteadt DA, Roberts RC, Conley RR, Dwivedi Y. Proinflammatory cytokines in the prefrontal cortex of teenage suicide victims. *J Psychiatr Res* 2012; **46**: 57-63 [PMID: 21906753 DOI: 10.1016/j.jpsychires.2011.08.006]

117   **Pandey GN**, Rizavi HS, Zhang H, Bhaumik R, Ren X. Abnormal protein and mRNA expression of inflammatory cytokines in the prefrontal cortex of depressed individuals who died by suicide J Psychiatry Neurosci 2018; 43: 376-385 [PMID: 30371993 DOI: 10.1503/jpn.170192]

118   **Black C**, Miller BJ. Meta-Analysis of Cytokines and Chemokines in Suicidality: Distinguishing Suicidal Versus Nonsuicidal Patients. *Biol Psychiatry* 2015; **78**: 28-37 [PMID: 25541493 DOI: 10.1016/j.biopsych.2014.10.014]

119   **Steiner J**, Walter M, Gos T, Guillemin GJ, Bernstein HG, Sarnyai Z, Mawrin C, Brisch R, Bielau H, Meyer zu Schwabedissen L, Bogerts B, Myint AM. Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: evidence for an immune-modulated glutamatergic neurotransmission? *J Neuroinflammation* 2011; **8**: 94 [PMID: 21831269 DOI: 10.1186/1742-2094-8-94]

120   **Yang C**, Wardenaar KJ, Bosker FJ, Li J, Schoevers RA. Inflammatory markers and treatment outcome in treatment resistant depression: A systematic review. *J Affect Disord* 2019; **257**: 640-649 [PMID: 31357161 DOI: 10.1016/j.jad.2019.07.045]

121   **Bonaccorso S**, Marino V, Puzella A, Pasquini M, Biondi M, Artini M, Almerighi C, Verkerk R, Meltzer H, Maes M. Increased depressive ratings in patients with hepatitis C receiving interferon-alpha-based immunotherapy are related to interferon-alpha-induced changes in the serotonergic system. *J Clin Psychopharmacol* 2002; **22**: 86-90 [PMID: 11799348 DOI: 10.1097/00004714-200202000-00014]

122   **Musselman DL**, Lawson DH, Gumnick JF, Manatunga AK, Penna S, Goodkin RS, Greiner K, Nemeroff CB, Miller AH. Paroxetine for the prevention of depression induced by high-dose

interferon alfa. *N Engl J Med* 2001; **344**: 961-966 [PMID: 11274622 DOI: 10.1056/nejm200103293441303]

123   **Reichenberg A**, Yirmiya R, Schuld A, Kraus T, Haack M, Morag A, Pollmächer T. Cytokine-associated emotional and cognitive disturbances in humans. *Arch Gen Psychiatry* 2001; **58**: 445-452 [PMID: 11343523 DOI: 10.1001/archpsyc.58.5.445]

124   **Wright CE**, Strike PC, Brydon L, Steptoe A. Acute inflammation and negative mood: mediation by cytokine activation. *Brain Behav Immun* 2005; **19**: 345-350 [PMID: 15944074 DOI: 10.1016/j.bbi.2004.10.003]

125   **Remus JL**, Dantzer R. Inflammation Models of Depression in Rodents: Relevance to Psychotropic Drug Discovery. *Int J Neuropsychopharmacol* 2016; **19** [PMID: 27026361 DOI: 10.1093/ijnp/pyw028]

126   **Black PH**. Stress and the inflammatory response: a review of neurogenic inflammation. *Brain Behav Immun* 2002; **16**: 622-653 [PMID: 12480495 DOI: 10.1016/S0889-1591(02)00021-1]

127   **Stepanichev M**, Dygalo NN, Grigoryan G, Shishkina GT, Gulyaeva N. Rodent models of depression: neurotrophic and neuroinflammatory biomarkers. *Biomed Res Int* 2014; **2014**: 932757 [PMID: 24999483 DOI: 10.1155/2014/932757]

128   **Sugama S**, Fujita M, Hashimoto M, Conti B. Stress induced morphological microglial activation in the rodent brain: involvement of interleukin-18. *Neuroscience* 2007; **146**: 1388-1399 [PMID: 17433555 DOI: 10.1016/j.neuroscience.2007.02.043]

129   **You Z**, Luo C, Zhang W, Chen Y, He J, Zhao Q, Zuo R, Wu Y. Pro- and anti-inflammatory cytokines expression in rat's brain and spleen exposed to chronic mild stress: involvement in depression. *Behav Brain Res* 2011; **225**: 135-141 [PMID: 21767575 DOI: 10.1016/j.bbr.2011.07.006]

130   **Godbout JP**, Chen J, Abraham J, Richwine AF, Berg BM, Kelley KW, Johnson RW. Exaggerated neuroinflammation and sickness behavior in aged mice following activation of the peripheral innate immune system. *FASEB J* 2005; **19**: 1329-1331 [PMID: 15919760 DOI: 10.1096/fj.05-3776fje]

131   **Henry CJ**, Huang Y, Wynne A, Hanke M, Himler J, Bailey MT, Sheridan JF, Godbout JP. Minocycline attenuates lipopolysaccharide (LPS)-induced neuroinflammation, sickness behavior, and anhedonia. *J Neuroinflammation* 2008; **5**: 15 [PMID: 18477398 DOI: 10.1186/1742-2094-5-15]

132   **Culley DJ**, Snayd M, Baxter MG, Xie Z, Lee IH, Rudolph J, Inouye SK, Marcantonio ER, Crosby G. Systemic inflammation impairs attention and cognitive flexibility but not associative learning in aged rats: possible implications for delirium. *Front Aging Neurosci* 2014; **6**: 107 [PMID: 24959140 DOI: 10.3389/fnagi.2014.00107]

133   **Capuron L**, Lasselin J, Castanon N. Role of Adiposity-Driven Inflammation in Depressive Morbidity. *Neuropsychopharmacology* 2017; **42**: 115-128 [PMID: 27402495 DOI: 10.1038/npp.2016.123]

134   **Kelley KW**, Dantzer R. Alcoholism and inflammation: neuroimmunology of behavioral and mood disorders. *Brain Behav Immun* 2011; **25** Suppl 1: S13-S20 [PMID: 21193024 DOI: 10.1016/j.bbi.2010.12.013]

135   **Gibney SM**, McGuinness B, Prendergast C, Harkin A, Connor TJ. Poly I:C-induced activation of the immune response is accompanied by depression and anxiety-like behaviours, kynurenine pathway activation and reduced BDNF expression. *Brain Behav Immun* 2013; **28**: 170-181 [PMID: 23201589 DOI: 10.1016/j.bbi.2012.11.010]

136   **O'Connor JC**, Lawson MA, André C, Briley EM, Szegedi SS, Lestage J, Castanon N, Herkenham M, Dantzer R, Kelley KW. Induction of IDO by bacille Calmette-Guérin is responsible for development of murine depressive-like behavior. *J Immunol* 2009; **182**: 3202-3212 [PMID: 19234218 DOI: 10.4049/jimmunol.0802722]

137   **O'Connor JC**, André C, Wang Y, Lawson MA, Szegedi SS, Lestage J, Castanon N, Kelley KW, Dantzer R. Interferon-gamma and tumor necrosis factor-alpha mediate the upregulation of indoleamine 2,3-dioxygenase and the induction of depressive-like behavior in mice in response to bacillus Calmette-Guerin. *J Neurosci* 2009; **29**: 4200-4209 [PMID: 19339614 DOI: 10.1523/JNEUROSCI.5032-08.2009]

138   **O'Connor JC**, Lawson MA, André C, Moreau M, Lestage J, Castanon N, Kelley KW, Dantzer R. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. *Mol Psychiatry* 2009; **14**: 511-522 [PMID: 18195714 DOI: 10.1038/sj.mp.4002148]

139   **Frenois F**, Moreau M, O'Connor J, Lawson M, Micon C, Lestage J, Kelley KW, Dantzer R, Castanon N. Lipopolysaccharide induces delayed FosB/DeltaFosB immunostaining within the mouse extended amygdala, hippocampus and hypothalamus, that parallel the expression of depressive-like behavior. *Psychoneuroendocrinology* 2007; **32**: 516-531 [PMID: 17482371 DOI: 10.1016/j.psyneuen.2007.03.005]

140   **Ge L**, Liu L, Liu H, Liu S, Xue H, Wang X, Yuan L, Wang Z, Liu D. Resveratrol abrogates lipopolysaccharide-induced depressive-like behavior, neuroinflammatory response, and CREB/BDNF signaling in mice. *Eur J Pharmacol* 2015; **768**: 49-57 [PMID: 26485503 DOI: 10.1016/j.ejphar.2015.10.026]

141   **Sulakhiya K**, Keshavlal GP, Bezbaruah BB, Dwivedi S, Gurjar SS, Munde N, Jangra A, Lahkar M, Gogoi R. Lipopolysaccharide induced anxiety- and depressive-like behaviour in mice are prevented by chronic pre-treatment of esculetin. *Neurosci Lett* 2016; **611**: 106-111 [PMID: 26620836 DOI: 10.1016/j.neulet.2015.11.031]

142 **Ji WW**, Wang SY, Ma ZQ, Li RP, Li SS, Xue JS, Li W, Niu XX, Yan L, Zhang X, Fu Q, Qu R, Ma SP. Effects of perillaldehyde on alternations in serum cytokines and depressive-like behavior in mice after lipopolysaccharide administration. *Pharmacol Biochem Behav* 2014; **116**: 1-8 [PMID: 24201050 DOI: 10.1016/j.pbb.2013.10.026]

143 **Yao W**, Zhang JC, Dong C, Zhuang C, Hirota S, Inanaga K, Hashimoto K. Effects of amycenone on serum levels of tumor necrosis factor-α, interleukin-10, and depression-like behavior in mice after lipopolysaccharide administration. *Pharmacol Biochem Behav* 2015; **136**: 7-12 [PMID: 26150007 DOI: 10.1016/j.pbb.2015.06.012]

144 **Mello BS**, Monte AS, McIntyre RS, Soczynska JK, Custódio CS, Cordeiro RC, Chaves JH, Vasconcelos SM, Nobre HV Jr, Florenço de Sousa FC, Hyphantis TN, Carvalho AF, Macêdo DS. Effects of doxycycline on depressive-like behavior in mice after lipopolysaccharide (LPS) administration. *J Psychiatr Res* 2013; **47**: 1521-1529 [PMID: 23835040 DOI: 10.1016/j.jpsychires.2013.06.008]

145 **Salazar A**, Gonzalez-Rivera BL, Redus L, Parrott JM, O'Connor JC. Indoleamine 2,3-dioxygenase mediates anhedonia and anxiety-like behaviors caused by peripheral lipopolysaccharide immune challenge. *Horm Behav* 2012; **62**: 202-209 [PMID: 22504306 DOI: 10.1016/j.yhbeh.2012.03.010]

146 **Heisler JM**, O'Connor JC. Indoleamine 2,3-dioxygenase-dependent neurotoxic kynurenine metabolism mediates inflammation-induced deficit in recognition memory. *Brain Behav Immun* 2015; **50**: 115-124 [PMID: 26130057 DOI: 10.1016/j.bbi.2015.06.022]

147 **Parrott JM**, Redus L, Santana-Coelho D, Morales J, Gao X, O'Connor JC. Neurotoxic kynurenine metabolism is increased in the dorsal hippocampus and drives distinct depressive behaviors during inflammation. *Transl Psychiatry* 2016; **6**: e918 [PMID: 27754481 DOI: 10.1038/tp.2016.200]

148 **Zhang JC**, Yao W, Hashimoto K. Brain-derived Neurotrophic Factor (BDNF)-TrkB Signaling in Inflammation-related Depression and Potential Therapeutic Targets. *Curr Neuropharmacol* 2016; **14**: 721-731 [PMID: 26786147 DOI: 10.2174/1570159x14666160119094646]

149 **Carniel BP**, da Rocha NS. Brain-derived neurotrophic factor (BDNF) and inflammatory markers: Perspectives for the management of depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2021; **108**: 110151 [PMID: 33096156 DOI: 10.1016/j.pnpbp.2020.110151]

150 **Pedard M**, Quirié A, Tessier A, Garnier P, Totoson P, Demougeot C, Marie C. A reconciling hypothesis centred on brain-derived neurotrophic factor to explain neuropsychiatric manifestations in rheumatoid arthritis. *Rheumatology (Oxford)* 2021; **60**: 1608-1619 [PMID: 33313832 DOI: 10.1093/rheumatology/keaa849]

151 **Kenis G**, Prickaerts J, van Os J, Koek GH, Robaeys G, Steinbusch HW, Wichers M. Depressive symptoms following interferon-α therapy: mediated by immune-induced reductions in brain-derived neurotrophic factor? *Int J Neuropsychopharmacol* 2011; **14**: 247-253 [PMID: 20667172 DOI: 10.1017/S1461145710000830]

152 **Uint L**, Bastos GM, Thurow HS, Borges JB, Hirata TDC, França JID, Hirata MH, Sousa AGMR. Increased levels of plasma IL-1b and BDNF can predict resistant depression patients. *Rev Assoc Med Bras (1992)* 2019; **65**: 361-369 [PMID: 30994834 DOI: 10.1590/1806-9282.65.3.361]

153 **Solati Z**, Jazayeri S, Tehrani-Doost M, Mahmoodianfard S, Gohari MR. Zinc monotherapy increases serum brain-derived neurotrophic factor (BDNF) levels and decreases depressive symptoms in overweight or obese subjects: a double-blind, randomized, placebo-controlled trial. *Nutr Neurosci* 2015; **18**: 162-168 [PMID: 24621065 DOI: 10.1179/1476830513Y.0000000105]

154 **Yang XH**, Song SQ, Xu Y. Resveratrol ameliorates chronic unpredictable mild stress-induced depression-like behavior: involvement of the HPA axis, inflammatory markers, BDNF, and Wnt/β-catenin pathway in rats. *Neuropsychiatr Dis Treat* 2017; **13**: 2727-2736 [PMID: 29138567 DOI: 10.2147/NDT.S150028]

155 **Tan X**, Du X, Jiang Y, Botchway BOA, Hu Z, Fang M. Inhibition of Autophagy in Microglia Alters Depressive-Like Behavior *via* BDNF Pathway in Postpartum Depression. *Front Psychiatry* 2018; **9**: 434 [PMID: 30349488 DOI: 10.3389/fpsyt.2018.00434]

156 **Guo J**, Lin P, Zhao X, Zhang J, Wei X, Wang Q, Wang C. Etazolate abrogates the lipopolysaccharide (LPS)-induced downregulation of the cAMP/pCREB/BDNF signaling, neuroinflammatory response and depressive-like behavior in mice. *Neuroscience* 2014; **263**: 1-14 [PMID: 24434771 DOI: 10.1016/j.neuroscience.2014.01.008]

157 **Li L**, Yu AL, Wang ZL, Chen K, Zheng W, Zhou JJ, Xie Q, Yan HB, Ren P, Huang X. Chaihu-Shugan-San and absorbed meranzin hydrate induce anti-atherosclerosis and behavioral improvements in high-fat diet ApoE$^{-/-}$ mice *via* anti-inflammatory and BDNF-TrkB pathway. *Biomed Pharmacother* 2019; **115**: 108893 [PMID: 31022598 DOI: 10.1016/j.biopha.2019.108893]

158 **Ren Z**, Yan P, Zhu L, Yang H, Zhao Y, Kirby BP, Waddington JL, Zhen X. Dihydromyricetin exerts a rapid antidepressant-like effect in association with enhancement of BDNF expression and inhibition of neuroinflammation. *Psychopharmacology (Berl)* 2018; **235**: 233-244 [PMID: 29058041 DOI: 10.1007/s00213-017-4761-z]

159 **Miao H**, Li R, Han C, Lu X, Zhang H. Minocycline promotes posthemorrhagic neurogenesis *via* M2 microglia polarization *via* upregulation of the TrkB/BDNF pathway in rats. *J Neurophysiol* 2018; **120**: 1307-1317 [PMID: 29790836 DOI: 10.1152/jn.00234.2018]

160 **Yang Y**, Song Y, Zhang X, Zhao W, Ma T, Liu Y, Ma P, Zhao Y, Zhang H. Ketamine relieves depression-like behaviors induced by chronic postsurgical pain in rats through anti-inflammatory, anti-oxidant effects and regulating BDNF expression. *Psychopharmacology (Berl)* 2020; **237**: 1657-1669 [PMID: 32125485 DOI: 10.1007/s00213-020-05490-3]

161   **Basu Mallik S**, Mudgal J, Hall S, Kinra M, Grant GD, Nampoothiri M, Anoopkumar-Dukie S, Arora D. Remedial effects of caffeine against depressive-like behaviour in mice by modulation of neuroinflammation and BDNF. *Nutr Neurosci* 2021; 1-9 [PMID: 33814004 DOI: 10.1080/1028415X.2021.1906393]

162   **Lotrich FE**, Albusaysi S, Ferrell RE. Brain-derived neurotrophic factor serum levels and genotype: association with depression during interferon-α treatment. *Neuropsychopharmacology* 2013; **38**: 985-995 [PMID: 23303061 DOI: 10.1038/npp.2012.263]

163   **Chan CB**, Ye K. Sex differences in brain-derived neurotrophic factor signaling and functions. *J Neurosci Res* 2017; **95**: 328-335 [PMID: 27870419 DOI: 10.1002/jnr.23863]

164   **Monteggia LM**, Luikart B, Barrot M, Theobold D, Malkovska I, Nef S, Parada LF, Nestler EJ. Brain-derived neurotrophic factor conditional knockouts show gender differences in depression-related behaviors. *Biol Psychiatry* 2007; **61**: 187-197 [PMID: 16697351 DOI: 10.1016/j.biopsych.2006.03.021]

165   **Derry HM**, Padin AC, Kuo JL, Hughes S, Kiecolt-Glaser JK. Sex Differences in Depression: Does Inflammation Play a Role? *Curr Psychiatry Rep* 2015; **17**: 78 [PMID: 26272539 DOI: 10.1007/s11920-015-0618-5]

166   **Moieni M**, Irwin MR, Jevtic I, Olmstead R, Breen EC, Eisenberger NI. Sex differences in depressive and socioemotional responses to an inflammatory challenge: implications for sex differences in depression. *Neuropsychopharmacology* 2015; **40**: 1709-1716 [PMID: 25598426 DOI: 10.1038/npp.2015.17]

167   **Han J**, Fan Y, Zhou K, Blomgren K, Harris RA. Uncovering sex differences of rodent microglia. *J Neuroinflammation* 2021; **18**: 74 [PMID: 33731174 DOI: 10.1186/s12974-021-02124-z]

168   **Xu Y**, Sheng H, Tang Z, Lu J, Ni X. Inflammation and increased IDO in hippocampus contribute to depression-like behavior induced by estrogen deficiency. *Behav Brain Res* 2015; **288**: 71-78 [PMID: 25907742 DOI: 10.1016/j.bbr.2015.04.017]

169   **Gomes C**, Ferreira R, George J, Sanches R, Rodrigues DI, Gonçalves N, Cunha RA. Activation of microglial cells triggers a release of brain-derived neurotrophic factor (BDNF) inducing their proliferation in an adenosine A2A receptor-dependent manner: A2A receptor blockade prevents BDNF release and proliferation of microglia. *J Neuroinflammation* 2013; **10**: 16 [PMID: 23363775 DOI: 10.1186/1742-2094-10-16]

170   **Schulte-Herbrüggen O**, Nassenstein C, Lommatzsch M, Quarcoo D, Renz H, Braun A. Tumor necrosis factor-alpha and interleukin-6 regulate secretion of brain-derived neurotrophic factor in human monocytes. *J Neuroimmunol* 2005; **160**: 204-209 [PMID: 15710474 DOI: 10.1016/j.jneuroim.2004.10.026]

171   **Tu Z**, Li Y, Dai Y, Li L, Lv G, Chen I, Wang B. MiR-140/BDNF axis regulates normal human astrocyte proliferation and LPS-induced IL-6 and TNF-α secretion. *Biomed Pharmacother* 2017; **91**: 899-905 [PMID: 28501777 DOI: 10.1016/j.biopha.2017.05.016]

172   **Zhang J**, Geula C, Lu C, Koziel H, Hatcher LM, Roisen FJ. Neurotrophins regulate proliferation and survival of two microglial cell lines in vitro. *Exp Neurol* 2003; **183**: 469-481 [PMID: 14552887 DOI: 10.1016/S0014-4886(03)00222-X]

173   **Zhang X**, Zeng L, Yu T, Xu Y, Pu S, Du D, Jiang W. Positive feedback loop of autocrine BDNF from microglia causes prolonged microglia activation. *Cell Physiol Biochem* 2014; **34**: 715-723 [PMID: 25171395 DOI: 10.1159/000363036]

174   **Joosten EA**, Houweling DA. Local acute application of BDNF in the lesioned spinal cord anti-inflammatory and anti-oxidant effects. *Neuroreport* 2004; **15**: 1163-1166 [PMID: 15129166 DOI: 10.1097/00001756-200405190-00016]

175   **Wu SY**, Pan BS, Tsai SF, Chiang YT, Huang BM, Mo FE, Kuo YM. BDNF reverses aging-related microglial activation. *J Neuroinflammation* 2020; **17**: 210 [PMID: 32664974 DOI: 10.1186/s12974-020-01887-1]

176   **Han R**, Liu Z, Sun N, Liu S, Li L, Shen Y, Xiu J, Xu Q. BDNF Alleviates Neuroinflammation in the Hippocampus of Type 1 Diabetic Mice *via* Blocking the Aberrant HMGB1/RAGE/NF-κB Pathway. *Aging Dis* 2019; **10**: 611-625 [PMID: 31165005 DOI: 10.14336/AD.2018.0707]

177   **Kim JM**, Stewart R, Kim JW, Kang HJ, Lee JY, Kim SY, Kim SW, Shin IS, Hong YJ, Ahn Y, Jeong MH, Yoon JS. Modifying effects of depression on the association between BDNF methylation and prognosis of acute coronary syndrome. *Brain Behav Immun* 2019; **81**: 422-429 [PMID: 31255678 DOI: 10.1016/j.bbi.2019.06.038]

178   **Jiang Y**, Wei N, Zhu J, Lu T, Chen Z, Xu G, Liu X. Effects of brain-derived neurotrophic factor on local inflammation in experimental stroke of rat. *Mediators Inflamm* 2010; **2010**: 372423 [PMID: 21490702 DOI: 10.1155/2010/372423]

179   **Makar TK**, Bever CT, Singh IS, Royal W, Sahu SN, Sura TP, Sultana S, Sura KT, Patel N, Dhib-Jalbut S, Trisler D. Brain-derived neurotrophic factor gene delivery in an animal model of multiple sclerosis using bone marrow stem cells as a vehicle. *J Neuroimmunol* 2009; **210**: 40-51 [PMID: 19361871 DOI: 10.1016/j.jneuroim.2009.02.017]

180   **Jiang Y**, Wei N, Lu T, Zhu J, Xu G, Liu X. Intranasal brain-derived neurotrophic factor protects brain from ischemic insult *via* modulating local inflammation in rats. *Neuroscience* 2011; **172**: 398-405 [PMID: 21034794 DOI: 10.1016/j.neuroscience.2010.10.054]

181   **Xu D**, Lian D, Wu J, Liu Y, Zhu M, Sun J, He D, Li L. Brain-derived neurotrophic factor reduces inflammation and hippocampal apoptosis in experimental Streptococcus pneumoniae meningitis. *J Neuroinflammation* 2017; **14**: 156 [PMID: 28778220 DOI: 10.1186/s12974-017-0930-6]

182   **Dugan AM**, Parrott JM, Redus L, Hensler JG, O'Connor JC. Low-Level Stress Induces Production of Neuroprotective Factors in Wild-Type but Not BDNF+/- Mice: Interleukin-10 and Kynurenic Acid. *Int J Neuropsychopharmacol* 2015; **19**: pyv089 [PMID: 26232788 DOI: 10.1093/ijnp/pyv089]

183   **Park HY**, Park C, Hwang HJ, Kim BW, Kim GY, Kim CM, Kim ND, Choi YH. 7,8-Dihydroxyflavone attenuates the release of pro-inflammatory mediators and cytokines in lipopolysaccharide-stimulated BV2 microglial cells through the suppression of the NF-κB and MAPK signaling pathways. *Int J Mol Med* 2014; **33**: 1027-1034 [PMID: 24535427 DOI: 10.3892/ijmm.2014.1652]

184   **Guan Z**, Fang J. Peripheral immune activation by lipopolysaccharide decreases neurotrophins in the cortex and hippocampus in rats. *Brain Behav Immun* 2006; **20**: 64-71 [PMID: 15922558 DOI: 10.1016/j.bbi.2005.04.005]

185   **Golia MT**, Poggini S, Alboni S, Garofalo S, Ciano Albanese N, Viglione A, Ajmone-Cat MA, St-Pierre A, Brunello N, Limatola C, Branchi I, Maggi L. Interplay between inflammation and neural plasticity: Both immune activation and suppression impair LTP and BDNF expression. *Brain Behav Immun* 2019; **81**: 484-494 [PMID: 31279682 DOI: 10.1016/j.bbi.2019.07.003]

186   **Wu SY**, Wang TF, Yu L, Jen CJ, Chuang JI, Wu FS, Wu CW, Kuo YM. Running exercise protects the substantia nigra dopaminergic neurons against inflammation-induced degeneration *via* the activation of BDNF signaling pathway. *Brain Behav Immun* 2011; **25**: 135-146 [PMID: 20851176 DOI: 10.1016/j.bbi.2010.09.006]

187   **Cortese GP**, Barrientos RM, Maier SF, Patterson SL. Aging and a peripheral immune challenge interact to reduce mature brain-derived neurotrophic factor and activation of TrkB, PLCgamma1, and ERK in hippocampal synaptoneurosomes. *J Neurosci* 2011; **31**: 4274-4279 [PMID: 21411668 DOI: 10.1523/JNEUROSCI.5818-10.2011]

188   **Tong L**, Balazs R, Soiampornkul R, Thangnipon W, Cotman CW. Interleukin-1 beta impairs brain derived neurotrophic factor-induced signal transduction. *Neurobiol Aging* 2008; **29**: 1380-1393 [PMID: 17467122 DOI: 10.1016/j.neurobiolaging.2007.02.027]

189   **Lapchak PA**, Araujo DM, Hefti F. Systemic interleukin-1 beta decreases brain-derived neurotrophic factor messenger RNA expression in the rat hippocampal formation. *Neuroscience* 1993; **53**: 297-301 [PMID: 8492907 DOI: 10.1016/0306-4522(93)90196-m]

190   **Barrientos RM**, Sprunger DB, Campeau S, Higgins EA, Watkins LR, Rudy JW, Maier SF. Brain-derived neurotrophic factor mRNA downregulation produced by social isolation is blocked by intrahippocampal interleukin-1 receptor antagonist. *Neuroscience* 2003; **121**: 847-853 [PMID: 14580934 DOI: 10.1016/S0306-4522(03)00564-5]

191   **Barrientos RM**, Sprunger DB, Campeau S, Watkins LR, Rudy JW, Maier SF. BDNF mRNA expression in rat hippocampus following contextual learning is blocked by intrahippocampal IL-1beta administration. *J Neuroimmunol* 2004; **155**: 119-126 [PMID: 15342202 DOI: 10.1016/j.jneuroim.2004.06.009]

192   **Solano Fonseca R**, Mahesula S, Apple DM, Raghunathan R, Dugan A, Cardona A, O'Connor J, Kokovay E. Neurogenic Niche Microglia Undergo Positional Remodeling and Progressive Activation Contributing to Age-Associated Reductions in Neurogenesis. *Stem Cells Dev* 2016; **25**: 542-555 [PMID: 26857912 DOI: 10.1089/scd.2015.0319]

193   **Liu C**, Chan CB, Ye K. 7,8-dihydroxyflavone, a small molecular TrkB agonist, is useful for treating various BDNF-implicated human disorders. *Transl Neurodegener* 2016; **5**: 2 [PMID: 26740873 DOI: 10.1186/s40035-015-0048-7]

194   **Groth R**, Aanonsen L. Spinal brain-derived neurotrophic factor (BDNF) produces hyperalgesia in normal mice while antisense directed against either BDNF or trkB, prevent inflammation-induced hyperalgesia. *Pain* 2002; **100**: 171-181 [PMID: 12435470 DOI: 10.1016/S0304-3959(02)00264-6]

195   **Davis J**, Maes M, Andreazza A, McGrath JJ, Tye SJ, Berk M. Towards a classification of biomarkers of neuropsychiatric disease: from encompass to compass. *Mol Psychiatry* 2015; **20**: 152-153 [PMID: 25349167 DOI: 10.1038/mp.2014.139]

196   **Kauer-Sant'Anna M**, Kapczinski F, Andreazza AC, Bond DJ, Lam RW, Young LT, Yatham LN. Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. *Int J Neuropsychopharmacol* 2009; **12**: 447-458 [PMID: 18771602 DOI: 10.1017/S1461145708009310]

197   **Nagatsu T**, Mogi M, Ichinose H, Togari A. Changes in cytokines and neurotrophins in Parkinson's disease. *J Neural Transm Suppl* 2000; 277-290 [PMID: 11205147 DOI: 10.1007/978-3-7091-6301-6_19]

198   **Zhang XY**, Tan YL, Chen DC, Tan SP, Yang FD, Wu HE, Zunta-Soares GB, Huang XF, Kosten TR, Soares JC. Interaction of BDNF with cytokines in chronic schizophrenia. *Brain Behav Immun* 2016; **51**: 169-175 [PMID: 26407757 DOI: 10.1016/j.bbi.2015.09.014]

199   **Chen C**, Li X, Ge G, Liu J, Biju KC, Laing SD, Qian Y, Ballard C, He Z, Masliah E, Clark RA, O'Connor JC, Li S.   GDNF-expressing macrophages mitigate loss of dopamine neurons and improve Parkinsonian symptoms in MitoPark mice. Sci Rep 2018; 8: 5460 [PMID: 29615705 DOI: 10.1038/s41598-018-23795-4]

200   **Chen C**, Guderyon MJ, Li Y, Ge G, Bhattacharjee A, Ballard C, He Z, Masliah E, Clark RA, O'Connor JC, Li S. Non-toxic HSC Transplantation-Based Macrophage/Microglia-Mediated GDNF Delivery for Parkinson's Disease. *Mol Ther Methods Clin Dev* 2020; **17**: 83-98 [PMID: 31890743 DOI: 10.1016/j.omtm.2019.11.013]

201   **Parrott JM**, Porter GA, Redus L, O'Connor JC. Brain derived neurotrophic factor deficiency

exacerbates inflammation-induced anhedonia in mice. *Psychoneuroendocrinology* 2021; **134**: 105404 [PMID: 34601342 DOI: 10.1016/j.psyneuen.2021.105404]

Molecular typing of familial temporal lobe epilepsy

Chao Liu, Xiao-Zhi Qiao, Zi-Han Wei, Mi Cao, Zhen-Yu Wu, Yan-Chun Deng

ORCID number: Chao Liu 0000-0002-8154-918X; Xiao-Zhi Qiao 0000-0001-9604-4929; Zi-Han Wei 0000-0003-0299-5163; Mi Cao 0000-0002-9307-939X; Zhen-Yu Wu 0000-0003-2118-7372; Yan-Chun Deng 0000-0002-1281-8999.

Author contributions: Liu C and Qiao XZ drafted the manuscript; Wei ZH, Cao M and Wu ZY helped with information retrieval; Deng YC conceived this review and provided essential revisions; all authors reviewed the paper.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

Supported by the National Key R&D Program of China, Precision Medicine Program -Cohort Study on Nervous System Diseases, No. 2017YFC0907702.

Country/Territory of origin: China

Specialty type: Neurosciences

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Chao Liu, Xiao-Zhi Qiao, Zi-Han Wei, Mi Cao, Yan-Chun Deng, Department of Neurology, The First Affiliated Hospital of Air Force Medical University, Xi'an 710032, Shaanxi Province, China

Zhen-Yu Wu, Department of Anatomy, Histology and Embryology and K.K. Leung Brain Research Centre, School of Basic Medicine, Air Force Medical University, Xi'an 710032, Shaanxi Province, China

Corresponding author: Yan-Chun Deng, MD, PhD, Chief Doctor, Professor, Department of Neurology, The First Affiliated Hospital of Air Force Medical University, No. 127 Changle West Road, Xi'an 710032, Shaanxi Province, China. yanchund@fmmu.edu.cn

Abstract

The pathogenesis of temporal lobe epilepsy (TLE) was originally considered to be acquired. However, some reports showed that TLE was clustered in some families, indicating a genetic etiology. With the popularity of genetic testing technology, eleven different types of familial TLE (FTLE), including ETL1-ETL11, have been reported, of which ETL9-ETL11 had not yet been included in the OMIM database. These types of FTLE were caused by different genes/Loci and had distinct characteristics. ETL1, ETL7 and ETL10 were characterized by auditory, visual and aphasia seizures, leading to the diagnosis of familial lateral TLE. ETL2, ETL3 and ETL6 showed prominent autonomic symptom and automatism with or without hippocampal abnormalities, indicating a mesial temporal origin. Febrile seizures were common in FTLEs such as ETL2, ETL5, ETL6 and ETL11. ETL4 was diagnosed as occipitotemporal lobe epilepsy with a high incidence of migraine and visual aura. Considering the diversity and complexity of the symptoms of TLE, neurologists enquiring about the family history of epilepsy should ask whether the relatives of the proband had experienced unnoticeable seizures and whether there is a family history of other neurological diseases carefully. Most FTLE patients had a good prognosis with or without anti-seizure medication treatment, with the exception of patients with heterozygous mutations of the *CPA6* gene. The pathogenic mechanism was diverse among these genes and spans disturbances of neuron development, differentiation and synaptic signaling. In this article, we describe the research progress on eleven different types of FTLE. The precise molecular typing of FTLE would facilitate the diagnosis and treatment of FTLE and genetic counseling for this disorder.

Key Words: Temporal lobe epilepsy; Gene mutation; Gene locus; Phenotypes; Prognosis

Core Tip: Eleven types of familial temporal lobe epilepsy (FTLE) caused by single gene mutations or specific gene loci had been identified to date. The phenotype of FTLE was heterogenous and includes typical temporal lobe seizures and specific symptoms. We herein describe the etiology, inheritance, phenotype and prognosis of each type of FTLE and summarize their similarities and differences.

INTRODUCTION

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate two unprovoked seizures > 24 h apart[1]. Epilepsy could be classified as focal, generalized, combined generalized and focal, and unknown according to the origin of the seizures[2]. Epilepsy affected approximately 50 million people worldwide, among which up to 60%-70% of affected individuals had focal epilepsy[3, 4]. Epilepsy and its comorbidities, such as memory and psychiatric disorders, severely lower the quality of life of patients[5]. Temporal lobe epilepsy (TLE), including mesial TLE (MTLE) and lateral TLE (LTLE), was the most common type of focal epilepsy, especially in adults[6]. The causes of TLE were heterogeneous, and the overall prognosis of TLE was far from satisfactory[7].

The first description of an instance of familial TLE (FTLE) could be traced back to 1895, before TLE had been defined[8,9]. In 1994, Berkovic *et al*[10] provided the first report of familial TLE, in which four individuals in two generations were diagnosed with TLE. The family aggregation of TLE indicated a genetic etiology. Although the characteristics of TLE had been extensively studied, the genetic etiology of TLE remains unclear, and the incidence of FTLE were severely underestimated due to the high rates of misdiagnosis and missed diagnosis in individuals with subtle symptoms [11]. Leucine-rich glioma inactivated-1 (*LGI1*) mutations was identified in approximately 50% of families with LTLE and 3% of sporadic LTLE cases[12,13]. Those findings had led to the hypothesis that LTLE was commonly caused by gene mutations and promoted the exploration of the genetic causes of LTLE[14]. Seventy percent of MTLE cases were considered to be caused by hippocampal sclerosis (HS) and was drug-refractory[15]. Most patients with drug-refractory MTLE had to undergo costly surgery, although 30% of such patients experience relapse within two years[16]. Many reports had shown that HS and MTLE were inheritable[17,18]. The mechanism seemed polygenic and was affected by multiple factors[19]. Further exploration of the underlying pathogenic genes and molecular mechanisms was critical for precision medicine.

Eleven genes/Loci responsible for FTLE have been reported to date (Table 1), including the genes *LGI1*, carboxypeptidase A6 (*CPA6*), reelin (*RELN*), galanin and GMAP prepropeptide (*GAL*), DEP domain containing 5 (*DEPDC5*), microtubule associated monooxygenase, calponin and LIM domain containing 1 (*MICAL-1*) and sodium voltage-gated channel alpha subunit 1 (*SCN1A*), along with gene loci on chromosomes (Chr) 12q22-q23.3, 4q13.2-q21.3, 9q21-q22, and 3q25-q26. These genes were involved in different biological processes. In this article, we describe the research progress on eleven types of FTLE, ETL1-ETL11, caused by these genes/Loci, of which ETL9-ETL11 had not yet been recorded in the OMIM database.

ETL1, RELATED TO LGI1 GENE MUTATION

ETL1 (OMIM 600512) was first reported by Ottman *et al*[20] in a family in which 11 members in three generations had seizures, with most seizures having auditory features, suggesting a neocortical (or lateral) temporal lobe origin. Linkage analysis

Table 1 Eleven different types of familial temporal lobe epilepsy

Phenotype	OMIM ID	Gene/locus	Inheritance	Age at seizure onset (yr)	Seizure types	EEG	MRI	Epilepsy types	Prognosis	Ref.
ETL1	600512	LGI1	AD	4-50	Aud, Aph, FBTCS	T ea	Nor	LTLE	Responsive to ASM	[20,24, 25]
ETL2	608096	Chr12q22-q23.3	AD	0.75-35	FS, FBTCS; Cog, Aut	Nor, T ea	HM	MTLE	Responsive to ASM or SR	[27,28]
ETL3	611630	Chr4q13.2-q21.3	AD	5-18	Cog, FBTCS, FIAS	Nor, T ea	Nor	MTLE	Responsive to ASM or SR	[32]
ETL4	611631	Chr9q21-q22	AD	0.58-63	Focal Mot; Cog, Sen, Aut, FIAS, FBTCS	Nor	Nor	OTLE	Responsive to ASM or SR; migraine 5/Mo – 2/y	[33]
ETL5	614417	CPA6	AR	0.75-5	FS, FBECTS, FIAS	T ea	T atr, HS	TLE	Responsive to ASM or SR	[36]
			AD	1.25-23	FS	-	T atr	TLE	Drug-refractory	[36]
ETL6	615697	Chr3q25-q26	AD	3-46	FS, FIAS, Cog, Sen, Aut, FBTCS	Nor, T ea, sa	Nor	MTLE	Responsive to ASMs	[37]
ETL7	616436	RELN	AD	8-40	Vis, Aud, FBECTS, FIAS	T ea	Nor	LTLE	Responsive to ASM or SR	[38,40]
ETL8	616461	GAL	AD	13	FIAS, Cog, Sen, Aut, FBTCS	T ea	Nor	TLE	Responsive to ASM	[43]
ETL9	-	DEPDC5	AD	8-13	FS,Cog, Sen,focal Mot; FBECTS	T ea	Nor	TLE	Responsive to ASM	[44,46, 47]
ETL10	-	MICAL-1	AD	6-30	Aud, Aph, FBECTS	T or FT ea	Nor	LTLE	Responsive to ASM	[48]
ETL11	-	SCN1A	AD	10-13	FS, FIAS, Aut; focal Mot, FBECTS	T ea	HS	TLE	Responsive to ASM	[50]

AD: Autosomal dominant; Aph: Aphasia; AR: Autosomal recessive; ASMs: Anti-seizure medications; atr: Atrophy; Aud: Auditory; Aut: Autonomic; Chr: Chromosome; CPA6: Carboxypeptidase A6; Cog: Cognitive; DEPDC5: DEP domain containing 5; ea: Epileptic activity; EEG: Electroencephalogram; Emo: Emotional; ETL: Epilepsy, familial temporal lobe; FBCTS: Focal to bilateral tonic-clonic seizures; FIAS: Focal impaired awareness seizure; FS: Febrile seizures; FT: Frontotemporal; GAL: Galanin and GMAP prepropeptide; HM: Hippocampal malrotation; HS: Hippocampal sclerosis; LGI1: Leucine-rich glioma inactivated-1; LTLE: Lateral TLE; MICAL-1: Microtubule associated monooxygenase, calponin and LIM domain containing 1; MTLE: Mesial TLE; Mot: Motor; MRI: Magnetic Resonance Imaging; Nor: Normal; OTLE: Occipitotemporal lobe Epilepsy; RELN: Reelin; sa: Slow activity; SCN1A: Sodium voltage-gated channel alpha subunit 1; Sen: Sensory; SR: Spontaneous remission; T: Temporal; TLE: Temporal lobe Epilepsy; Vis: Visual.

revealed that the candidate epilepsy gene was located on Chr 10q22–q24. In 2002, an *LGI1* gene mutation on Chr 10q22–q24 was identified as the pathogenic cause[21]. LGI1 is a 60-kDa secreted protein that is predominantly expressed in neuronal cells in the brain and is involved in cortical neuronal migration, neuronal excitability and synaptic transmission. *LGI1* mutations could lead to protein folding failure and destroy the interaction with its ligand, *ADAM22*[22].

More than 40 *LGI1* variants related to ETL1 had been detected to date[23]. The variants were usually inherited from the affected parents and were rarely de novo, and the overall penetrance of the disorder was 61%-67%. The age of seizure onset was 4-50 years, usually 12-30 years[24]. Auditory and/or sensory aphasia seizures were the most common seizure types, and interictal electroencephalogram (EEG) showed temporal lobe origin, which supports the diagnosis of LTLE. The auditory symptoms ranged from unformed sounds, such as humming and ringing, to distortions and volume changes. Autonomic symptoms were less common. Most patients had experienced focal to bilateral tonic-clonic seizures (FBCTS). The prognosis was good with anti-seizure medications (ASMs), such as phenytoin and carbamazepine[25]. Some research has shown that treatment with the chemical corrector 4-phenylbutylate

ameliorates the increased seizure susceptibility of *LGI1* mutant mice, which provides potential new therapeutic options for *LGI1*-mediated epilepsy[26].

ETL2, RELATED TO THE 12Q22-Q23.3 LOCUS

Depondt *et al*[27] reported a 5-generation family in which 22 members had TLE and febrile seizures without HS. Claes *et al*[28] linked this phenotype, namely, ETL2 (OMIM 608096), to Chr 12q22-q23.3, which includes 280 genes. ETL2 was autosomal dominant inherited, and the penetrance was approximately 80%. Those patients had a high incidence of febrile seizures, and all febrile seizures disappeared before 6 years of age. The mean age at onset of afebrile seizures was 8 years. The most common seizure types included focal seizures with or without impaired awareness, such as sensation in the head, fear, confusion and viscerosensory and tonic-clonic seizures. Ten of the patients were diagnosed with MTLE. Hippocampal malrotation was common in this family, even in individuals without seizures. The prognosis was good, with 11 individuals experiencing spontaneous remission. In addition, there was a report of a family in which seven members had febrile seizures that evolved to tonic-clonic seizures. The genetic linkage analysis mapped to Chr 12q22-q23.3[29]. Recently, Maria *et al*[30] reported a sporadic case with TLE and febrile seizures who had a 12 Mb duplication at Chr12q22-q23.3. She presented with growth retardation. Her seizure was well controlled with carbamazepine. These findings indicated that Chr 12q22-q23.3 had a broad phenotypic spectrum, similar to most well-known epileptogenic genes[31]. The symptoms of patients from the same family showed high similarity, which might be related to the common mutation sites and genetic backgrounds. The exact pathogenic mechanism required further research.

ETL3, RELATED TO THE 4Q13.2-Q21.3 LOCUS

Hedera *et al*[32] reported a 4-generation family in which 11 individuals were diagnosed with MTLE or ETL3 (OMIM 611630). Linkage analysis mapped the phenotype to Chr 4q13.2-q21.3, which include 359 genes without homology to the well-known epileptic genes. ETL3 showed autosomal dominant inheritance with incomplete penetrance. The age of seizure onset was 5-18 years and most patients were 10-20 years. Ten individuals had focal cognitive seizures with feelings of déjà vu associated with dizziness or nausea, and 8 also had focal seizures with altered awareness and staring. Four individuals had FBCTS. Brain magnetic resonance imaging (MRI) was performed on 3 patients and the findings were not significant. EEG was performed on 6 patients, of whom 5 patients exhibited normal EEG and 1 had left anterior temporal sharp waves. Only 4 patients were treated with ASMs.

ETL4, RELATED TO THE 9Q21-Q22 LOCUS

ETL4 (OMIM 611631) was reported in a 5-generation family of which 14 individuals had occipitotemporal lobe epilepsy and migraine with visual aura[33]. Genome-wide linkage and haplotype analysis mapped the phenotype to Chr 9q21-q22, which include 604 genes. ETL4 was autosomal dominant and was inherited with a low penetrance of 75%. The age at seizure onset ranged from 7 mo to 63 years, and the median age was 21 years. Age at migraine onset ranged from 30 to 65 years, with a median age of 42 years. Ten individuals had occipitotemporal lobe epilepsy and 5 of them also had migraine with aura. Nine of the 10 patients had focal motor or nonmotor seizures, such as visual, autonomic, and somatosensory symptoms, olfactory and auditory hallucinations, and cognitive seizures excluding déjà vu. Three of the 10 patients had focal seizures with altered awareness and 3 had FBCTS. Four had a single isolated seizure, and 1 of them also had migraine with aura. Seizures and migraine attacks were temporally independent in all patients except one. EEG and brain MRI were normal except in 2 patients with age-related white matter changes.

Approximately 6% of migraine patients have seizures, and 8%-15% of epilepsy patients have migraines[34]. Tikka-Kleemola *et al*[35] reported that among 33 families of patients experiencing migraine with visual aura, 22 families were linked to Chr 9q21-q22. None of these family members had seizures. These findings indicated that epilepsy and migraine have a common genetic basis and that Chr 9q21-q22 was closely

related to epilepsy and migraine.

ETL5, RELATED TO CPA6 GENE MUTATION

Salzmann *et al*[36] reported four children with recessive familial forms of febrile seizures and TLE born to healthy first-cousin parents. A *CPA6* gene homozygous mutation was found associated with the phenotype and was named ETL5 (OMIM 614417). All 4 patients had febrile seizure onset before 4 years of age. One of them had TLE. His MRI showed right temporal atrophy, and EEG showed right temporal spikes and waves. They all became seizure-free with or without ASMs. In vitro research showed that *CPA6* variants reduced the level of protein expression and secretion and/or destroyed carboxypeptidase activity. Salzmann *et al*[36] also reported a sporadic case with drug-refractory TLE carrying compound heterozygous mutations in the *CPA6* gene. MRI showed cavernous malformation. His grandfather had a history of febrile seizures. Four unrelated patients with febrile seizures and refractory TLE carrying *CPA6* gene heterozygous mutations were also reported, suggesting that ETL5 was both recessively and dominantly inherited[36]. The seizure onset of these 4 patients ranged from 15 mo to 23 years of age. Among them, one had febrile seizures and left temporal lobe origin seizures with HS. His brother had a history of febrile seizures. Two patients had temporal lobe seizures originating from the temporo-parietal junction and bitemporal lobes. These two patients had neonatal sequelae and bitemporal atrophy on MRI. The last patient had febrile seizures, and his mother also had a history of febrile seizures. The prognosis of patients with homozygous mutations seemed to be better than that of patients with heterozygous mutations.

ETL6, RELATED TO THE 3Q25-Q26 LOCUS

Only one ETL6 (OMIM 615697) family had been reported to date by Chahine *et al*[37] in 2013. In the 4-generation family surveyed in the study, 7 individuals had TLE, and 4 had febrile seizures during childhood but no subsequent epilepsy. Genetic linkage analysis linked the phenotype to Chr 3q25-q26 containing 453 genes. ETL6 was autosomal dominant and inherited with incomplete penetrance. The age of onset of temporal seizures ranged from 3 to 46 years. The 4 patients with isolated febrile seizures had onset between 5 mo to 5 years of age. Seizure types included focal aware seizures, focal impaired awareness seizures, FBCTS and rarely status epilepticus. Many of the seizures were suggestive of a mesial temporal origin, and occurred with auras including abdominal discomfort, rising numbness, floating sensation, strange grabbing feeling, déjà vu and dizziness. Brain MRI, performed in 3 patients, was normal. EEG was normal except in 1 patient who exhibited sharp right temporal waves and irregular slow activity. The seizures of the patients were responsive to ASMs.

ETL7, RELATED TO RELN GENE MUTATION

Dazzo *et al*[38] identified seven different heterozygous missense mutations in the *RELN* gene in 7 unrelated families with LTLE or ETL7 (OMIM 616436). The RELN gene is crucial for the correct cytoarchitecture of laminated structures during embryonic development and modulates dendritic growth and synaptic plasticity in the postnatal and adult stages[39]. Their research revealed that the expression of reelin was reduced in the hippocampus of ETL7 patients and reelin promoter methylation was greater with severe granule cell dispersion, which supports a compromised reelin signaling pathway and identifies promoter methylation as an epigenetic mechanism in the pathogenesis of ETL7[38]. The clinical features of ETL7 were found to be similar to those of ETL1[40]. The mean age at seizure onset was 20 years. Seizure types included focal visual seizures, auditory seizures, déjà vu, FBTCS and focal seizures with impairment of consciousness. These patients were seizure-free with or without ASMs treatment. Previous work revealed that homozygous *RELN* gene mutations caused lissencephaly with cerebellar hypoplasia[41]. Three small consanguineous LCH-affected families had been reported thus far. The heterozygous individuals in these families exhibited reduced levels of reelin in their sera and were reported to be clinically normal[42]. The apparent normal phenotype of these individuals was

consistent with the low penetrance of *RELN* mutations.

ETL8, RELATED TO GAL GENE MUTATION

ETL8 (OMIM 616461) was reported by Guipponi *et al*[43] in a pair of monozygotic twin brothers with TLE carrying a heterozygous missense mutation in the *GAL* gene. The *GAL* gene encodes galanin, which is a neuropeptide highly expressed in the central nervous system. The mutant galanin identified in their study led to antagonistic activity against GALR1-mediated responses, decreased binding affinity and reduced agonist properties for GALR2 in vitro, suggesting that the variants impaired galanin signaling in the hippocampus and led to increased glutamatergic excitation[43]. The age of seizure onset was 13 years in both patients. Both had focal abdominal sensory seizures, incoherent speech, blurred vision, auditory hallucinations, slow ideation déjà vu and occasional FBCTS. Brain MRI findings were normal. Seizures were well controlled by ASMs.

ETL9, A DEPDC5- RELATED FTLE

In 2013, Shida *et al*[44] reported two families with TLE caused by *DEPDC5* gene heterogenous mutations. The patients had focal nonmotor and motor seizures and their interictal EEG showed slow waves and sharp waves in the temporal lobes[45]. DEPDC5 proteins have no homology with ion channel proteins. DEPDC5 protein formed a GATOR1 complex with NPRL2 and NPRL3, which inhibited the aggregation of mTORC1. In vitro, mutant mRNA products are degraded by the nonsense-mediated decay system, and DEPDC5 haploinsufficiency was likely to be the cause of the disease [44]. Striano *et al*[46] detected a *DEPDC5* gene nonsense mutation, p.Tyr306∗, in a family with two individuals diagnosed with MTLE. In the proband and her mother, the seizures were characterized by déjà vu, anxiety, derealization and epigastric sensation. During follow-up, the proband showed significant auditory seizures weekly, suggesting a diagnosis of LTLE[47]. The reports to date indicated that the phenotype of *DEPDC5*-related TLE was variable and that *DEPDC5* variants were responsible for both MTLE and LTLE.

ETL10, AN MICAL-1-RELATED FAMILIAL LTLE

Dazzo *et al*[48] identified three different *MICAL-1* gene heterozygous missense mutations in three LTE families without *LGI1* or *RELN* gene mutations. The *MICAL-1* gene is expressed ubiquitously, with higher expression levels in the embryonic and nervous systems. In vitro, the variants significantly increased *MICAL-1* oxidoreductase activity and induced cell contraction, which likely resulted from deregulation of F-actin dynamics[49]. These results suggested that the dysregulation of actin cytoskeleton dynamics was a likely mechanism by which *MICAL-1* gene pathogenic variants led to LTE. The seizure onset age was 6-30 years, with most patients experiencing onset at 6-10 years. Affected individuals had auditory auras and some of them had aphasic symptoms. Most patients had FBCTS. EEG revealed temporal or fronto-temporal abnormal epileptic activity. Their 1.5-Tesla brain MRI scans were unremarkable. Seizures were well controlled with ASMs such as carbamazepine, methylhydantoin and vigabatrin.

ETL11, AN SCN1A-RELATED FTLE

In 2007, a southern Italian family was reported by Colosimo *et al*[50], in which 13 members over 3 generations had febrile seizures and TLE associated with the *SCN1A* p.M145T mutation. The *SCN1A* gene encodes the alpha subunit of the NaV1.1 sodium channel and is highly expressed in the central nervous system. *SCN1A* gene mutations were associated with a broad spectrum of epilepsy phenotypes and were commonly reported in epilepsies characterized by frequent febrile seizures during childhood; few had been reported in TLE[51]. The *SCN1A* p.M145T mutation was the first missense mutation found in DIS1 of *SCN1A* and caused a loss of function of the NaV1.1 channel

[52]. All 13 living members had febrile seizures onset from 5 to 45 mo. Nine subjects were affected with only febrile seizures and had normal EEG. Three individuals later developed TLE with epileptiform temporal spikes on EEG, and two of them had HS. The onset age of TLE was 10-13 years. Seizure types included focal seizures with or without awareness and rare nocturnal FBCTS. Seizures in the patient without HS were completely controlled with valproate. Seizures in 1 patient with HS were well controlled with the combination of carbamazepine and primidone. In another patient with HS, seizures continued despite treatment with the combination of topiramate and phenobarbital.

CONCLUSION

FTLE was always underestimated due to itsheterogeneous intrafamily clinical manifestations. Some family members with subtle symptoms had not received a diagnosis of epilepsy prior to detailed enquiry by a neurologist[11]. Eleven types of FTLE have been identified thus far (Table 1).

In addition to typical temporal lobe seizures, special phenotypes also exist within some types of FTLE, such as migraine and febrile seizures. In 2000, Gambardella *et al* [53] reported a family with ETL4, in which migraine was a common phenotype among the TLE patients. Chr. 9q21-q22, harboring 604 genes, was correlated with both migraine and ETL4. Understanding of the pathogenetic mechanisms requires the identification of the genes responsible for the phenotype. ETL2, ETL5, ETL6 and ETL11 were associated with a high incidence of febrile seizures, which was also found to be a prominent feature in a number of genetically determined epilepsy cases[54]. Febrile seizures affect approximately 3% of children and increase the risk of developing HS [55]. Moreover, febrile seizures and TLE were associated with common genetic variation, such as the *CPA6* and *SCN1A* genes[36,56]. The prognosis of FTLE with a high incidence of febrile seizures was almost good. However, in some patients with genetically based MTLE-HS and histories of febrile seizures, the prognosis was poor, and the underlying pathogenic genes remain unknown[57]. A growing number of studies had proven that HS and MTLE had polygenic or multifactorial modes of inheritance. The mechanism involves neuron development, differentiation, synaptic signaling, immune response and vascular development, which might provide directions for therapy of MTLE-HS[19].

LTLE was mostly genetic in etiology related to *LGI1*, *RELN*, *MICAL-1* and *DEPDC5* gene mutations. *LGI1* and *RELN* mutations were reported in approximately 35 and 17.5 % of LTLE families respectively[12,38]. The phenotypes of familial LTLE caused by pathogenic mutations of the *LGI1*, *RELN* and *MICAL-1* genes were similar. However, the molecular functions of these genes were discrepant, indicating that the mechanism of LTLE was complicated. Notably, some candidate loci were also gradually being recognized, such as the Chr 9q13.11–q13.31 Locus (not mentioned above), which was related to familial LTLE with a higher frequency of febrile seizures and migraine and a lower recurrence of focal to bilateral seizures than ETL1, ETL7 and ETL10[58].

Four gene loci on Chr 12q22-q23.3, 4q13.2-q21.3, 9q21-q22, and 3q25-q26, were closely related to FTLE. These loci each contain 280-604 genes, but the specific pathogenic genes for TLE had not yet been identified. Reports on each type of FTLE were rare, which limits our knowledge and hinders in-depth research. Reaching a complete understanding of the genetics of TLE is still a long-term prospect.

REFERENCES

1   **Fisher RS**, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, Engel J Jr. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 2005; **46**: 470-472 [PMID: 15816939 DOI: 10.1111/j.0013-9580.2005.66104.x]

2   **Scheffer IE**, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, Hirsch E, Jain S, Mathern GW, Moshé SL, Nordli DR, Perucca E, Tomson T, Wiebe S, Zhang YH, Zuberi SM. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017; **58**: 512-521 [PMID: 28276062 DOI: 10.1111/epi.13709]

3   **Thijs RD**, Surges R, O'Brien TJ, Sander JW. Epilepsy in adults. *Lancet* 2019; **393**: 689-701 [PMID: 30686584 DOI: 10.1016/s0140-6736(18)32596-0]

4   **Zhang X**, Huang Z, Liu J, Li M, Zhao X, Ye J, Wang Y. Phenotypic and Genotypic Characterization

of DEPDC5-Related Familial Focal Epilepsy: Case Series and Literature Review. *Front Neurol* 2021; **12**: 641019 [PMID: 34239491 DOI: 10.3389/fneur.2021.641019]

5   **Operto FF**, Pastorino GMG, Mazza R, Di Bonaventura C, Marotta R, Pastorino N, Matricardi S, Verrotti A, Carotenuto M, Roccella M. Social cognition and executive functions in children and adolescents with focal epilepsy. *Eur J Paediatr Neurol* 2020; **28**: 167-175 [PMID: 32718867 DOI: 10.1016/j.ejpn.2020.06.019]

6   **Labate A**, Aguglia U, Tripepi G, Mumoli L, Ferlazzo E, Baggetta R, Quattrone A, Gambardella A. Long-term outcome of mild mesial temporal lobe epilepsy: A prospective longitudinal cohort study. *Neurology* 2016; **86**: 1904-1910 [PMID: 27164663 DOI: 10.1212/wnl.0000000000002674]

7   **Roy PL**, Ronquillo LH, Ladino LD, Tellez-Zenteno JF. Risk factors associated with drug resistant focal epilepsy in adults: A case control study. *Seizure* 2019; **73**: 46-50 [PMID: 31734466 DOI: 10.1016/j.seizure.2019.10.020]

8   **Eadie M**. Familial temporal lobe epilepsy in the 19th century. *Seizure* 2018; **54**: 7-10 [PMID: 29172094 DOI: 10.1016/j.seizure.2017.11.010]

9   **Crichton-Browne J**.   The Cavendish Lecture: On Dreamy Mental States. Delivered Before the West London Medico-chirurgical Society. Baillière, Tindall and Cox; 1895

10   **Berkovic SF**. Familial temporal lobe epilepsy: a new syndrome with adolescent/adult onset and a benign course. *Epileptic Seizures and Syndromes* 1994; 257-263

11   **Pellinen J**, Tafuro E, Yang A, Price D, Friedman D, Holmes M, Barnard S, Detyniecki K, Hegde M, Hixson J, Haut S, Kälviäinen R, French J; Human Epilepsy Project Co-Investigators. Focal nonmotor *vs* motor seizures: The impact on diagnostic delay in focal epilepsy. *Epilepsia* 2020; **61**: 2643-2652 [PMID: 33078409 DOI: 10.1111/epi.16707]

12   **Ottman R**, Winawer MR, Kalachikov S, Barker-Cummings C, Gilliam TC, Pedley TA, Hauser WA. LGI1 mutations in autosomal dominant partial epilepsy with auditory features. *Neurology* 2004; **62**: 1120-1126 [PMID: 15079011 DOI: 10.1212/01.wnl.0000120098.39231.6e]

13   **Kesim YF**, Uzun GA, Yucesan E, Tuncer FN, Ozdemir O, Bebek N, Ozbek U, Iseri SA, Baykan B. Screening LGI1 in a cohort of 26 Lateral temporal lobe epilepsy patients with auditory aura from Turkey detects a novel de novo mutation. *Epilepsy Res* 2016; **120**: 73-78 [PMID: 26773249 DOI: 10.1016/j.eplepsyres.2015.12.006]

14   **Bisulli F**, Rinaldi C, Pippucci T, Minardi R, Baldassari S, Zenesini C, Mostacci B, Fanella M, Avoni P, Menghi V, Caporali L, Muccioli L, Tinuper P, Licchetta L. Epilepsy with auditory features: Contribution of known genes in 112 patients. *Seizure* 2021; **85**: 115-118 [PMID: 33453592 DOI: 10.1016/j.seizure.2020.12.015]

15   **Ayas S**, Kurtish SY, Tanrıverdi T, Yeni SN. Evaluation of patients with late-onset and medically refractory temporal lobe epilepsy with mesial temporal sclerosis. *Clin Neurol Neurosurg* 2020; **198**: 106209 [PMID: 32987311 DOI: 10.1016/j.clineuro.2020.106209]

16   **Schulz R**, Hoppe M, Boesebeck F, Gyimesi C, Pannek HW, Woermann FG, May T, Ebner A. Analysis of reoperation in mesial temporal lobe epilepsy with hippocampal sclerosis. *Neurosurgery* 2011; **68**: 89-97; discussion 97 [PMID: 21099715 DOI: 10.1227/NEU.0b013e3181fdf8f8]

17   **Andrade-Valença LP**, Valença MM, Velasco TR, Carlotti CG Jr, Assirati JA, Galvis-Alonso OY, Neder L, Cendes F, Leite JP. Mesial temporal lobe epilepsy: clinical and neuropathologic findings of familial and sporadic forms. *Epilepsia* 2008; **49**: 1046-1054 [PMID: 18294201 DOI: 10.1111/j.1528-1167.2008.01551.x]

18   **Cvetkovska E**, Kuzmanovski I, Babunovska M, Boshkovski B, Cangovska TC, Trencevska GK. Phenotypic spectrum in families with mesial temporal lobe epilepsy probands. *Seizure* 2018; **58**: 13-16 [PMID: 29605745 DOI: 10.1016/j.seizure.2018.03.019]

19   **Guelfi S**, Botia JA, Thom M, Ramasamy A, Perona M, Stanyer L, Martinian L, Trabzuni D, Smith C, Walker R, Ryten M, Reimers M, Weale ME, Hardy J, Matarin M. Transcriptomic and genetic analyses reveal potential causal drivers for intractable partial epilepsy. *Brain* 2019; **142**: 1616-1630 [PMID: 30932156 DOI: 10.1093/brain/awz074]

20   **Ottman R**, Risch N, Hauser WA, Pedley TA, Lee JH, Barker-Cummings C, Lustenberger A, Nagle KJ, Lee KS, Scheuer ML. Localization of a gene for partial epilepsy to chromosome 10q. *Nat Genet* 1995; **10**: 56-60 [PMID: 7647791 DOI: 10.1038/ng0595-56]

21   **Kalachikov S**, Evgrafov O, Ross B, Winawer M, Barker-Cummings C, Boneschi FM, Choi C, Morozov P, Das K, Teplitskaya E, Yu A, Cayanis E, Penchaszadeh G, Kottmann AH, Pedley TA, Hauser WA, Ottman R, Gilliam TC. Mutations in LGI1 cause autosomal-dominant partial epilepsy with auditory features. *Nature Genetics* 2002; **30**: 335-341

22   **Yamagata A**, Miyazaki Y, Yokoi N, Shigematsu H, Sato Y, Goto-Ito S, Maeda A, Goto T, Sanbo M, Hirabayashi M, Shirouzu M, Fukata Y, Fukata M, Fukai S. Structural basis of epilepsy-related ligand-receptor complex LGI1-ADAM22. *Nat Commun* 2018; **9**: 1546 [PMID: 29670100 DOI: 10.1038/s41467-018-03947-w]

23   **Yamagata A**, Fukai S. Insights into the mechanisms of epilepsy from structural biology of LGI1-ADAM22. *Cell Mol Life Sci* 2020; **77**: 267-274 [PMID: 31432233 DOI: 10.1007/s00018-019-03269-0]

24   **Michelucci R**, Pasini E, Nobile C. Lateral temporal lobe epilepsies: clinical and genetic features. *Epilepsia* 2009; **50** Suppl 5: 52-54 [PMID: 19469848 DOI: 10.1111/j.1528-1167.2009.02122.x]

25   **Dazzo E**, Santulli L, Posar A, Fattouch J, Conti S, Lodén-van Straaten M, Mijalkovic J, De Bortoli M, Rosa M, Millino C, Pacchioni B, Di Bonaventura C, Giallonardo AT, Striano S, Striano P, Parmeggiani A, Nobile C. Autosomal dominant lateral temporal epilepsy (ADLTE): novel structural

and single-nucleotide LGI1 mutations in families with predominant visual auras. *Epilepsy Res* 2015; **110**: 132-138 [PMID: 25616465 DOI: 10.1016/j.eplepsyres.2014.12.004]

26　**Yokoi N**, Fukata Y, Kase D, Miyazaki T, Jaegle M, Ohkawa T, Takahashi N, Iwanari H, Mochizuki Y, Hamakubo T, Imoto K, Meijer D, Watanabe M, Fukata M. Chemical corrector treatment ameliorates increased seizure susceptibility in a mouse model of familial epilepsy. *Nat Med* 2015; **21**: 19-26 [PMID: 25485908 DOI: 10.1038/nm.3759]

27　**Depondt C**, Van Paesschen W, Matthijs G, Legius E, Martens K, Demaerel P, Wilms G. Familial temporal lobe epilepsy with febrile seizures. *Neurology* 2002; **58**: 1429-1433 [PMID: 12011300 DOI: 10.1212/wnl.58.9.1429]

28　**Claes L**, Audenaert D, Deprez L, Van Paesschen W, Depondt C, Goossens D, Del-Favero J, Van Broeckhoven C, De Jonghe P. Novel locus on chromosome 12q22-q23.3 responsible for familial temporal lobe epilepsy associated with febrile seizures. *J Med Genet* 2004; **41**: 710-714 [PMID: 15342703 DOI: 10.1136/jmg.2004.019257]

29　**Gurnett CA**, Dobbs MB, Keppel CR, Pincus ER, Jansen LA, Bowcock AM. Additional evidence of a locus for complex febrile and afebrile seizures on chromosome 12q22-23.3. *Neurogenetics* 2007; **8**: 61-63 [PMID: 16972079 DOI: 10.1007/s10048-006-0063-z]

30　**Vari MS**, Traverso M, Bellini T, Madia F, Pinto F, Minetti C, Striano P, Zara F. De novo 12q22.q23.3 duplication associated with temporal lobe epilepsy. *Seizure* 2017; **50**: 80-82 [PMID: 28633043 DOI: 10.1016/j.seizure.2017.06.011]

31　**Wei Z**, Liu C, Wu Z, Cao M, Qiao X, Han T, Zhang Y, Liu Y, Deng Y. The prognosis of epilepsy patients with CACNA1H missense variants: A longitudinal cohort study. *Seizure* 2021; **91**: 52-59 [PMID: 34098317 DOI: 10.1016/j.seizure.2021.05.019]

32　**Hedera P**, Blair MA, Andermann E, Andermann F, D'Agostino D, Taylor KA, Chahine L, Pandolfo M, Bradford Y, Haines JL, Abou-Khalil B. Familial mesial temporal lobe epilepsy maps to chromosome 4q13.2-q21.3. *Neurology* 2007; **68**: 2107-2112 [PMID: 17377072 DOI: 10.1212/01.wnl.0000261246.75977.89]

33　**Teive HA**, Piovesan EJ, Kowacs PA, Werneck LC. Familial occipitotemporal lobe epilepsy and migraine with visual aura: linkage to chromosome 9q new evidence for a genetic link between epilepsy and migraine. *Neurology* 2008; **70**: 896; author reply 896-896; author reply 897 [PMID: 18332351 DOI: 10.1212/01.wnl.0000307659.43996.ca]

34　**Nye BL**, Thadani VM. Migraine and epilepsy: review of the literature. *Headache* 2015; **55**: 359-380 [PMID: 25754865 DOI: 10.1111/head.12536]

35　**Tikka-Kleemola P**, Artto V, Vepsäläinen S, Sobel EM, Räty S, Kaunisto MA, Anttila V, Hämäläinen E, Sumelahti ML, Ilmavirta M, Färkkilä M, Kallela M, Palotie A, Wessman M. A visual migraine aura locus maps to 9q21-q22. *Neurology* 2010; **74**: 1171-1177 [PMID: 20385888 DOI: 10.1212/WNL.0b013e3181d8ffcb]

36　**Salzmann A**, Guipponi M, Lyons PJ, Fricker LD, Sapio M, Lambercy C, Buresi C, Ouled Amar Bencheikh B, Lahjouji F, Ouazzani R, Crespel A, Chaigne D, Malafosse A. Carboxypeptidase A6 gene (CPA6) mutations in a recessive familial form of febrile seizures and temporal lobe epilepsy and in sporadic temporal lobe epilepsy. *Hum Mutat* 2012; **33**: 124-135 [PMID: 21922598 DOI: 10.1002/humu.21613]

37　**Chahine L**, Abou-Khalil B, Siren A, Andermann F, Hedera P, Ge Q, Andermann E, Pandolfo M. A new locus for familial temporal lobe epilepsy on chromosome 3q. *Epilepsy Res* 2013; **106**: 338-344 [PMID: 24021842 DOI: 10.1016/j.eplepsyres.2013.07.007]

38　**Dazzo E**, Fanciulli M, Serioli E, Minervini G, Pulitano P, Binelli S, Di Bonaventura C, Luisi C, Pasini E, Striano S, Striano P, Coppola G, Chiavegato A, Radovic S, Spadotto A, Uzzau S, La Neve A, Giallonardo AT, Mecarelli O, Tosatto SC, Ottman R, Michelucci R, Nobile C. Heterozygous reelin mutations cause autosomal-dominant lateral temporal epilepsy. *Am J Hum Genet* 2015; **96**: 992-1000 [PMID: 26046367 DOI: 10.1016/j.ajhg.2015.04.020]

39　**Faini G**, Del Bene F, Albadri S. Reelin functions beyond neuronal migration: from synaptogenesis to network activity modulation. *Curr Opin Neurobiol* 2021; **66**: 135-143 [PMID: 33197872 DOI: 10.1016/j.conb.2020.10.009]

40　**Michelucci R**, Pulitano P, Di Bonaventura C, Binelli S, Luisi C, Pasini E, Striano S, Striano P, Coppola G, La Neve A, Giallonardo AT, Mecarelli O, Serioli E, Dazzo E, Fanciulli M, Nobile C. The clinical phenotype of autosomal dominant lateral temporal lobe epilepsy related to reelin mutations. *Epilepsy Behav* 2017; **68**: 103-107 [PMID: 28142128 DOI: 10.1016/j.yebeh.2016.12.003]

41　**Hong SE**, Shugart YY, Huang DT, Shahwan SA, Grant PE, Hourihane JO, Martin ND, Walsh CA. Autosomal recessive lissencephaly with cerebellar hypoplasia is associated with human RELN mutations. *Nat Genet* 2000; **26**: 93-96 [PMID: 10973257 DOI: 10.1038/79246]

42　**Zaki M**, Shehab M, El-Aleem AA, Abdel-Salam G, Koeller HB, Ilkin Y, Ross ME, Dobyns WB, Gleeson JG. Identification of a novel recessive RELN mutation using a homozygous balanced reciprocal translocation. *Am J Med Genet A* 2007; **143A**: 939-944 [PMID: 17431900 DOI: 10.1002/ajmg.a.31667]

43　**Guipponi M**, Chentouf A, Webling KE, Freimann K, Crespel A, Nobile C, Lemke JR, Hansen J, Dorn T, Lesca G, Ryvlin P, Hirsch E, Rudolf G, Rosenberg DS, Weber Y, Becker F, Helbig I, Muhle H, Salzmann A, Chaouch M, Oubaiche ML, Ziglio S, Gehrig C, Santoni F, Pizzato M, Langel Ü, Antonarakis SE. Galanin pathogenic mutations in temporal lobe epilepsy. *Hum Mol Genet* 2015; **24**: 3082-3091 [PMID: 25691535 DOI: 10.1093/hmg/ddv060]

44　**Ishida S**, Picard F, Rudolf G, Noé E, Achaz G, Thomas P, Genton P, Mundwiller E, Wolff M,

Marescaux C, Miles R, Baulac M, Hirsch E, Leguern E, Baulac S. Mutations of DEPDC5 cause autosomal dominant focal epilepsies. *Nat Genet* 2013; **45**: 552-555 [PMID: 23542701 DOI: 10.1038/ng.2601]

45   **Picard F**, Baulac S, Kahane P, Hirsch E, Sebastianelli R, Thomas P, Vigevano F, Genton P, Guerrini R, Gericke CA, An I, Rudolf G, Herman A, Brice A, Marescaux C, LeGuern E. Dominant partial epilepsies. A clinical, electrophysiological and genetic study of 19 European families. *Brain* 2000; **123** (Pt 6): 1247-1262 [PMID: 10825362 DOI: 10.1093/brain/123.6.1247]

46   **Striano P**, Serioli E, Santulli L, Manna I, Labate A, Dazzo E, Pasini E, Gambardella A, Michelucci R, Striano S, Nobile C. DEPDC5 mutations are not a frequent cause of familial temporal lobe epilepsy. *Epilepsia* 2015; **56**: e168-e171 [PMID: 26216793 DOI: 10.1111/epi.13094]

47   **Pippucci T**, Licchetta L, Baldassari S, Palombo F, Menghi V, D'Aurizio R, Leta C, Stipa C, Boero G, d'Orsi G, Magi A, Scheffer I, Seri M, Tinuper P, Bisulli F. Epilepsy with auditory features: A heterogeneous clinico-molecular disease. *Neurol Genet* 2015; **1**: e5 [PMID: 27066544 DOI: 10.1212/nxg.0000000000000005]

48   **Dazzo E**, Rehberg K, Michelucci R, Passarelli D, Boniver C, Vianello Dri V, Striano P, Striano S, Pasterkamp RJ, Nobile C. Mutations in MICAL-1cause autosomal-dominant lateral temporal epilepsy. *Ann Neurol* 2018; **83**: 483-493 [PMID: 29394500 DOI: 10.1002/ana.25167]

49   **Luo J**, Xu Y, Zhu Q, Zhao F, Zhang Y, Peng X, Wang W, Wang X. Expression pattern of Mical-1 in the temporal neocortex of patients with intractable temporal epilepsy and pilocarpine-induced rat model. *Synapse* 2011; **65**: 1213-1221 [PMID: 21638339 DOI: 10.1002/syn.20961]

50   **Colosimo E**, Gambardella A, Mantegazza M, Labate A, Rusconi R, Schiavon E, Annesi F, Cassulini RR, Carrideo S, Chifari R, Canevini MP, Canger R, Franceschetti S, Annesi G, Wanke E, Quattrone A. Electroclinical features of a family with simple febrile seizures and temporal lobe epilepsy associated with SCN1A loss-of-function mutation. *Epilepsia* 2007; **48**: 1691-1696 [PMID: 17565594 DOI: 10.1111/j.1528-1167.2007.01153.x]

51   **Scheffer IE**, Nabbout R. SCN1A-related phenotypes: Epilepsy and beyond. *Epilepsia* 2019; **60** Suppl 3: S17-S24 [PMID: 31904117 DOI: 10.1111/epi.16386]

52   **Mantegazza M**, Gambardella A, Rusconi R, Schiavon E, Annesi F, Cassulini RR, Labate A, Carrideo S, Chifari R, Canevini MP, Canger R, Franceschetti S, Annesi G, Wanke E, Quattrone A. Identification of an Nav1.1 sodium channel (SCN1A) loss-of-function mutation associated with familial simple febrile seizures. *Proc Natl Acad Sci U S A* 2005; **102**: 18177-18182 [PMID: 16326807 DOI: 10.1073/pnas.0506818102]

53   **Gambardella A**, Messina D, Le Piane E, Oliveri RL, Annesi G, Zappia M, Andermann E, Quattrone A, Aguglia U. Familial temporal lobe epilepsy autosomal dominant inheritance in a large pedigree from southern Italy. *Epilepsy Res* 2000; **38**: 127-132 [PMID: 10642040 DOI: 10.1016/s0920-1211(99)00080-7]

54   **Kasperaviciute D**, Catarino CB, Matarin M, Leu C, Novy J, Tostevin A, Leal B, Hessel EV, Hallmann K, Hildebrand MS, Dahl HH, Ryten M, Trabzuni D, Ramasamy A, Alhusaini S, Doherty CP, Dorn T, Hansen J, Krämer G, Steinhoff BJ, Zumsteg D, Duncan S, Kälviäinen RK, Eriksson KJ, Kantanen AM, Pandolfo M, Gruber-Sedlmayr U, Schlachter K, Reinthaler EM, Stogmann E, Zimprich F, Théâtre E, Smith C, O'Brien TJ, Meng Tan K, Petrovski S, Robbiano A, Paravidino R, Zara F, Striano P, Sperling MR, Buono RJ, Hakonarson H, Chaves J, Costa PP, Silva BM, da Silva AM, de Graan PN, Koeleman BP, Becker A, Schoch S, von Lehe M, Reif PS, Rosenow F, Becker F, Weber Y, Lerche H, Rössler K, Buchfelder M, Hamer HM, Kobow K, Coras R, Blumcke I, Scheffer IE, Berkovic SF, Weale ME; UK Brain Expression Consortium, Delanty N, Depondt C, Cavalleri GL, Kunz WS, Sisodiya SM. Epilepsy, hippocampal sclerosis and febrile seizures linked by common genetic variation around SCN1A. *Brain* 2013; **136**: 3140-3150 [PMID: 24014518 DOI: 10.1093/brain/awt233]

55   **Moreira-Filho CA**, Bando SY, Bertonha FB, Iamashita P, Silva FN, Costa Lda F, Silva AV, Castro LH, Wen HT. Community structure analysis of transcriptional networks reveals distinct molecular pathways for early- and late-onset temporal lobe epilepsy with childhood febrile seizures. *PLoS One* 2015; **10**: e0128174 [PMID: 26011637 DOI: 10.1371/journal.pone.0128174]

56   **Perucca P**, Scheffer IE, Harvey AS, James PA, Lunke S, Thorne N, Gaff C, Regan BM, Damiano JA, Hildebrand MS, Berkovic SF, O'Brien TJ, Kwan P. Real-world utility of whole exome sequencing with targeted gene analysis for focal epilepsy. *Epilepsy Res* 2017; **131**: 1-8 [PMID: 28199897 DOI: 10.1016/j.eplepsyres.2017.02.001]

57   **Jobst BC**. It Goes Downhill From Here but Do Not Despair: Mesial Temporal Lobe Epilepsy Is a Progressive Disease, but It Can Be Benign. *Epilepsy Curr* 2016; **16**: 380-381 [PMID: 27857615 DOI: 10.5698/1535-7511-16.6.380]

58   **Bisulli F**, Naldi I, Baldassari S, Magini P, Licchetta L, Castegnaro G, Fabbri M, Stipa C, Ferrari S, Seri M, Gonçalves Silva GE, Tinuper P, Pippucci T. Autosomal dominant partial epilepsy with auditory features: a new locus on chromosome 19q13.11-q13.31. *Epilepsia* 2014; **55**: 841-848 [PMID: 24579982 DOI: 10.1111/epi.12560]

Emergence of bariatric psychiatry as a new subspecialty

Alfonso Troisi

ORCID number: Alfonso Troisi 0000-0002-3483-1318.

Author contributions: Troisi A conceived and wrote the review.

Conflict-of-interest statement: The author declares no conflict of interests for this article.

Country/Territory of origin: Italy

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Alfonso Troisi, Department of Systems Medicine, University of Rome Tor Vergata, Rome 00133, Italy

Corresponding author: Alfonso Troisi, MD, Associate Professor, Department of Systems Medicine, University of Rome Tor Vergata, Via Montpellier 1, Rome 00133, Italy. alfonso.troisi@uniroma2.it

Abstract

Bariatric surgery is the branch of surgery aimed at helping a person with obesity lose weight. The implementation of surgical treatment of obesity is growing at an impressive rate. As expected, the expanding implementation of bariatric procedures has progres-sively revealed critical issues that were not evident when the number of obese patients treated with surgery was relatively small. One critical issue is the importance of mental health assessment and care of bariatric patients. The aim of this review is to provide readers with an up-to-date summary of the goals, methods, and clinical strategies of bariatric psychiatry. The aims can be grouped into three distinct categories. First, to ascertain that there are no psychiatric contraindications to safe bariatric surgery. Second, to diagnose and treat pre-surgery mental conditions that could predict poor weight loss. Third, to diagnose and treat post-surgery mental conditions associated with poor quality of life. Although bariatric psychiatry has gained the status of a new subspecialty within the field of mental health and psychopathology, many clinical questions remain unsolved. We need more long-term data on outcome measures such as quality of life, adherence to behavioral guidelines, risk of suicide, and post-surgery prevalence of psychological disturbances and mental disorders.

Key Words: Bariatric surgery; Psychiatry; Weight loss; Mental health; Quality of life; Preoperative assessment; Postoperative follow-up

Core Tip: Bariatric psychiatry has gained the status of a new subspecialty within the field of mental health and psychopathology. The aims of bariatric psychiatry can be grouped into three distinct categories. First, to ascertain that there are no psychiatric contraindications to safe bariatric surgery. Second, to diagnose and treat pre-surgery mental conditions that could predict poor weight loss. Third, to diagnose and treat post-surgery mental conditions associated with poor quality of life. Future research should

focus on post-surgery quality of life, adherence to behavioral guidelines, risk of suicide, and prevalence of psychological disturbances and mental disorders.

INTRODUCTION

Bariatric surgery is the branch of surgery aimed at helping a person with obesity lose weight. Compared to traditional treatments of obesity (*e.g.*, diet, exercise, behavior modifications, and weight loss medications), bariatric surgery generally leads to more consistent outcomes in terms of significant and long-lasting weight loss, up to 30% of total body weight[1]. Another peculiarity of bariatric surgery is its favorable impact on metabolic complications associated with obesity (*e.g.*, type 2 diabetes). Thus, some reports refer to bariatric surgery as "weight and metabolic surgery".

Bariatric surgery includes different surgical procedures (*i.e.*, sleeve gastrectomy, Roux-en-Y gastric bypass abbreviated to RYGB, biliopancreatic diversion, adjustable gastric banding and intragastric balloons) almost always done *via* laparoscopic surgery. The implementation of surgical treatment of obesity is growing at an impressive rate. The data reported by the American Society for Metabolic and Bariatric Surgery (ASMBS) show that, in the years between 2011 and 2019, the number of patients who underwent weight loss surgery in the United States rose from 158000 to 256000[2]. The latest edition of the Global Registry published by the International Federation for the Surgery of Obesity and Related Disorders (IFSO, 2019) reports that worldwide operations increased from 100092 in 2014 to 833687 in 2019[3].

As expected, the expanding implementation of bariatric procedures has progressively revealed critical issues that were not evident when the number of obese patients treated with surgery was relatively small. One critical issue is the importance of mental health assessment and care of bariatric patients. Bariatric surgery is not a hit-and-run technical operation like many other surgical procedures. Rather, it is a "voyage" affecting patients' life for years. After surgery, patients experience major changes in their physiological functions, psychological processes, lifestyle habits, and social interactions. Therefore, they need extensive and prolonged interactions with mental health professionals that should start in the preoperative stage and continue throughout the postoperative years. In spite of their importance in the multi-disciplinary teams that take care of patients seeking weight-loss surgery, often psychologists and psychiatrists still play a marginal or poorly defined role in preoperative assessment and postoperative follow-up.

Fortunately, in the last decade, many studies focusing on a variety of aspects related to preoperative assessment and postoperative follow-up have partially reduced the gap between bariatric surgery and psychiatry. The body of evidence derived from these studies is so large and diverse to allow the conclusion that bariatric psychiatry has gained the status of a new subspecialty within the field of mental health and psychopathology[4].

The aim of this review is to provide readers with an up-to-date summary of the goals, methods, and clinical strategies of bariatric psychiatry. The review is organized as follows. The first section outlines the *raison d'être* of bariatric psychiatry. The following three sections summarize the clinical issues addressed by preoperative and postoperative psychiatric assessment. The final section focuses on the specific skills required to mental health professionals who take care of bariatric patients before and after surgery.

THE AIMS OF BARIATRIC PSYCHIATRY

It is unusual for patients undergoing surgical operations to be interviewed by a psychiatrist before surgery and to be re-evaluated over time after surgery. So, why should bariatric patients follow a different route from that usual for other surgical

patients? Most bariatric candidates ask such a question and need an explanation that clarifies the aims of mental health assessment. The aims can be grouped into three distinct categories. First, to ascertain that there are no psychiatric contraindications to safe bariatric surgery. Second, to diagnose and treat pre-surgery mental conditions that could predict poor weight loss. Third, to diagnose and treat post-surgery mental conditions associated with poor quality of life.

The definition of the three categories listed above has been a gradual acquisition since the rise of bariatric surgery. Initially, for many years, the only reason for mental health assessment was the exclusion of patients with psychiatric disorders that could increase the risk of medical complications. Later on, it became clear that the primary goal of bariatric surgery (*i.e.*, weight loss) was influenced by a variety of psychological and behavioral variables. As a result, the identification of these variables in the individual patient became an additional task for the examining psychiatrist. Still today, weight loss is the only measure of success in many follow-up studies focusing on the psychological predictors of bariatric outcome. Yet, in the last few years, researchers and clinicians have begun to pay greater attention to the post-surgery quality of life of patients. Successful bariatric surgery should not only be safe and cause significant weight loss but it should also improve patients' quality of life. Below, I will briefly discuss each of the three aims of contemporary bariatric psychiatry (Table 1).

DEFINING PSYCHIATRIC CONTRAINDICATIONS

Although, at the dawn of bariatric surgery, the definition of psychiatric contraindications was the only task of mental health assessment, still today there is no clear consensus among official guidelines regarding which psychiatric conditions merit recommending delay or denial of surgery. For example, the *Interdisciplinary European Guidelines on Metabolic and Bariatric Surgery*[5] list non-stabilized psychotic disorders, severe depression, personality and eating disorders, alcohol abuse or drug dependencies as definite contraindications to bariatric surgery. Likewise, the *Resource Document on Bariatric Surgery and Psychiatric Care* of the American Psychiatric Association[6] states: "*The most common reasons for deferring bariatric surgery are significant psychopathology such as active psychosis (including thought disorder symptoms), current substance dependence, untreated eating disorders (specifically anorexia nervosa or bulimia nervosa), untreated depression and/or active suicidal ideation.*" (p. 2). Yet, a diligent reading of these documents reveals that the sole presence of any particular psychiatric symptom or syndrome is not a sufficient element for contraindicating surgery because clinicians should make their determinations based on a more comprehensive assessment. The European document specifies that the conditions listed above are contraindications "*unless specifically advised by a psychiatrist experienced in obesity*" (p. 453) and the American document states that "*a psychiatric disorder per se should not be viewed as an exclusion criterion for bariatric surgery.*" (p. 2).

Regardless of the ambiguity of the recommendations reported by different guidelines, a fact that emerges clearly from the most recent reports addressing the issue of psychiatric contraindications is a progressive expansion of eligibility criteria [4]. Conditions that in the past were considered contraindications are now judged as compatible with bariatric surgery. Two reasons may explain such a progressive expansion of eligibility criteria. First, the decline in the medical complications associated with bariatric surgery[7]. Second, the emphasis on weight loss as the primary measure of successful outcome. Yet, the view that a psychiatric condition is a contraindication only if it increases medical risks and/or impairs weight loss is questionable. Such a permissive approach ignores the recent finding that, over a 10-year study period, there was an increase in mental health service presentations after surgery, particularly among those who had prior psychiatric illnesses[8].

We need standardized guidelines for psychiatric eligibility based on longitudinal data that focus not only on medical complications and weight loss but also on post-surgery mental health and quality of life. Standardized guidelines are needed to protect both patients and health professionals. The lack of unambiguous and agreed-upon recommendations specifying which individual factors turn a potential psychiatric contraindication into a manageable pre-surgery condition exposes evaluating clinicians to the risk of facing a medical malpractice lawsuit and charge them with the burden of deciding case-by-case.

Table 1 The aims of bariatric psychiatry
Aims of bariatric psychiatry
To ascertain that there are no psychiatric contraindications to safe bariatric surgery
To diagnose and treat pre-surgery mental conditions that predict poor weight loss
To diagnose and treat post-surgery mental conditions associated with poor quality of life

PREDICTING WEIGHT LOSS

Weight loss is the primary goal of bariatric psychiatry and the key measure of successful outcome. A recent study[9] defined a favorable weight loss response as ≥ 50% excess weight loss or ≥ 20% total weight loss. Among the wide range of individual variables that can impact weight loss, personality traits and psychiatric conditions play a relevant role.

Two recent systematic reviews have analyzed the relationship between personality traits and bariatric surgery outcomes[10,11]. Better weight loss response is predicted by a combination of different personality traits including high cooperativeness, high persistence, low novelty seeking, low impulsivity, an internal locus of control, a low tendency toward externalizing behaviors, a secure attachment style, and low levels of alexithymia. Each of these personality traits is associated with a variety of individual and social behaviors that promote successful postoperative treatment plans including the capacity and willingness to modify dietary habits, to increase levels of routine physical activity, to restrain alcohol consumption, and to attend monitoring appointments. Thus, during preoperative clinical interviews, personality assessment should integrate diagnostic procedures aimed at detecting the presence of those psychiatric syndromes that impact negatively on weight loss. Eating, depressive, and anxiety disorders are the psychiatric syndromes most analyzed by follow-up studies.

Obese patients seeking bariatric surgery have a high prevalence of eating disordered behavior. In particular, binge eating disorder (BED) is frequently diagnosed in bariatric candidates but there is no definitive evidence on the association between preoperative BED and weight loss outcomes after surgery. There are studies showing that patients with and without BED show similar outcomes in terms of after-surgery weight loss and weight regain[12]. However, other studies identified a diagnosis of BED as a negative predictor of outcome. Ivezaj et al[13] have described the "Bariatric Binge-Eating Disorder" (Bar-BED) defined as an eating pathology meeting all criteria for BED, except for the requirement of an unusually large amount of food. In their study, the outcome of patients who underwent sleeve gastrectomy surgery and developed Bar-BED was worse than the outcome of patients without such a diagnosis. Thus, it is likely that a pejorative impact of BED on bariatric outcome is exclusive to, or more frequent in, those patients who retain their pre-surgery eating pathology[14].

Whereas the relationship between eating disorders and the outcome of bariatric surgery has been largely investigated, fewer studies have analyzed the impact of preoperative depression and anxiety. Some studies based on small samples reported a negative association between baseline depression and postoperative weigh loss. For example, de Zwaan et al[15] found that the presence of a depressive disorder was significantly associated with a lower degree of weight loss at 24-36 mo, but not at 6-12 mo (n = 107). By contrast, Gill et al[16] concluded that preoperative depression scores did not predict outcomes of postoperative body mass index (BMI). A possible confounding variable is the chronological course of affective and mood symptoms. de Zwaan et al[15] reported a differential effect of lifetime and current anxiety disorders on weight loss. Whereas current anxiety disorders had no impact, lifetime anxiety disorders were of negative prognostic value for postoperative weight loss. However, when successful outcome is measured in terms of weight loss, the majority of prospective studies shows that the impact of preoperative anxiety is negligible[16].

MONITORING POST-SURGERY MENTAL HEALTH AND QUALITY OF LIFE

Bariatric surgery is a turning point in patients' lives. Patients are typically faced with initial dietary restrictions, permanent changes in eating and dietary habits, altered body sensations and experiences, shifting body image and self-care behaviors, new

cognitions and feelings, and an emerging and different lifestyle. In addition, they may sometimes realize unexpected and significant changes in relationships that may result in marked stress[17]. All these changes inevitably impact patients' mental health and quality of life, for better or worse. After an initial improvement in psychiatric symptoms and psychosocial functioning (the honeymoon phase lasting about 2 years), some patients show a progressive decline in their mental wellbeing. One of the major tasks of contemporary bariatric psychiatry is to improve our understanding of which individual variables can predict and explain such a biphasic post-surgery course.

Doubtless, pre-existing psychiatric disorders are a risk factor for post-surgery mental disturbance. The increase in mental health service presentations reported by Morgan *et al*[8] over a 10-year study period after surgery involved especially those patients who had prior psychiatric illnesses. Psychiatric disorders are common among patients seeking surgical treatment of obesity, as shown by Dawes *et al*[18] in their meta-analysis of 59 studies reporting the preoperative prevalence of mental health conditions in 65363 bariatric candidates. The three most common individual diagnoses, based on random-effects estimates of prevalence, were depression (19%), BED (17%) and anxiety disorders (12%). Whereas anxiety symptoms do not improve after surgery, eating pathology and depression tend to remit during the first 2 years and to recur thereafter[4].

The scope of preoperative assessment is not limited to psychiatric diagnosis and should be expanded to include patients' motivations and expectations. Poor satisfaction with surgery outcomes often derives from unrealistic expectations and may cause postoperative frustration, depression and opposition to implement behavioral changes[19]. In the preoperative phase, it is important to discuss and correct naïve hopes that surgery would simply "fix" things including bad eating habits without personal effort. Common beliefs among bariatric candidates are that they have lost control over their own diet and the ability to lose weight, and this control cannot be regained through personal effort. Choosing to undergo bariatric surgery is seen as a way to end the never-ending, unwinnable struggle with food and weight, and hand control over to a surgeon who will release them from obesity by changing how their body works[20]. If not modified, such a passive attitude may undermine patients' collaboration with postoperative treatment strategies.

Post-surgery decline in mental wellbeing is not necessarily related to unmet expectations about weight loss and eating behavior. Mental health professionals taking care of bariatric patients should be aware that weight loss is not the only variable making the difference in terms of psychological well-being. Personal characteristics can offset the psychological reward of weight loss. A good example is child maltreatment. Bariatric patients with a history of child maltreatment experience weight loss similar to those without histories of abuse. However, they often report greater levels of depression as well as mood and anxiety disorders both prior to and following surgery. Additionally, victims of childhood adverse experiences are more vulnerable to psychiatric hospitalizations and suicidal behavior following surgery, especially those who are suffering from mood or substance use disorders[21].

Another psychological variable largely independent from weight loss is body dissatisfaction. In most cases, body image improves after bariatric surgery. However, some aspects of body image do not improve with weight loss or do not reach norms (*e.g.*, average scores of people with BMIs in the normal range and no eating disorder). The way patients feel and think about their physical appearance may lag behind the rapid changes in weight and body shape following surgery. Thus, the process of rebuilding a positive body image may be lengthy and complicated, although a decrease of body dissatisfaction is generally expected after surgery[22].

Although symptoms reflecting anxiety, depression, disordered eating and body dissatisfaction require prompt diagnosis and treatment, the two most alarming psychiatric complications of bariatric surgery are suicide and addiction. There is a growing concern that post-bariatric surgery patients may have an increased risk for completed suicide, attempted suicide and self-harm compared to age-, sex-, and BMI-matched controls[23,24]. A variety of pre- and post-surgical psychosocial, pharmacokinetic, physiologic, and medical factors may be involved in increasing self-harm and suicide risk[25]. A meta-analysis published in 2019 and based on 32 studies with 148643 subjects reports the most recent data on completed suicide, attempted suicide and self-harm in post-bariatric surgery patients[26]. Mortality from suicide after bariatric surgery was 2.7 per 1000 patients and the suicide attempt/self-harm event rate was 17 per 1000 patients. The calculated event rate in post-bariatric surgery patients was eight times higher than average suicide rates in the general populations from countries with the highest suicide rates in the world. The strongest predictor of post-surgery risk was a lifetime history of suicide ideation and/or self-injurious

behavior. Therefore, preoperative assessment conducted by an expert mental health professional is crucial for effective prevention of self-harm and suicide in bariatric patients. The 2016 edition of the guidelines of the Italian Society of Bariatric Surgery [27] includes a lifetime history of attempted suicide among the absolute contraindications to bariatric surgery.

Post-surgery substance use disorders are emerging as one of the most critical psychiatric complications of bariatric surgery[28,29]. Long-term studies indicate that these problems tend to develop after a relatively long latency following surgery, typically about 1 year to 2 years after surgery, and some evidence suggests that the risk for onset of such problems continues to increase, rather than decrease, over many years following surgery[30]. Risk factors for post-surgery substance use disorders have been consistently described and include type of surgery, a personal history of substance use disorder, a family history of substance use disorder, a history of early trauma, pre-existing psychiatric disorders, low social support, younger age, male sex and alcohol sensitization after surgery. By contrast, the mechanisms linking bariatric surgery and substance use disorders are not fully understood. Several hypotheses have been advanced to explain post-surgery increased risk. Prevalent explanations focus on altered pharmacokinetics induced by the anatomical and physiological changes that result from surgical procedures. Addiction transfer is an alternative (or complementary) explanation. The hypothesis assumes that, being physically prevented from comfort eating after bariatric surgery, some patients employ substances or compulsive behaviors as a way to manage the problem of their unmet emotional and psychological needs.

WHY A SUBSPECIALTY?

The title of the present review elevates bariatric psychiatry to the rank of subspecialty. The emergence of a new medical subspecialty is justified if knowledge in the field expands so rapidly to impose the further specialization of clinicians. Subspecialization allows clinicians to focus their abilities and learn more about the best strategies to diagnose and treat patients with specific medical problems. Psychological assessment and care of bariatric patients have reached such a level of complexity to require dedicated programs conducted by mental health professionals with a high degree of expertise. This was clearly stated as early as 2004 by the American Society for Bariatric Surgery[31]: "*ASBS believes that the application and interpretation of objective tests, the ability to identify discrete risk factors not amenable to testing, as well as the capacity to conduct pertinent clinical interviews and to organize this information in a way that directly speaks to the adjustment of the individual after surgery requires a particular level and kind of experience that is specific to bariatric surgery.*" (p. 15).

I refer the reader to my recent book[5] for a detailed discussion of the clinical skills required to psychiatrists who take care of bariatric patients. Here, I will summarize the basic aspects that differentiate the clinical care of bariatric patients from standard psychiatric practice (Table 2).

The evaluating psychiatrist should be aware of the complexity of informed consent in bariatric psychiatry[32]. Patients should be able to articulate their rationale for surgery and why it is right at this time in their life. The psychiatrist should ascertain if the patient has a good understanding: (1) Of the nature and mechanics of surgery as well as the possible risks and complications of the procedure; and (2) Of what is expected postoperatively, including diet, exercise, follow-up, support group attendance, *etc.* If patients are unable to demonstrate a basic and clear understanding of these factors, they are referred back to the surgeon and/or nutritionist for additional counseling. It is clear that, in order to conduct an accurate investigation of patients' motivations and expectations, the evaluating psychiatrist should have a solid knowledge of the physiological and psychological changes caused by bariatric surgery.

Another critical aspect that makes preoperative evaluation different from standard psychiatric interview is the dependability of the information reported by patients. Bariatric surgery candidates tend to present themselves in an overly favorable light during the psychological evaluation. This response style is associated with less reporting of psychological problems and might interfere with the accurate assessment of patient mental condition[33]. Mental health professionals interviewing bariatric candidates should be trained to circumvent patients' reticence in sharing information that could make them not eligible for bariatric surgery. This can be made by explaining the importance of psychological assessment for postoperative long-term well-being and by assessing personality traits (*e.g.*, impulsivity or attachment style)

Table 2 Specific skills required to bariatric psychiatrists
Specific skills
Understanding the complexity of informed consent by bariatric candidates
Capacity to circumvent patients' reticence in sharing information that could make them not eligible for bariatric surgery
Ability to detect and diagnose problematic eating behaviors other than bulimia nervosa, anorexia nervosa and binge eating disorder
In-depth understanding of psychiatric medication absorption and altered pharmacokinetics after surgery, as well as the impact of psychiatric medication on weight loss

that, compared to symptoms, are less subjected to conscious alteration.

As explained previously, bariatric surgery candidates often report problematic and/or eating disordered behaviors. For most patients, these eating behaviors improve after surgery. A subset, however, experience a recurrence or new onset of problematic eating behaviors as early as 2 mo to 18 mo after surgery, which can result in compromised weight loss/excessive weight regain[34]. During standard diagnostic interviews, clinical psychiatrists generally limit their assessment to symptoms reflecting bulimia nervosa, anorexia nervosa or BED. When interviewing bariatric patients, the diagnostic scope should be widened to include other problematic eating behaviors that are not yet included in official classifications such as grazing, night eating, emotional eating, and food addiction.

Finally, psychiatric care of bariatric patients requires a solid background in psychopharmacology. Studies have estimated that approximately 35%-38% of bariatric surgery candidates were taking psychiatric medications before surgery[35]. Many of these patients continue to take psychotropic medications after surgery. The complex management of drug therapy after surgery require an in-depth understanding of psychiatric medication absorption and altered pharmacokinetics, as well as the impact of psychiatric medications on weight loss and psychiatric symptoms after surgery[36].

CONCLUSION

Bariatric psychiatry is on the move. The role of mental health professionals is currently more important than in the recent past and it is likely to gain even greater responsibility in the future. Yet, many clinical questions remain unsolved. We need more long-term data on outcome measures such as quality of life, adherence to behavioral guidelines, risk of suicide, and post-surgery prevalence of psychological disturbances and mental disorders. These data will be instrumental in deciding "how much psychiatry is too much" for bariatric patients. In fact, whereas some authors have argued for more intensive preoperative and postoperative psychosocial interventions [37], others have even criticized the requirement of preoperative psychological evaluation for all patients seeking bariatric surgery[38].

REFERENCES

1 **Shanti H**, Patel AG. Surgery for obesity. *Medicine* 2019; **47**: 184-187 [DOI: 10.1016/j.mpmed.2018.12.011]

2 **American Society for Metabolic and Bariatric Surgery**. Estimates of bariatric surgery numbers, 2011-2019. [cited 5 October 2021]. In: American Society for Metabolic and Bariatric Surgery [Internet]. Available from: https://asmbs.org/resources/estimate-of-bariatric-surgery-numbers

3 **Ramos A**, Kow L, Brown W, Wellbourne R, Dixon J, Kinsman R, Walton P. Fifth IFSO Global Registry Report 2019. Dendrite Clinical Systems Ltd, Henley-on-Thames, RG9 1AY

4 **Troisi A**. Bariatric Psychology and Psychiatry. Chan, Switzerland: Springer Nature, 2020 [DOI: 10.1007/978-3-030-44834-9]

5 **Fried M**, Yumuk V, Oppert JM, Scopinaro N, Torres AJ, Weiner R, Yashkov Y, Frühbeck G; European Association for the Study of Obesity; International Federation for the Surgery of Obesity - European Chapter. Interdisciplinary European Guidelines on metabolic and bariatric surgery. *Obes Facts* 2013; **6**: 449-468 [PMID: 24135948 DOI: 10.1159/000355480]

6 **Sockalingam S**, Micula-Gondek W, Lundblad W, Fertig AM, Hawa R; Council on Psychosomatic Medicine. Bariatric Surgery and Psychiatric Care. *Am J Psychiatry* 2017; **174**: 81-82 [PMID: 28041006 DOI: 10.1176/appi.ajp.2016.1731001]

7 **Rutledge T**, Ellison JK, Phillips AS. Revising the bariatric psychological evaluation to improve

clinical and research utility. *J Behav Med* 2020; **43**: 660-665 [PMID: 31127435 DOI: 10.1007/s10865-019-00060-1]

8   **Morgan DJR**, Ho KM, Platell C. Incidence and Determinants of Mental Health Service Use After Bariatric Surgery. *JAMA Psychiatry* 2020; **77**: 60-67 [PMID: 31553420 DOI: 10.1001/jamapsychiatry.2019.2741]

9   **Grover BT**, Morell MC, Kothari SN, Borgert AJ, Kallies KJ, Baker MT. Defining Weight Loss After Bariatric Surgery: a Call for Standardization. *Obes Surg* 2019; **29**: 3493-3499 [PMID: 31256357 DOI: 10.1007/s11695-019-04022-z]

10   **Bordignon S**, Aparício MJG, Bertoletti J, Trentini CM. Personality characteristics and bariatric surgery outcomes: a systematic review. *Trends Psychiatry Psychother* 2017; **39**: 124-134 [PMID: 28614435 DOI: 10.1590/2237-6089-2016-0016]

11   **Generali I**, De Panfilis C. Personality Traits and Weight Loss Surgery Outcome. *Curr Obes Rep* 2018; **7**: 227-234 [PMID: 30051313 DOI: 10.1007/s13679-018-0315-x]

12   **Kops NL**, Vivan MA, Fülber ER, Fleuri M, Fagundes J, Friedman R. Preoperative Binge Eating and Weight Loss After Bariatric Surgery: A Systematic Review and Meta-analysis. *Obes Surg* 2021; **31**: 1239-1248 [PMID: 33219919 DOI: 10.1007/s11695-020-05124-9]

13   **Ivezaj V**, Barnes RD, Cooper Z, Grilo CM. Loss-of-control eating after bariatric/sleeve gastrectomy surgery: Similar to binge-eating disorder despite differences in quantities. *Gen Hosp Psychiatry* 2018; **54**: 25-30 [PMID: 30056316 DOI: 10.1016/j.genhosppsych.2018.07.002]

14   **Niego SH**, Kofman MD, Weiss JJ, Geliebter A. Binge eating in the bariatric surgery population: a review of the literature. *Int J Eat Disord* 2007; **40**: 349-359 [PMID: 17304586 DOI: 10.1002/eat.20376]

15   **de Zwaan M**, Enderle J, Wagner S, Mühlhans B, Ditzen B, Gefeller O, Mitchell JE, Müller A. Anxiety and depression in bariatric surgery patients: a prospective, follow-up study using structured clinical interviews. *J Affect Disord* 2011; **133**: 61-68 [PMID: 21501874 DOI: 10.1016/j.jad.2011.03.025]

16   **Gill H**, Kang S, Lee Y, Rosenblat JD, Brietzke E, Zuckerman H, McIntyre RS. The long-term effect of bariatric surgery on depression and anxiety. *J Affect Disord* 2019; **246**: 886-894 [PMID: 30795495 DOI: 10.1016/j.jad.2018.12.113]

17   **Snyder AG**. Psychological assessment of the patient undergoing bariatric surgery. *Ochsner J* 2009; **9**: 144-148 [PMID: 21603431]

18   **Dawes AJ**, Maggard-Gibbons M, Maher AR, Booth MJ, Miake-Lye I, Beroes JM, Shekelle PG. Mental Health Conditions Among Patients Seeking and Undergoing Bariatric Surgery: A Meta-analysis. *JAMA* 2016; **315**: 150-163 [PMID: 26757464 DOI: 10.1001/jama.2015.18118]

19   **Ghaferi AA**, Varban OA. Setting Appropriate Expectations After Bariatric Surgery: Evaluating Weight Regain and Clinical Outcomes. *JAMA* 2018; **320**: 1543-1544 [PMID: 30326107 DOI: 10.1001/jama.2018.14241]

20   **Opolski M**, Chur-Hansen A, Wittert G. The eating-related behaviours, disorders and expectations of candidates for bariatric surgery. *Clin Obes* 2015; **5**: 165-197 [PMID: 26173752 DOI: 10.1111/cob.12104]

21   **Mitchell JE**, Crosby R, de Zwaan M, Engel S, Roerig J, Steffen K, Gordon KH, Karr T, Lavender J, Wonderlich S. Possible risk factors for increased suicide following bariatric surgery. *Obesity (Silver Spring)* 2013; **21**: 665-672 [PMID: 23404774 DOI: 10.1002/oby.20066]

22   **Ivezaj V**, Grilo CM. The complexity of body image following bariatric surgery: a systematic review of the literature. *Obes Rev* 2018; **19**: 1116-1140 [PMID: 29900655 DOI: 10.1111/obr.12685]

23   **Courcoulas A**. Who, Why, and How? *Ann Surg* 2017; **265**: 253-254 [PMID: 27735820 DOI: 10.1097/SLA.0000000000002037]

24   **Dixon JB**. Self-harm and suicide after bariatric surgery: time for action. *Lancet Diabetes Endocrinol* 2016; **4**: 199-200 [PMID: 26781231 DOI: 10.1016/S2213-8587(16)00013-9]

25   **Müller A**, Hase C, Pommnitz M, de Zwaan M. Depression and Suicide After Bariatric Surgery. *Curr Psychiatry Rep* 2019; **21**: 84 [PMID: 31410656 DOI: 10.1007/s11920-019-1069-1]

26   **Castaneda D**, Popov VB, Wander P, Thompson CC. Risk of Suicide and Self-harm Is Increased After Bariatric Surgery-a Systematic Review and Meta-analysis. *Obes Surg* 2019; **29**: 322-333 [PMID: 30343409 DOI: 10.1007/s11695-018-3493-4]

27   **Italian Society of Obesity Surgery and Metabolic Diseases**.   Linee guida di chirurgia dell'obesità. Edizione 2016. [cited 5 October 2021]. In: Italian Society of Obesity Surgery and Metabolic Diseases [Internet]. Available from: http://www.sicob.org/03_attivita/pubblicazioni_linee_guida.aspx

28   **Li L**, Wu LT. Substance use after bariatric surgery: A review. *J Psychiatr Res* 2016; **76**: 16-29 [PMID: 26871733 DOI: 10.1016/j.jpsychires.2016.01.009]

29   **King WC**, Chen JY, Courcoulas AP, Dakin GF, Engel SG, Flum DR, Hinojosa MW, Kalarchian MA, Mattar SG, Mitchell JE, Pomp A, Pories WJ, Steffen KJ, White GE, Wolfe BM, Yanovski SZ. Alcohol and other substance use after bariatric surgery: prospective evidence from a U.S. multicenter cohort study. *Surg Obes Relat Dis* 2017; **13**: 1392-1402 [PMID: 28528115 DOI: 10.1016/j.soard.2017.03.021]

30   **Ivezaj V**, Benoit SC, Davis J, Engel S, Lloret-Linares C, Mitchell JE, Pepino MY, Rogers AM, Steffen K, Sogg S. Changes in Alcohol Use after Metabolic and Bariatric Surgery: Predictors and Mechanisms. *Curr Psychiatry Rep* 2019; **21**: 85 [PMID: 31410716 DOI: 10.1007/s11920-019-1070-8]

31   **LeMont D**, Moorehead M, Parish M, Reto C, Ritz S.   Suggestions for the presurgical psychological

assessment of bariatric surgery candidates. [cited 5 October 2021]. In: American Society for Metabolic and Bariatric Surgery [Internet]. Available from: https://asmbs.org/app/uploads/2014/05/PsychPreSurgicalAssessment.pdf

32   **Wee CC**, Pratt JS, Fanelli R, Samour PQ, Trainor LS, Paasche-Orlow MK. Best practice updates for informed consent and patient education in weight loss surgery. *Obesity (Silver Spring)* 2009; **17**: 885-888 [PMID: 19396067 DOI: 10.1038/oby.2008.567]

33   **Ambwani S**, Boeka AG, Brown JD, Byrne TK, Budak AR, Sarwer DB, Fabricatore AN, Morey LC, O'Neil PM. Socially desirable responding by bariatric surgery candidates during psychological assessment. *Surg Obes Relat Dis* 2013; **9**: 300-305 [PMID: 21924688 DOI: 10.1016/j.soard.2011.06.019]

34   **Brode CS**, Mitchell JE. Problematic Eating Behaviors and Eating Disorders Associated with Bariatric Surgery. *Psychiatr Clin North Am* 2019; **42**: 287-297 [PMID: 31046930 DOI: 10.1016/j.psc.2019.01.014]

35   **Hawkins M**, Lee A, Leung S, Hawa R, Wnuk S, Yanofsky R, Sockalingam S. Prevalence and Factors Associated With Psychiatric Medication Use in Bariatric Surgery Candidates. *Psychosomatics* 2019; **60**: 449-457 [PMID: 30558795 DOI: 10.1016/j.psym.2018.11.007]

36   **Sockalingam S**, Leung SE, Wnuk S, Cassin SE, Yanofsky R, Hawa R. Psychiatric Management of Bariatric Surgery Patients: A Review of Psychopharmacological and Psychological Treatments and Their Impact on Postoperative Mental Health and Weight Outcomes. *Psychosomatics* 2020; **61**: 498-507 [PMID: 32451127 DOI: 10.1016/j.psym.2020.04.011]

37   **David LA**, Sijercic I, Cassin SE. Preoperative and post-operative psychosocial interventions for bariatric surgery patients: A systematic review. *Obes Rev* 2020; **21**: e12926 [PMID: 31970925 DOI: 10.1111/obr.12926]

38   **Morledge MD**, Pories WJ. Mental Health in Bariatric Surgery: Selection, Access, and Outcomes. *Obesity (Silver Spring)* 2020; **28**: 689-695 [PMID: 32202073 DOI: 10.1002/oby.22752]

Mental health promotion for elderly populations in World Health Organization South-East Asia Region: Needs and resource gaps

Nisha Mani Pandey, Rakesh Kumar Tripathi, Sujita Kumar Kar, K L Vidya, Nitika Singh

ORCID number: Nisha Mani Pandey 0000-0002-2198-7225; Rakesh Kumar Tripathi 0000-0003-3925-9821; Sujita Kumar Kar 0000-0003-1107-3021; K L Vidya 0000-0002-6521-2253; Nitika Singh 0000-0002-6834-8471.

Author contributions: Pandey NM conceptualized the topic, prepared an outline, and discussed the research question for writing the manuscript; Kar SK wrote the introduction; Pandey NM wrote about the approach adopted for preparing the manuscript; Singh N and Vidya KL were involved in data acquisition and contributed to writing two subsections of the manuscript; Tripathi RK prepared the discussion part; Pandey NM prepared the abstract and the core tip by Kar SK; all authors reviewed the article, gave their valuable input.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Country/Territory of origin: India

Specialty type: Health care sciences and services

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific

Nisha Mani Pandey, Rakesh Kumar Tripathi, K L Vidya, Department of Geriatric Mental Health, King George's Medical University, Lucknow 226003, Uttar Pradesh, India

Sujita Kumar Kar, Nitika Singh, Department of Psychiatry, King George's Medical University, Lucknow 226003, Uttar Pradesh, India

Corresponding author: Nisha Mani Pandey, PhD, Associate Professor, Department of Geriatric Mental Health, King George's Medical University, Shahmina Road Chowk, Lucknow 226003, Uttar Pradesh, India. nishamani@kgmcindia.edu

Abstract

The accelerated population growth of the elderly (individuals aged 60 years or more) across the globe has many indications, including changes in demography, health, the psycho-social milieu, and economic security. This transition has given rise to varied challenges; significant changes have been observed in regard to developing strategies for health care systems across the globe. The World Health Organization (WHO) is also engaging in initiatives and mediating processes. Furthermore, advocacy is being conducted regarding a shift toward the salutogenic model from the pathogenic model. The concept behind this move was to shift from disablement to enablement and from illness to wellness, with the notion of mental health promotion (MHP) being promoted. This article attempts to discuss the MHP of elderly individuals, with special reference to the need to disseminate knowledge and awareness in the community by utilizing the resources of the health sector available in the WHO South-East Asia Region countries. We have tried to present the current knowledge gap by exploring the existing infrastructure, human resources, and financial resources. There is much to do to promote the mental health of the elderly, but inadequate facilities are available. Based on available resources, a roadmap for MHP in elderly individuals is discussed.

Key Words: Mental health promotion; Elderly; Mental healthcare needs; Resource gaps; World health organization

Core Tip: In gross domestic product South-East Asia Region Organization (SEARO) countries, the aging population is increasing exponentially; with this increment, mental health issues and care needs are increasing drastically. The mental health promotion of elderly people needs adequate awareness, enough human resources and infrastructure, good psychosocial support, the use of innovations in care, research, and reasonable funding. The mental health care needs of the elderly in SEARO countries are tremendously high, and there is a considerable gap in terms of trained human resources and infrastructure. Thus, there is a need to recognize both at-risk activities and the current care deficiencies that need to be resolved in the right direction for the potential boom that we foresee occurring in the elderly population.

INTRODUCTION

Demographic scenario

The global population is aging, and life expectancy is following an increasing trend. With an increased global growth rate of the elderly population (aged 60 years and older), the mental health issues of this group need thoughtful attention. The enormous mental health morbidity in this population group gives rise to a higher number of consumers of mental health care services. Thus, mental health care needs are also increasing. As per the World Health Organization (WHO) report, the global elderly population is expected to double by 2050 from the baseline level reported in 2015[1]. It is likely that by 2050, four out of every five elderly individuals will be located in low- and middle-income countries[1]. By 2019, the number of people in the world who were older than 60 years was reportedly 1 billion; this number is expected to increase to 1.4 billion by 2030 and 2.1 billion by 2050[2]. As the number of elderly individuals in the South-East Asia Region Organization (SEARO) is increasing rapidly, their mental health care needs will also increase significantly in the days to come.

The era of MHP and healthy aging

Health promotion refers to the process that empowers a person to improve his or her strengths to retain health[3]. In contrast, MHP advocates maintaining one's psychological well-being by adopting a scheduled routine, lifestyle, and a helpful environment[4,5]. In the late 19th century, the concept of preventing illness by promoting health came into existence after a conference held in Ottawa[3]. Mental health promotion (MHP) for elderly individuals stipulates a procedure that attempts to develop an integrated approach for providing quality of life to the elderly population so that they can lead their life in a meaningful way with dignity. Studies suggest that socializing and upgrading one's emotional and functional potentials for MHP may be glorified[6].

The WHO's document entitled "*Decade of Healthy Aging 2021−2030*" discusses the concept of healthy aging and emphasizes enhancing the functional abilities of the elderly population to promote healthy aging[7]. This document also discusses the vision for healthy aging by 2030 and appeals to the government and various other stakeholders to invest in and monitor healthy aging among the general population in the community[7]. The global strategy and action plan for aging and health (2016–2020) emphasizes the long and healthy life of every elderly population in the world[8]. The Sustainable Development Goals (SDGs), adopted by the United Nations member states, emphasize the good health and well-being of every individual, including those who are elderly[9].

Including 11 member states (Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste), the SEARO is one of the most heavily populated regions of the world[10]. The WHO SEARO caters to nearly one-fourth of the global population and is primarily

affected by war, terrorism, political crisis, natural calamities, unemployment, and poverty[10]. The training for and teaching about geriatric mental health in the medical curriculum in South-East Asia are also inadequate, which affects the care of the elderly population[11]. Another major challenge of developing countries is that a large chunk of the geriatric population seeks help from nonqualified persons and traditional healers for their mental ailments[11]. Many South Asian countries, such as Japan, Singapore, China, Malaysia, and Thailand, have undertaken initiatives to develop country-specific policies to protect the rights of the elderly population and provide them with quality care[12]. The Ministry of Social Justice and Empowerment, Government of India, also developed a national policy for older persons in 1999, which was subsequently amended as per the needs of the elderly population[13].

Aging and mental health in the SEARO

The significant bulk of the population in the SEARO resides in India. In India, the elderly population comprises approximately 104 million individuals, which corresponds to 9% of the nation's total population[14]. It has been projected that by 2026, the elderly population (> 60 years) will rise to 14% of the total population, and by 2050, it is expected to be 19% of the total population[14].

Older adults globally face several challenges in regard to their deteriorating general physical health and increased risk of mental health issues, including neurocognitive disorders, loss of job, grief, loneliness, isolation, and abuse[14,15]. All these challenges compromise the quality of life of an individual. Commonly encountered mental health issues in the elderly are depression, other mood disorders and neurocognitive disorders[15-17]. Elderly populations are also victims of negatively expressed emotions[15].

There is a lack of resources and infrastructure for the care of the elderly population [18], which is evident in almost all WHO SEARO regions. In regard to the mental health care of the geriatric population, there are even fewer facilities[18]; the same/worse scenario is found everywhere in WHO SEARO countries. Generally, the geriatric population receives health care facilities from the general health care system, alternative medicine, home-based care, and other resources. Unfortunately, a more significant proportion of older adults are deprived of timely care for their health ailments[15].

The Mental health challenges of elderly

Existing shreds of evidence suggest a massive burden of mental health issues among the elderly population. However, in low-income countries, resource scarcity is more serious and affects the geriatric population's mental health care[19]. In South-East Asia, several countries fall into the group of low-income countries, and their health care systems struggle with the scarcity of human resources and infrastructure. It has also been reported that the prevailing infrastructure necessary to meet mental health care needs among the elderly is sparse in India[20]. As a result of this vast gap in health care delivery, the existing health care sectors are overburdened, and older adults in need of help are deprived of care. A significant chunk of people with dementia live in developing countries. It is expected that by 2040, the exponential growth of people living with dementia in South-East Asian countries will exceed 300% of the baseline figure reported in 2001[19]. It has also been reported that loneliness is commonly seen among 3/4th of older adults suffering from depression[20]. Furthermore, loneliness is a common issue among the elderly and is a well-known risk factor for depression. Thus, it may influence perceived social support among the elderly population.

Another challenge found in developing countries is the lack or poor implementation of policies and programs that facilitate the care and protection of the elderly[21]. However, some countries lack specified indicators or targets against which the implementation of these policies/programs could be monitored, and some places hardly have any existing programs. Resources in terms of budgetary allocations and physical and human infrastructure are also questionable in some WHO SEARO countries. Such problems may be resolved by promoting the mental health of the elderly population, which attempts to sustain the psychological well-being of elderly individuals by committed efforts, for which an in-depth need availability vis. a vis. gap analysis in terms of various domains, such as housing, safety, security, financial, psychosocial, emotional, health, and other ancillary needs, would be required. This article attempts to discuss the various dimensions of MHP for the aging population in WHO SEARO countries in view of the available mental health resources, needs, and existing gaps.

APPROACH ADOPTED TO UNDERSTAND MHP FOR AGING POPULATIONS IN WHO SEARO COUNTRIES

We aimed to accomplish this review with a broad focus on MHP, including general and specific questions that are suitable for a comprehensive analysis of the subject. We aimed to conduct this review research in view of our own experiences and the existing literature on the topic to explore the needs, available resources, and gaps. This led us to provide a roadmap for further developments in the field of MHP in elderly individuals. The review was conducted in a phasewise manner.

Stage 1-Preparatory phase: First, the corresponding author approached four mental health professionals with experience in the field and discussed writing the manuscript. After obtaining consent from each participating author, we performed two subsequent meetings. Subsequently, the following research questions were identified: what are the mental health issues of the elderly population in general, and generally, how are they handled? What is needed for the better mental health of the elderly population? What services are available to balance the mental health and well-being of the elderly population? What health promotion strategies exist to maintain the mental health of the elderly population? The discussion led to identifying our research topic. With consensus, the topic was finalized as "*Mental health promotion for the aging population in WHO SEARO countries: Needs and resource gaps.*" After identifying our review topic and question, we discussed the aim and objectives and finalized them. Then, decisions were made regarding strings to search the literature, time, and language.

Stage 2-Identification of related articles: With the help of keywords—mental health, promotion, and (older adults or Geriatrics or elderly)—two of the authors (VKL and NS) started including manuscripts (original and review) initially with the help of PubMed. A total of 195 articles were extracted from PubMed; of these, only six articles were suitable. Then, using an exact keyword search of articles, PubMed Central (PMC) was utilized. PMC revealed 51322 articles, and exploring articles from this huge bulk in a limited period was difficult; thus, the string was changed to MHP AND elderly OR Older adults AND WHO SEAR, which revealed 327 articles. Of these, only one article was found to be relevant. The selection of articles was limited to peer-reviewed and pragmatic research related to the goal of our study to make an evidence-based foundation to understand the MHP status in WHO SEARO countries.

Furthermore, as per the document's significance, a decision was made to include supplementary data from other sources. Documentation of the essential details was also performed simultaneously. The primary focus was on MHP, existing MHP programs, and related stakeholders. We tried to include almost all the articles and references with relevant documentation to avoid missing any related information obtained from the subsequent supplementary search.

MHP IN WHO SEARO COUNTRIES-THE STATUS

MHP needs: The WHO states that the basic tenet of MHP for the elderly population is active and healthy aging itself[22]. Peace, shelter, education, food, income, a stable ecosystem, sustainable resources, equity, and social justice are prerequisites for health. Health promotion is not just the health sector's responsibility; rather, it goes beyond healthy lifestyles to well-being[23]. With advancing age, few specific issues affect mental health, such as physical ailments, financial insecurity, and inadequate social support[24]. Promoting mental health in the elderly population depends on helping them meet these specific needs, such as financial security, adequate housing, social support, general health care, and protection against ageism and abuse[22]. Some of these needs are universal and address the whole population, while others are selected and as indicated, target those with significant risks[25]. Promoting general health, preventing disease, and managing chronic illnesses go a long way in promoting the mental health of the elderly population. Therefore, training all health providers in working with issues and disorders related to aging is essential. Effective, community-level primary mental health care for older people is crucial. Health care training, education, and support to the caregivers must be provided[22].

The WHO considers the scope for interventions that address the risk factors for poor health and modify unhealthy behaviors and functional status to promote the health of the elderly population in general. Strategies have been recommended in the manual for primary care physicians under Integrated Care for Older People (ICOPE) [26]. Apart from this, the WHO has also provided recommendations, strategies, and support to member states/government agencies at the global level under different comprehensive action plans, including health promotion in general and specific strategies for promoting mental health.

Resources available for MHP: To understand the needs of MHP, the overall resource gaps and the ways to mitigate them, it is necessary first to have a general overview of the available mental health resources available in all eleven SEARO countries.

Table 1 depicts the availability of facilities in terms of policy, plan, legislation, and budgetary allocations[27]. The table is generated based on the Mental Health Atlas of 2017 and information available about the SDGs of SEARO countries[27-38]. Table 1 reveals that except for the Maldives and Nepal, most countries spend 5% or less of their total gross domestic product (GDP).

Table 1 and Figure 1 also indicate that mental health policies or plans containing specified indicators or targets against which the implementation of these plans and policies can be monitored are present in most nations but not implemented in Bangladesh, the Maldives, and Sri Lanka. However, the stand-alone law for mental health is available in all SEAR countries except Bhutan, the Maldives, Myanmar, Nepal, and Timor-Leste. However, a dedicated authority or independent body to assess the compliance of mental health legislation with international human rights exists only in India, Korea, and Thailand. This also provides the periodic inspections of facilities and the partial enforcement of mental health legislation (Table 1 and Figure 1). Regarding the financial aspects, the government's total expenditure on mental health as a % of the total government health expenditure is also below par in most SEARO nations, ranging from as low as 0.30% in Thailand to 1.50% in India and 6% in Indonesia. The WHO recommends that the mental health budget accounts for 5%–15 % of a country's health care expenditures (Table 1).

Table 2 shows the mental health human resources (rate per 100000 population) of the SEARO countries[27]. The total mental health workers per 100000 population ranged from as low as 0.64 in Bhutan to 14.36 in Thailand, but the number of psychiatrists available per 1 Lakh population in all SEARO countries showed alarming data of even less than one, except in Korea and the Maldives, where it was 5.79 and 2.39, respectively. Additionally, among the psychiatrists available, those trained to deal appropriately with the complexities of geriatric mental health are scarce.

Table 3 shows the availability of physical infrastructure and its uptake in SEARO nations[27]. The outpatient facilities attached to a hospital and community-based/nonhospital mental health outpatient available are not on par per the population of these respective nations. It is also alarming that countries such as Bangladesh, Sri Lanka, and Nepal have such a considerable scarcity of mental hospitals. Table 3 shows that MHP and prevention strategies are not functional. Data regarding the existence of at least two functioning programs are not available for Indonesia, Myanmar, and Nepal.

The gap: Table 4 and Figures 2, 3.

The objective of MHP comprises those activities that can enhance one's psychological well-being. To improve the elderly population's psychological well-being, we need to have inclusive legislation, proper mental health services in terms of physical and human infrastructure, social and financial security, and an elderly individual-friendly environment. We have tried to search for such exclusively available resources, but there are hardly any in existence. Thus, we have considered overall the available facilities for mental health care and other services. The recommendations gap for overall human resources are estimated based on the available literature[18,39].

ROADMAP TO THE WAY FORWARD

The WHO recommendations for the ICOPE: To accomplish the MHP activities of the elderly, we have to look into the recommendations made by the WHO. These recommendations are related to various domains of individual life linked to essential and psychosocial, financial, and environmental amendments.

Nutrition and dietary advice: Although the requirement for energy declines with age, due to diminishing sensory faculties such as taste and smell and dental issues, the elderly population is at risk for malnutrition. Adequate protein and limited salt intake are recommended, and foods with antioxidant properties such as green, yellow, and orange vegetables and fruits are recommended. The typical nutritional deficiencies are iron, fiber, folic acid, vitamin C, vitamin D, vitamin B12, calcium, zinc, riboflavin, and vitamin A[40]. The intake of calcium and vitamin D found in milk, curds, cheese, small fish, and certain green vegetables is advised. Exposure to sunlight is necessary to make the skin produce vitamin D. The routine prescription of multivitamins to be avoided, but vegetarians require vitamin B12 supplementation[40]. These findings have implications for physical well-being, specifically in terms of preventing cognitive decline and maintaining mood. Further, older adults need proper and suitable remedies for their

Table 1 Existing health facilities with special reference to mental health (policy/plans/budgetary allocations) in World Health Organization South- East Asia Region Organization countries

Mental health policies and implementations	India	Bangladesh	Bhutan	Indonesia	Korea	Maldives	Myanmar	Nepal	Sri Lanka	Thailand	Timor-leste
Current health expenditure as share of GDP	3.6%	2.4%	3.5%	3.1%	Not found	10.6%	5.1%	6.3%	4.2%	3.7%	2.4%
Domestic general government health expenditure	3.1	3.4	8.3	8.3	-	20.2	4.8	5.3	8.6	15.3	3.2
Health worker density (per 10000 population)	27.5	8.3	19.3	24.4	81	50	17.9	33.5	31.7	38.15	25.04
Stand-alone policy or plan for mental health	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The mental health policy/plan	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Policy/plan in line with human rights covenants	5	4	3	5	4	5	4	5	4	5	4
Stand-alone law for mental health	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	No
Dedicated authority or independent body assessing the compliance	Yes	No	No	Not found	Yes	Not found	Nonfunctional	Not found	Not found	Irregular and partial	Not found
Law is in line with human rights covenants	5	2	2	5	3	Not found	Not found	Not found	5	4	5
Existence of at least two functioning programs	Yes	Yes	Yes	Not found	Yes	Not found	Not found	Not found	Yes	Yes	Yes
Existence of a suicide prevention strategy	No	No	Yes	Not found	Yes	No	No	No	Yes	Yes	Yes
Total mental health expenditure/-person (reported currency)	4 INR	2.4 BDT (2.0 INR)	6.73 BTN (6.73 INR)	Not found	76370.40 KRW (5014 INR)	Not found	58.92 MMK (3 INR)	Not found	Not found	46.48 THB (112.4 INR)	Not found
The government's expenditure on mental health as % of total health expenditure	1.30%	0.50%	0.30%	6.00%	3.80%	Not found	0.36%	Not found	Not found	0.30%	Not found

GDP: Gross domestic product; BDT: Currency code of Bangladesh; INR: Indian Ruppee; KRW: Korea won; MMK: Official currency of Myanmar; THB: Thailand Baht.

health and psychological wellbeing within their limits, which is hard to approach in low and middle-income countries[41].

Exercise: Compared to older individuals who exercise and those who do not, the former have better physical health and better cognitive functioning. Older people should perform at least 150 min of moderate-intensity aerobic physical activity throughout the week. When older people cannot perform the recommended amount of physical activity due to their health condition, they should be as physically active as their abilities and conditions allow[42]. A lower frequency of vigorous physical activity is significantly associated with higher rates of diagnosed depression in the elderly population[43].

Social support and interaction: Social networks and interactions help promote older people's mental health and prevent mental illness. Social support to promote health must provide a sense of belonging and intimacy. It also helps people be more competent and self-efficacious[43].

Prevention of substance abuse: Chewing tobacco is a common practice among the elderly in the South-East Asian region, as is smoking. The intake of alcohol is also

Table 2 Availability of mental health manpower in World Health Organization South- East Asia Region Organization countries

Mental health human resources[1] (per 100000 population)	India	Bangladesh	Bhutan	Indonesia	Korea	Maldives	Myanmar	Nepal	Sri Lanka	Thailand	Timor-leste
Total number of mental health professionals (government and non government)	25312	1893	5	7751	20301	27	627	413	1480	9436	45
Total mental health workers	1.93	1.17	0.64	3.00	40.13	6.45	1.20	1.44	7.14	14.36	3.63
Psychiatrists	0.29	0.13	0.51	0.31	5.79	2.39	0.38	0.36	0.52	0.99	0.08
Child psychiatrists	0	0	Not found	Not found	0.38	Not found	Not found	0.003	0.03	0.26	0.24
Geriatric psychiatrists	24	Hardly available									
Other specialist doctors	0.15	0.01	Not found	Not found	Not found	Not found	Not found	Not found	1.47	1.24	Not found
Mental health nurses	0.80	0.87	0.13	2.52	13.66	Not found	0.32	0.56	3.28	6.74	1.37
Psychologists	0.07	0.12	Not found	0.17	1.59	2.15	0	0.52	0.25	0.75	0.08
Social workers	0.06	0	Not found	Not found	8.40	0.48	0.01	Not found	0.28	0.91	1.61
Occupational therapists	0.03	0	Not found	Not found	0.08	0.24	0	Not found	0.22	0.98	0.16
Speech therapists	0.17	0	Not found	Not found	Not found	1.20	Not found	Not found	0.05	0.19	0.08
Other paid mental health workers	0.36	0.03	Not found	Not found	10.21	Not found	0.47	Not found	1.04	1893.45	Not found

[1]This includes trained geriatric psychiatrists only.

Table 3 Available physical infrastructure for providing mental health services in South- East Asia Region Organization countries

Mental health infrastructure	India	Bangladesh	Bhutan	Indonesia	Korea	Maldives	Myanmar	Nepal	Sri Lanka	Thailand	Timorleste
Mental hospitals	136	2	Not found	48	181	Not found	2	6	1	19	Not found
Psychiatric units in general hospitals	389	56	1	269	197	1	22	18	31	104	1
Mental health outpatient facilities attached to a hospital	952	69	28	Not found	518	6	33	29	230	830	6
Private practitioners	1217	Not found	Not found	Not found	313	Not found	3	Not found	20	2	69

prevalent. Apart from these issues, benzodiazepine abuse is also common, which adds to cognitive and mood deterioration in the long term[24]. Managing these conditions would work as a mental health-promoting strategy by reducing the risk of cognitive decline and mood dysregulation[40].

Prevention of polypharmacy: Polypharmacy increases cognitive deterioration and other geriatric syndromes. The indiscriminate use of appetite stimulants, high-calorie nutritional supplements, benzodiazepines, and antimicrobials to treat bacteriuria without specific symptoms of urinary tract infections should be avoided as much as possible[40].

Table 4 Estimated human resource requirements for mental health care of elderly individuals in World Health Organization South- East Asia Region Organization countries

Human resources requirement norms for the general population[37]	Human resources requirement for total population of WHO SEARO countries on Feburary 18, 2021(2537079071)[a]	Human resources requirement for elderly population 248633749[b] (@ 9.8%-WHO) SEARO countries as per norms of general population	Older adults with mental health problems @ 20% (tiwari and pandey, 2012) in SEARO 49726750 population as per general population norms	Availability of manpower in WHO SEARO countries	The gap (requirement - availability)
Psychiatrists (1 per 50000 population)	50741.6	4972.7	(4972.7 × 5) 24863.5	994.5 × 5 = 4972.5	9945.2
Clinical psychologists 1 per 25000 population	10148316	9945.3	(9945.3 × 5) 49726.5	1989.7 × 5 = 9948.5	19893.8
Psychiatric social workers 1 for 25000 population	10148316	9945.3	(9945.3 × 5) 49726.5	1989.7 × 5 = 9948.5	19893.8
Psychiatric nurses 1 per 25 000 population	10148316	9945.3	(9945.3 × 5) 49726.5	1989.7 × 5 = 9948.5	19893.8

[a]https://www.worldometers.info/world-population/asia-population/ accessed on Feburary 18, 2021.
[b]https://www.WHO.int/southeastasia/health-topics/ageing#:~:text=the%20population%20in%20WHO%20south,2030%20and%20by%202050%2c%20respectively. Accessed on Feburary 18, 2021.
WHO: World health organization; SEARO: South-east asia region organization.
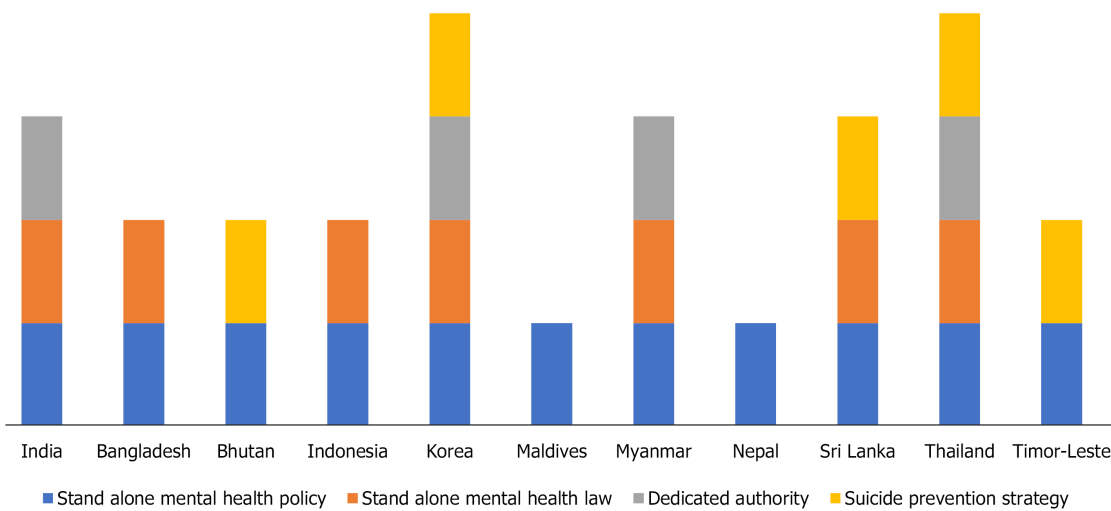
Figure 1 Status of available mental health policy, law, authority and suicide prevention strategies in World Health Organization South-East Asia Region Organization countries.

The WHO recommendations and support to governments at the global level

The WHO supports member states in strengthening and promoting mental health in the elderly population; it also advocates for integrating effective strategies into policies and plans. The World Health Assembly adopted the Global Strategy and Action Plan on Aging and Health in 2016[41], the objectives of which include the following[42]: Commitment to action on *healthy aging* in every country; Developing age-friendly environments; Aligning health systems to the needs of older populations; Developing sustainable and equitable systems for providing long-term care (home, communities, institutions); and Improving measurement, monitoring, and research on *healthy aging*.

In May 2017, the World Health Assembly endorsed the Global Action Plan on the Public Health Response to Dementia 2017–2025[44]. This plan provides a comprehensive blueprint for action, including increasing the awareness of dementia and reducing the risk for dementia. Apart from this, the WHO Mental Health Gap Action
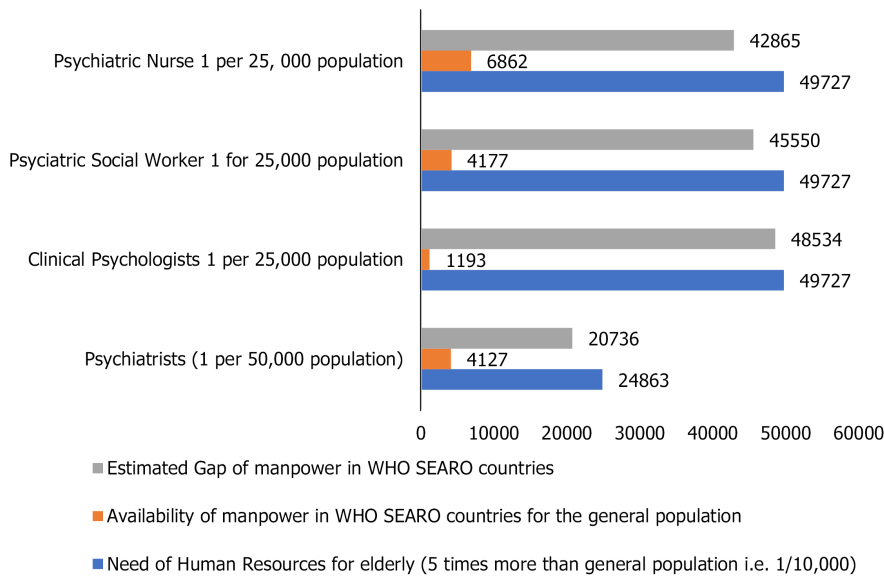
Figure 2 Estimated requirement and gap of human resources in World Health Organization South- East Asia Region Organization countries.
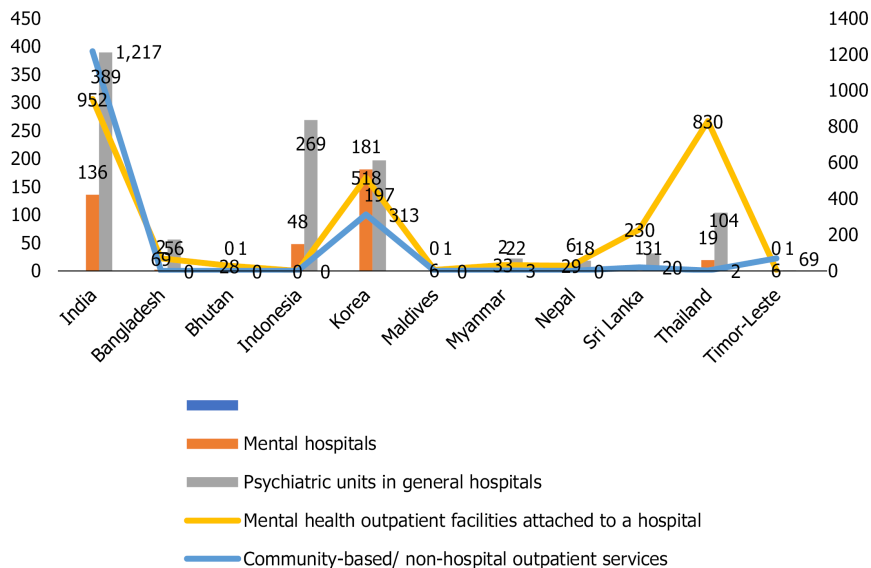
Figure 3 Available physical infrastructure for providing mental health services in South- East Asia Region Organization countries.

Programme (mhGAP) package consists of interventions for the prevention and management of priority conditions such as depression, psychosis, suicide, and substance use disorders in nonspecialized health settings, including those for older people[45]. Under universal health coverage, the WHO also recommends protecting the elderly population from financial risks, designing age-friendly benefit packages, and extending social insurance schemes for older people[46], which is another way to promote mental health in older people.

Limitation

This article provides an overview regarding the available resources in mental health in order to promote the mental health of the elderly population, which can be utilized in the community by generating awareness. However, we did not discuss the availability, needs, and gaps of various resources, such as housing facilities, social safety, support, financial security, *etc.* Articles were sourced from the PubMed and WHO websites.

CONCLUSION

Conclusion and Future Implications

With the rapidly shifting aging demographic and changing family dynamics, the elderly population forms a sector of the population that needs specific focus. The sound mental health of elderly individuals is a cornerstone in ensuring quality and dignity of life. Thus, it is crucial to understand the sociocultural and economic factors that contribute to their mental well-being. MHP plays a vital role in establishing healthy practices, which in the long run sensitize and protect the elderly population against the deterioration of overall functionality. Elderly individuals located in the WHO SEARO region share remarkably similar sociocultural profiles. The research available in this area provides actionable data and clear pathways of MHP to improve the existing conditions for the elderly populations in these countries. There is a need to identify at-risk behavior and the existing gaps for providing care to elderly individuals. At present, we need to address these issues and challenges to maintain societal equilibrium and correct the future boom we expect in regard to the population of older adults.

ACKNOWLEDGEMENTS

REFERENCES

1   **WHO**. World report on Ageing and health. 2015.
2   **WHO**. Ageing and health. 2021.
3   **WHO**. Ottawa Charter for Health Promotion. 1986.
4   **WHO**. Promoting mental health: Concepts, emerging evidence, practice: Summary report. 2004.
5   **WHO**. Prevention and Promotion in Mental Health. 2002.
6   **Delle Fave A**, Bassi M, Boccaletti ES, Roncaglione C, Bernardelli G, Mari D. Promoting Well-Being in Old Age: The Psychological Benefits of Two Training Programs of Adapted Physical Activity. *Front Psychol* 2018; **9**: 828 [PMID: 29910755 DOI: 10.3389/fpsyg.2018.00828]
7   **WHO**. Decade of healthy ageing: baseline report. 2020.
8   **WHO**. Clinical Consortium on Healthy Ageing 2019. 2020.
9   **UNDP**. Sustainable Development Goals. 2019.
10 **WHO**. Regional Office for South-East Asia. 2013.
11 **Heok KE**. Elderly people with mental illness in South-East Asia: rethinking a model of care. *Int Psychiatry* 2010; **7**: 34-36 [PMID: 31508029]
12 **Shankardass MK**. Policy initiatives on population ageing in select Asian countries and their relevance to the Indian context. Population Ageing in India 155. *Cambridge University Press*. 2014 [DOI: 10.1017/cbo9781139683456.008]
13 Ministry of Social Justice and Empowerment. National Policy on Older Persons. Government of India. [DOI: 10.1007/978-3-7643-8298-8_1]
14 **de Mendonça Lima CA**, Ivbijaro G. Mental health and wellbeing of older people: opportunities and challenges. *Ment Health Fam Med* 2013; **10**: 125-127 [PMID: 24427178]
15 **Girdhar R**, Sethi S, Vaid RP, et al Geriatric mental health problems and services in India: A burning issue.
    J Geriatr Care Res 2019; 6: 15–19 [DOI: 10.4103/jgmh.jgmh_1_19]
16 **Tiwari SC**, Tripathi RK, Kumar A, Kar AM, Singh R, Kohli VK, Agarwal GG. Prevalence of psychiatric morbidity among urban elderlies: Lucknow elderly study. *Indian J Psychiatry* 2014; **56**: 154-160 [PMID: 24891703 DOI: 10.4103/0019-5545.130496]
17 **Tiwari SC**, Srivastava G, Tripathi RK, Pandey NM, Agarwal GG, Pandey S, Tiwari S. Prevalence of psychiatric morbidity amongst the community dwelling rural older adults in northern India. *Indian J Med Res* 2013; **138**: 504-514 [PMID: 24434257]
18 **Tiwari SC**, Pandey NM. Status and requirements of geriatric mental health services in India: an evidence-based commentary. *Indian journal of psychiatry* 2012; **54**: 8-14 [PMID: 22556431 DOI: 10.4103/0019-5545.94639]
19 **Prince M**, Livingston G, Katona C. Mental health care for the elderly in low-income countries: a

health systems approach. *World psychiatry* 2007; **6**: 5-13 [PMID: 17342213]

20   **Grover S**, Avasthi A, Sahoo S, Lakdawata B, Dan A, Nebhinani N, Dutt A, Tiwan SC, Gania AM, Subramanyam AA, Kedare J, Suthar N. Relationship of loneliness and social connectedness with depression in elderly: A multicentric study under the aegis of Indian Association for Geriatric Mental Health. *Journal of Geriatric Mental Health* 2018; 5: 99 [DOI: 10.4103/jgmh.jgmh_26_18]

21   **Levkoff SE**, MacArthur IW, Bucknall J. Elderly mental health in the developing world. *Soc Sci Med* 1995; **41**: 983-1003 [PMID: 8545673 DOI: 10.1016/0277-9536(94)00434-u]

22   **WHO**.   Promoting mental health: concepts, emerging evidence, practice: a report of the World Health Organization, Department of Mental Health and Substance Abuse in collaboration with the Victorian Health Promotion Foundation and the University of Melbourne. 2005.

23   **Kumar S**, Preetha G. Health promotion: an effective tool for global health. *Indian J Community Med* 2012; **37**: 5-12 [PMID: 22529532 DOI: 10.4103/0970-0218.94009]

24   **Fillit HM**, Butler RN, O'Connell AW, Albert MS, Birren JE, Cotman CW, Greenough WT, Gold PE, Kramer AF, Kuller LH, Perls TT, Sahagan BG, Tully T. Achieving and maintaining cognitive vitality with aging. *Mayo Clin Proc* 2002; **77**: 681-696 [PMID: 12108606 DOI: 10.4065/77.7.681]

25   **Mrazek P**, Haggerty R. Reducing risks of mental disorder: frontiers for preventive intervention research. *Washington: National Academy Press* 1994 [DOI: 10.1192/s0007125000064655]

26   **WHO**.   Regional Office for South-East Asia. Integrated care for older people: a manual for primary care physicians (trainee's handbook). 2020.

27   **WHO**.   Mental Health ATLAS [Internet]. 2017.

28   **Asia WHORO for S-E**.   2019 Health SDG profile: India. 2019.

29   **Asia WHORO for S-E**.   2019 Health SDG profile: Bangladesh. 2019.

30   **Asia WHORO for S-E**.   2019 Health SDG profile: Bhutan. 2019.

31   **Asia WHORO for S-E**.   2019 Health SDG profile: Indonesia. 2019.

32   **Asia WHORO for S-E**.   2019 Health SDG Profile: Democratic People's Republic of Korea. 2019.

33   **Asia WHORO for S-E**.   2019 Health SDG profile: Maldives. 2019.

34   **Asia WHORO for S-E**.   2019 Health SDG profile: Myanmar. 2019.

35   **Asia WHORO for S-E**.   2019 Health SDG profile: Nepal. 2019.

36   **Asia WHORO for S-E**.   2019 Health SDG profile: Sri Lanka. 2019.

37   **Asia WHORO for S-E**.   2019 Health SDG profile: Thailand. 2019.

38   **Health SDG profile**.   Timor-Leste [Internet]. 2019.

39   **Desai NG**, Tiwari SC, Nambi S, Shah B, Singh RA, Kumar D, Trivedi JK, Palaniappan V, Tripathi A, Pali C, Pal N, Maurya A, Mathew M. Urban mental health services in India: how complete or incomplete? *Indian J Psychiatry* 2004; **46**: 195-212 [PMID: 21224901]

40   **WHO**.   Integrated care for older people: a manual for primary care physicians (trainee's handbook). Regional Office for South-East Asia. 2020.

41   **Rudnicka E**, Napierała P, Podfigurna A, Męczekalski B, Smolarczyk R, Grymowicz M. The World Health Organization (WHO) approach to healthy ageing. *Maturitas* 2020; **139**: 6-11 [PMID: 32747042 DOI: 10.1016/j.maturitas.2020.05.018]

42   **WHO**.   The Global strategy and action plan on ageing and health 2016–2020: towards a world in which everyone can live a long and healthy life. 2016.

43   **Bishwajit G**, O'Leary DP, Ghosh S, Yaya S, Shangfeng T, Feng Z. Physical inactivity and self-reported depression among middle- and older-aged population in South Asia: World health survey. *BMC Geriatr* 2017; **17**: 100 [DOI: 10.1186/s12877-017-0489-1]

44   **WHO**.   Global action plan on the public health response to dementia, 2017–2025. Geneva: WHO. 2017 [DOI: 10.1016/j.jalz.2017.07.758]

45   **WHO**.   Mental Health Gap Action Programme (mhGAP). 2016.

46   **WHO**.   The world health report: health systems financing: the path to universal coverage: executive summary. 2010 [DOI: 10.2471/blt.10.078741]

Current progress in neuroimaging research for the treatment of major depression with electroconvulsive therapy

Xin-Ke Li, Hai-Tang Qiu

Xin-Ke Li, College of Medical Informatics, Chongqing Medical University, Chongqing 400016, China

Hai-Tang Qiu, Mental Health Center, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China

Corresponding author: Xin-Ke Li, PhD, Associate Professor, Postdoc, College of Medical Informatics, Chongqing Medical University, No. 1 Medical School Road, Yuzhong District, Chongqing 400016, China. zmdcg@126.com

Abstract

Electroconvulsive therapy (ECT) uses a certain amount of electric current to pass through the head of the patient, causing convulsions throughout the body, to relieve the symptoms of the disease and achieve the purpose of treatment. ECT can effectively improve the clinical symptoms of patients with major depression, but its therapeutic mechanism is still unclear. With the rapid development of neuroimaging technology, it is necessary to explore the neurobiological mechanism of major depression from the aspects of brain structure, brain function and brain metabolism, and to find that ECT can improve the brain function, metabolism and even brain structure of patients to a certain extent. Currently, an increasing number of neuroimaging studies adopt various neuroimaging techniques including functional magnetic resonance imaging (MRI), positron emission tomography, magnetic resonance spectroscopy, structural MRI, and diffusion tensor imaging to reveal the neural effects of ECT. This article reviews the recent progress in neuroimaging research on ECT for major depression. The results suggest that the neurobiological mechanism of ECT may be to modulate the functional activity and connectivity or neural structural plasticity in specific brain regions to the normal level, to achieve the therapeutic effect.

Key Words: Neuroimaging; Major depression; Electroconvulsive therapy; Magnetic resonance imaging; Positron emission tomography; Magnetic resonance spectroscopy

Core tip: Longitudinal neuroimaging studies in patients with major depression before

and after electroconvulsive therapy (ECT) have shown that ECT has effects on specific brain areas. However, these ECT-regulated brain regions and their changes are uncertain. Based on recent studies with various neuroimaging techniques, this paper reviews longitudinal neuroimaging findings in recent years and discusses the relatively consistent results.

INTRODUCTION

Major depressive disorder (MDD) has become a major public health problem throughout the world. Approximately 322 million people suffer from depression worldwide, with a prevalence rate of 4.4%. More than 1 million people commit suicide due to depression every year[1]. Neuroimaging studies have shown that the structural and functional alterations in frontal lobe, cingulate gyrus (CG), hippocampus, basal ganglia and other brain regions are closely related to the pathogenesis of depression [2].

Electroconvulsive therapy (ECT) is essentially a method of using electrical current to induce epileptiform discharges in the cortex, causing a systemic seizure to control mental symptoms. Since ECT was invented by Italian scientists Cerletti and Bini in 1938, it has been extensively applied to the treatment of mental disorders for > 80 years[3]. At present, ECT is an indispensable treatment in the field of psychiatry. It is still the first choice for patients with severe depression with stubborn suicidal thoughts, delusions, and food refusal, followed by schizophrenia and mania[4]. ECT has attracted increasing attention in neurologic diseases due to its rapid and high response rate in patients with depression[5,6].

Currently, the neural mechanisms underlying the clinical response to ECT for MDD remain uncertain, and there are no widely accepted biomarkers that can be used to assist in the diagnosis or treatment options for individual patients. It only relies on subjective judgments based on clinical features and lacks objective and reliable evidence[7]. To facilitate treatment development, a clearer understanding of the neural correlates of successful antidepressant responses is essential[8]. Neuroimaging technology has the potential to identify objective neurobiological markers that reflect the underlying pathophysiological process in a given mental illness, and it is a noninvasive research method for observing brain changes. Various neuroimaging techniques such as positron emission tomography (PET) and magnetic resonance imaging (MRI) have promoted research on neuropsychiatric diseases. At the same time, this provides a new window for the study of the therapeutic mechanism of ECT in depression.

Longitudinal studies of neuroimaging in patients with major depression before and after ECT have shown that ECT has effects on specific brain regions and circuits. Some studies in the late 1980s focused on refuting the hypothesis that ECT caused brain damage and found no overall evidence of structural changes or harmful effects[9-11]. After the first high-resolution (1 mm³) MRI study determined ECT-induced structural changes by detecting the increase in hippocampal volume[12], several subsequent studies confirmed that ECT can also induce alterations in hippocampal structure and other brain regions[13-16]. Recent research using machine learning and MRI can help patients and psychiatrists make more informed decisions about ECT as a treatment option[17,18]. These studies use machine learning algorithms to identify patients who are most likely to benefit from ECT at the individual level. Using these methods also helps to discover biomarkers in the brain that can predict the response to ECT treatment.

Although an increasing number of neuroimaging studies have attempted to reveal the neurological effects of ECT, these ECT-regulated brain regions and their changes are usually inconsistent. Therefore, based on recent longitudinal neuroimaging findings related to ECT treatment in depression, we investigated the progress made in these studies.

BRAIN FUNCTIONAL IMAGING STUDY FOR DEPRESSION WITH ECT

Functional MRI

Blood oxygenation level-dependent functional MRI (BOLD-fMRI) has been applied in the field of brain function research since the 1990s and has become the most rapidly developing functional detection technology. BOLD-fMRI has the advantages of being noninvasive, nonradioactive, repeatable, and having high temporal and spatial resolution. It also allows analysis on a single-subject basis to reflect the dynamic activity of neurons and the different patterns of response between adjacent cortices throughout the process. The spontaneous low-frequency activity information collected in the resting state is defined as the baseline brain function information, which reflects the spontaneous functional activities of the central nervous system in the basic state [19,20]. Therefore, fMRI in the resting state has obvious clinical advantages. Resting-state fMRI (rs-fMRI) is also particularly suitable for the study of patients with major depression because it does not require the patient to perform a specific task. Thus, rs-fMRI is increasingly widely used in the study of brain function in depression.

ECT can cause changes in the functional connectivity (FC) in specific brain regions in patients with depression. These changes may reveal that the clinical improvement of depression is related to the treatment effect of ECT through fMRI. Assessing changes in FC requires analyzing the differences before and after ECT. In recent years, different results have been reported[21]. In the voxel-analysis method, the CG is generally regarded as an important area related to ECT. There were significant changes in ECT, including a decrease in resting state FC (rsFC) in the left dorsal anterior cingulate cortex (dACC) and an increase in rsFC in the bilateral posterior cingulate cortex (PCC). Other important areas found in the rsFC after ECT are the frontal cortex, parietal cortex and temporal cortex, including the bilateral anterior central gyrus, dorsomedial prefrontal cortex, bilateral superior frontal gyrus (SFG), left angular gyrus (LAG), left precuneus, bilateral hippocampus, right superior temporal gyrus, right island, and cerebellum[21]. For instance, Wei *et al*[22] adopted FC strength (FCS) to identify brain hubs through resting-state fMRI at three time points, *i.e.*, prior to ECT, at the completion of ECT, and 1 mo after the completion of ECT. The results showed that the FCS of the LAG of patients with depression after ECT was significantly increased. Mo *et al*[23] found that the FC of the LAG with the bilateral inferior temporal gyrus (ITG), bilateral middle frontal gyrus, and other areas was significantly increased, accompanied by emotional improvement. Sun *et al*[24] used fMRI data to make preliminary predictions of individual response to ECT, and the results showed that the predictive areas were concentrated in the prefrontal and temporal cortices and the subcortical nuclei.

In seed-based analysis, CG is usually also selected as the seed region. After ECT, it was found that rsFC of the left subgenual anterior cingulate cortex (sgACC) with the left parahippocampal gyrus (PHG) increased, while rsFC of the contralateral temporal pole decreased[25]. During ECT treatment, rsFC of the subcallosal cingulate cortex with bilateral hippocampus, bilateral temporal poles, and ventral prefrontal cortex was significantly reduced[26]. Some studies also pointed out that rsFC of the sgACC with the amygdala and fusiform gyrus changed significantly after ECT treatment. Using fMRI data, Leaver *et al*[27] found that rsFC between the left dorsolateral prefrontal cortex (DLPFC) and sgACC was probably an important feature of the ECT response to depression. With regard to network-based and region-of-interest (ROI) analysis, the changes in rsFC in the left cerebellum, default mode network, ACC, and PCC were more frequent after ECT treatment.

ECT can also cause regional functional activity changes in patients with depression. It is an important method to study the regional functional activity changes in brain regions through fMRI. The indicators include amplitude of low frequency fluctuations (ALFF), fractional ALFF (fALFF), and regional homogeneity (ReHo). Qiu *et al*[28] found that ReHo of rs-fMRI showed significant differences in brain activity before and after ECT. MDD patients who received eight courses of ECT showed higher ReHo values in the bilateral frontal lobes, bilateral parietal lobes, and right caudate nucleus. Decreased ReHo values were observed in the left anterior cerebellar lobe, right CG, right superior temporal gyrus, and right medial temporal gyrus. Argyelan *et al*[29] used rs-fMRI to compare patients with treatment-resistant depression before ECT with normal controls and found that the fALFF of the right cingulate cortex increased significantly in patients, suggesting that local brain functional activity is hyperactive. The fALFF in the cingulate cortex in patients after ECT was significantly lower than that before ECT, and there was no significant difference compared with normal controls, indicating that ECT can significantly improve abnormal brain function activities. In addition, ReHo of the LAG[23] and ALFF of the dorsal medial prefrontal

cortex[30] in MDD patients increased significantly after ECT treatment. In a sham-controlled fMRI study, Miskowiak *et al*[31] found that the regulation of medial prefrontal hyperactivity during the encoding of negative affectional information may be a common mechanism for different biological depression treatments. In response to negative emotional stimulation for depression, the activity in the amygdala increases abnormally. Redlich *et al*[32] used fMRI data to find that the patient's amygdala function normalized after ECT.

PET

PET is a modern imaging technology to detect and identify metabolic changes that occur prior to structural changes in tissues and organs under disease conditions at the molecular level. It measures and displays the biological activities of cells and molecules by injecting radioisotope drugs with appropriate half-life into the body. According to the concentration of the tracer, cerebral blood perfusion and glucose and neurotransmitter metabolism levels can be inferred, and it has the advantages of high sensitivity and accurate quantitative analysis.

PET is currently used to study changes in specific neurotransmitter receptors after ECT. Masuoka *et al*[33] used [^{18}F]FE-PE2I PET to examine MDD patients before, during and after treatment and found that all patients had a reduced striatal dopamine transporter-binding potential (BP_{ND}). Combined with the patient's clinical response, it has been proven that the dopamine nervous system is part of the mechanism of ECT. Tiger *et al*[34] used PET and [^{11}C]raclopride to examine patients with severe MDD before and after ECT, and healthy controls. Compared with the control group, the [^{11}C]raclopride binding rate in all three parts of the striatum decreased significantly in the patients. However, there was no significant effect of ECT on D_2/D_3 binding in the patients. Baldinger-Melich *et al*[35] used PET and radioligand [^{11}C]harmine to evaluate cerebral monoamine oxidase A (MAO-A) distribution volumes (V_T). The results showed no significant difference in MAO-A V_T between patients with post-ECT treatment-resistant depression and healthy controls at baseline. This suggested that MAO-A V_T is not related to the clinically relevant mechanism of action of ECT. Using [^{18}F]Setoperone PET, Yatham *et al*[36] found that serotonin$_2$ (5-HT$_2$) receptor binding was extensively reduced in all cortical regions of MDD patients after ECT. Furthermore, the reduction in the 5-HT$_2$ receptor in the right PHG, right lingual gyrus and right medial frontal gyrus was correlated with the improvement of depressive symptoms. These results were consistent with research on antidepressants[37-39]. Lanzenberger *et al*[40] used highly selective radioligand [carbonyl-^{11}C] WY100635-PET scans and compared the voxels of serotonin-1A (5-HT$_{1A}$) receptor binding (BP_{ND}) before and after ECT. The results showed extensive decreases in cortical and subcortical areas, except for the cerebellum and the occipital cortex. This PET study proposed the whole-brain involvement of postsynaptic 5-HT$_{1A}$ receptor binding in ECT effects.

PET is utilized to evaluate ECT-related changes in [^{18}F]-fluorodeoxyglucose (FDG) to measure the rate of local brain metabolism of glucose. The most consistent finding in pre- and post-ECT comparisons was decreased glucose metabolism in the bilateral frontal medial and inferior frontal areas and right frontal operculum[41]. The areas with increased glucose metabolism included the hippocampus, middle temporal lobe, left occipital lobe, parietal lobe and pons. Bak *et al*[42] used [^{18}F]-FDG PET to study the efficacy of ECT in a 55-year-old woman with late-onset depression. ^{18}F-FDG PET/computed tomography (CT) images of the patient's brain showed a diffuse decrease in brain metabolism. After the patient's symptoms were improved by ECT, her PET imaging showed her brain metabolism was normal. After improving the patient's symptoms through ECT, PET imaging showed that her brain metabolism was normal. Hassamal *et al*[43] adopted ^{18}F-FDG-PET/CT before ECT to show extensive hypometabolism in the frontal, parietal and temporal cortices. After eight sessions of ECT, symptoms of psychosis and anxiety symptoms as well as cognitive impairment were resolved. ^{18}F-FDG-PET/CT showed improvement in hypometabolism of the cerebral cortex, especially in the left parietal cortex, left temporal/occipital cortex, and bilateral frontal areas. The improvement of brain glucose hypometabolism may represent the neurophysiological mechanism of ECT for the treatment of psychotic episodes. However, Reininghaus *et al*[6] reported inconsistent results. They employed FDG-PET scans to measure the effects of a series of ECT treatments on brain glucose metabolism in depressed subjects before and after treatment. They found that there was almost no change in brain glucose metabolism. Therefore, they did not think that FDG-PET can evaluate the functional brain changes that may occur after ECT.

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) is used to determine abnormal metabolic conditions in tissues by measuring changes in the concentration of metabolites in the human body and observing different peaks and ratios of the spectrum curve. MRS is a noninvasive detection technology that can measure neurobiochemical information in specific brain functional areas and analyze the content of neurobiochemical substances. These compounds include γ-aminobutyric acid (GABA), glutamate (Glu), choline-containing compounds, N-acetyl-L-aspartic acid (NAA), glutamine (Gln), myoinositol, and creatine (Cr).

Glu plays a key role in the pathophysiology of depression[44]. There was evidence that the levels of Glu and Gln in pgACC were reduced[45,46], while the concentration of Glu in the DLPFC was unchanged[47,48]. ECT caused changes in glutamatergic neurotransmission that seem to be closely related to its antidepressant effects[49,50]. Njau *et al*[51] reported that Glx (Glu and Gln) increased in sgACC but decreased in the left hippocampus in patients with depression after ECT treatment, and these changes were related to the improvement of mood. Glx disorders in MDD patients and the regulation of Glx levels by ECT vary from region to region. Although some studies reported increased Glx levels in the DLPFC and ACC after ECT[49,52], one study was unable to replicate these findings[48]. There were similar contradictory reports for the hippocampus. A recent study reported the correlation between elevated hippocampal Glx and ECT response in patients with medication-resistant depression[53], while another report was unable to confirm these results[54]. In general, brain metabolism of Glu has been an important component of ECT efficacy, but there are differences in the exact mechanism.

In addition, reduced levels of GABA in cerebrospinal fluid and plasma, as well as in the frontal cortex, were reported in patients with depression[55]. Thus, increased serum levels and occipital GABA concentrations were observed after ECT[56,57]. However, Knudsen *et al*[58] used MRS to measure GABA changes in the prefrontal and occipital cortex in patients before and after ECT. There were no significant differences in GABA/Cr levels in the prefrontal cortex or occipital lobe between baseline patients and healthy subjects, and there was no statistically significant difference in GABA, Glu, glutamine, choline or GSH before and after ECT. They concluded that GABA should not be considered a key factor in the treatment of major depression with ECT.

NAA is a marker of neurons and axons, and its concentration can reflect the number and functional status of neurons. Proton MRS (H-MRS) showed that ECT can increase the content of NAA in the anterior CG and amygdala, suggesting that ECT has a nerve-promoting effect. Njau *et al*[51] detected MDD patients with ECT through ^{1}H-MRS and found that compared with the control group, the content of NAA in the left hippocampus of the patients was reduced before treatment. Meanwhile, the NAA levels of the dACC and right hippocampus also decreased significantly after ECT treatment.

Tosun *et al*[59] observed the metabolic changes of ACC in MDD patients after ECT through ^{1}H-MRS. There was no significant difference in the levels of ACC metabolites between the patients and the control group at baseline. ECT was associated with a statistically significant decrease in the NAA/Cr ratio in ACC. All patients responded to ECT treatment as measured by the clinical scale. These results suggest that a relative increase in Cr levels after ECT in MDD appears to be associated with an improvement in clinical severity. However, Ende *et al*[60] found that hippocampal NAA did not change after ECT, and the choline content increased, indicating that ECT may be related to increased membrane transformation and may reflect neurogenesis.

Because the different neurotransmitter systems involved in the antidepressant effect of ECT are connected to each other through a complex signal transduction network and the changes in the content of neurobiochemical substances are also complicated, the above findings based on MRS have presented inconsistent results.

BRAIN STRUCTURAL IMAGING STUDY FOR DEPRESSION WITH ECT

Structural MRI

ECT can improve brain function and change the brain structure in patients with depression. Many MRI structural studies in patients with MDD have shown morphological abnormalities, mainly manifested as cortical thickness, gray matter volume, and white matter integrity[61]. Longitudinal structural neuroimaging studies have proven that ECT increases the volume of the hippocampus, amygdala, caudate

nucleus, and temporal lobe. Some studies have found that ECT increases the volume of the hippocampus and amygdala in the temporal lobe system in patients with depression[62-64]. The strongest evidence of structural changes in the brain after ECT was an increase in the volume of the temporal lobe and subcortical structures, such as the hippocampal-amygdala complex, anterior cingulate cortex and striatum[65].

Voxel-based morphology (VBM) is a powerful and objective method for studying brain structural changes in patients with depression before and after ECT through MRI. Due to its simplicity of use, VBM has inspired many neuroscientists to characterize specific abnormalities in brain gray matter volume in MDD[66,67].

Some studies have used ROI methods to analyze brain regions closely associated with depression. Tendolkar *et al*[62] took the bilateral hippocampus and amygdala as regions of interest and found that ECT could increase the gray matter volume of the bilateral hippocampus and amygdala in patients with refractory depression. Accordingly, the Hamilton Depression Scale score was significantly reduced after ECT, and the severity of depressive symptoms was reduced. Gryglewski *et al*[68] found that structural changes were observed in the hippocampal subregions and amygdala after ECT. These structural changes are particularly involved in the pathophysiology of depression and stress-related diseases and still have high neuroplasticity in adulthood. Cao *et al*[69] used the latest hippocampal segmentation method and found that ECT induced cornu ammonis subfields, granule cell layer, molecular layer, and hypothalamic volume increases. It also accurately predicted the quantitative efficacy of ECT for each patient. Joshi *et al*[70] used FreeSurfer to segment the hippocampus and amygdala and found that ECT induced neuroplasticity processes related to clinical responses, which can correct the reduction in the structure of the hippocampus and amygdala associated with MDD. Patients with small hippocampal volumes were most likely to show an increase in volume and improve clinical response. Therefore, changes in the structure of the hippocampus and amygdala could serve as potential biomarkers for the development of other rapidly effective therapies. Jorgensen *et al*[54] used structural MRI (sMRI) of the hippocampus, amygdala, DLPFC, orbitofrontal cortex, and hypothalamus and found that the hippocampus and amygdala volume increased in patients with major depression after ECT, while the volume of the DLPFC decreased slightly. However, due to the lack of correlation between these changes and the antidepressant effect, this remodeling of the brain structure does not appear to directly affect the antidepressant effect of ECT. Wade *et al*[8] conducted a longitudinal study on the cortical volume, cortical thickness and cortical surface area of the caudate nucleus, putamen, pallidum, and nucleus accumbens through surface-based morphometry. Compared with the control group, the volume of the nucleus accumbens and nucleus pallidum were smaller in MDD patients. ECT caused an increase in the volume of the left putamen. In patients defined as responders to treatment, there was an increase in overall nucleus accumbens volume and local changes in globus pallidus and caudate nucleus volume. Thus, ECT induces structural plasticity in the dorsal and ventral striatum/pallium.

In some studies, VBM has been effectively used to evaluate anatomical abnormalities in the whole brain. Ota *et al*[71] found that the volume of the bilateral medial temporal cortex, inferior temporal cortex and right anterior CG increased significantly after ECT. In addition, the rate of increase was associated with clinical improvement as measured by the Hamilton Depression Scale. Van Eijndhoven *et al*[72] compared the brain images of treatment-resistant MDD patients before and after ECT with normal controls and found that there was no significant difference in the thickness of the whole cerebral cortex between patients before ECT and normal controls. After ECT, the patients had increased cerebral cortex thickness in the left temporal pole, left middle temporal gyrus, and right insula compared with the control group. Meanwhile, the Hamilton Depression Scale score was significantly lower than before treatment, with an average decrease of 57%. Sartorius *et al*[16] analyzed sMRI before and after ECT and found that the gray matter volume of the whole brain increased in most patients after ECT, while the white matter volume of the brain did not significantly change. Further voxel-based morphological analysis showed that the volume of gray matter in the bilateral temporal lobe, the middle CG, the insular lobe and the putamen increased after treatment. Jiang *et al*[73] adopted six GM areas including the right hippocampus/parahippocampus, the right orbitofrontal gyrus, the right ITG, the left posterior middle gyrus/anterior process, the left auxiliary motor area and the left lingual gyrus to be identified as predictors of ECT response. They revealed that GM density only increased in the left auxiliary motor cortex and the left middle posterior gyrus/protrusion after ECT. The results indicate that the treatment prediction area and the treatment response area may be anatomically different. Pirnia *et al*[74] found that the thickness increased in the bilateral anterior cingulate cortex,

superior temporal cortex *etc*. ECT resulted in extensive neuroplasticity in the neocortex, limbic and paralimbic areas. Moreover, changes in ACC thickness can distinguish treatment responders and predict early responses during ECT.

Gbyl and Videbech[75] concluded that current MRI studies do not support the hypothesis that ECT causes brain damage. They confirmed that ECT causes an increase in the volume of the limbic area of the frontal lobe, and further research should explore the relationship between these increases and treatment effects and cognitive side effects. Many studies have shown an increase in hippocampal volume following ECT, but there are conflicting results as to whether the increase in hippocampal volume is associated with clinical response. Other studies have found increased GMV or cortical thickness in areas such as the amygdala, frontotemporal cortex, lingual gyrus, thalamus, and striatum.

Diffusion tensor imaging

Diffusion tensor imaging (DTI) is a derivative technique of diffusion-weighted imaging that can noninvasively detect the direction and integrity of white matter tracts by evaluating the diffusion of water molecules in nerve tissue. It has important applications in neuroimaging research.

Chen *et al*[76] performed a meta-analysis of microstructural brain abnormalities in drug-naïve patients with major depression through DTI. They observed that the main areas of fractional anisotropy reduction included the bilateral anterior limb of the internal capsule, body of the corpus callosum, right SFG, and right ITG. Gbyl and Videbech[74] found that an ECT-induced increase in the integrity of the white matter pathways in the frontal and temporal lobes through a meta-analysis of DTI, but the correlation between the increase in volume and the treatment effect and the mechanism of action of ECT are still uncertain. Yrondi *et al*[77] found a reduction in the hippocampus and left amygdala during ECT in patients with treatment-resistant depression using mean diffusivity (MD) measure. They concluded that ECT can correct the microstructural integrity of these structures. Gryglewski *et al*[78] conducted a DTI study on patients with treatment-resistant depression using unilateral ECT and found that axial diffusivity was increased in the posterior limb of the internal capsule in the right hemisphere. Compared with the left hemisphere, the increase in this region was higher on the right. However, no correlation between this effect and treatment response was found. Repple *et al*[79] used DTI to analyze the alterations in the white matter structure in patients with depression before and after ECT and found that MD of the right hemisphere increased after ECT, which was a specific effect in the ECT group. Kubicki *et al*[80] revealed alterations in the structural connections of the hippocampal neural circuits after ECT. It also means that glial, neurotrophic or inflammatory response mechanisms affect the integrity of the axons. Lyden *et al*[81] observed a significant increase in fractional anisotropy in the dorsal frontolimbic circuits including the anterior cingulate, forceps, and left superior longitudinal fascia between baseline and transition to maintenance therapy. Radial and MD in overlapping regions and anterior thalamic radiation were reduced. Changes in DTI indicators related to treatment response indicated that ECT effects significantly differed between MDD and control groups. Alterations in white matter microstructure in the pathways connecting the frontal and limbic regions that occur in MDD are regulated by ECT and are associated with treatment response.

CONCLUSION

In recent years, the rapid development of neuroimaging technologies represented by MRI has played a major role in promoting the study of neurological mechanisms of mental diseases. With the continuous emergence of new technologies, they have been able to provide different levels of physiological and pathological information from macroscopic tissue morphology to microscopic subcellular structure, and from blood flow and energy metabolism to high-level brain functional networks, which embodies the characteristics of multidimensional and multimodal information. Research on the neural effects of ECT needs to consider the physical and mental state of patients with major depression to adopt appropriate neuroimaging technology. At present, MRI is the most commonly used method, and there are very few studies using single-photon emission CT.

In general, the findings of current neuroimaging studies are inconsistent. The main reasons are as follows: (1) The operating methods of ECT such as electrode position, electric dose, and treatment times are different; (2) Data collection and analysis

Table 1 Consistent findings in neuroimaging research on electroconvulsive therapy effects

Neuroimaging technologies	Methods/measures	Relatively consistent findings
fMRI	Functional connectivity strength	Changes in cingulate cortex, frontal cortex, and left angel gyrus
	Functional activity of local brain regions	Changes in cingulate cortex and prefrontal cortex
PET	Neurotransmitters	Downregulation of brain serotonin receptors
	Glucose metabolism	Reduction in glucose metabolism after ECT in bilateral anterior and posterior frontal areas
MRS	Gln/Glx, GABA, NAA, Cho, mI, Cr	None
sMRI	Gray matter volumn	Increase in hippocampus and amygdala
DTI	White matter	Alterations in microstructure and pathways

fMRI: Functional magnetic resonance imaging; PET: Positron emission tomography; MRS: Magnetic resonance spectroscopy; sMRI: Structural magnetic resonance imaging; DTI: Diffusion tensor imaging; Gln: Glutamine; Glx: Glutamate and Gln; GABA: γ-aminobutyric acid; NAA: N-acetyl-L-aspartic acid; Cho: Choline-containing compounds; mI: Myoinositol; Cr: Creatine; ECT: Electroconvulsive therapy.

methods are different; (3) Sample size collected for research is too small; and (4) Physiological disorders of patients with depression are heterogeneous. Despite these shortcomings, it is not possible to fully understand how ECT works, and there are still some encouraging findings. Table 1 gives a summary of relatively consistent findings. In the fMRI study of ECT treatment, the significant changes in the functional connection strength of the cingulate cortex, frontal cortex, and left angel gyrus were relatively consistent. Significant changes in the functional activity of the cingulate cortex and frontal cortex are also response markers for ECT treatment. For PET studies, consistent conclusions include a reduction in glucose metabolism after ECT in the bilateral anterior and posterior frontal areas and downregulation of brain serotonin receptors. Due to the complex neurobiochemical alterations in the brain, no consistent results have been obtained in the current studies on the treatment of depression with ECT based on MRS. Many sMRI studies have found that the increased volumes of the hippocampus and amygdala are the most important imaging markers for improving depression after ECT. Among white matter DTI studies, much evidence supports an increase in white matter pathway integrity after ECT.

REFERENCES

1   **World Health Organization**. Depression and Other Common Mental Disorders: Global Health Estimates. Geneva: World Health Organization, 2017
2   **Stippl A**, Kirkgöze FN, Bajbouj M, Grimm S. Differential Effects of Electroconvulsive Therapy in the Treatment of Major Depressive Disorder. *Neuropsychobiology* 2020; **79**: 408-416 [PMID: 32344410 DOI: 10.1159/000505553]
3   **Gazdag G**, Ungvari GS. Electroconvulsive therapy: 80 years old and still going strong. *World J Psychiatry* 2019; **9**: 1-6 [PMID: 30631748 DOI: 10.5498/wjp.v9.i1.1]
4   **Micallef-Trigona B**, Spiteri J. Maintenance electroconvulsive therapy in a patient with treatment-resistant paranoid schizophrenia and comorbid epilepsy. *Case Rep Psychiatry* 2012; **2012**: 374752 [PMID: 22953149 DOI: 10.1155/2012/374752]
5   **Luchini F**, Medda P, Mariani MG, Mauri M, Toni C, Perugi G. Electroconvulsive therapy in catatonic patients: Efficacy and predictors of response. *World J Psychiatry* 2015; **5**: 182-192 [PMID: 26110120 DOI: 10.5498/wjp.v5.i2.182]
6   **Reininghaus EZ**, Reininghaus B, Ille R, Fitz W, Lassnig RM, Ebner C, Annamaria P, Hofmann P, Kapfhammer HP, Reingard A, Fazekas F, Ropele S, Enzinger C. Clinical effects of electroconvulsive therapy in severe depression and concomitant changes in cerebral glucose metabolism--an exploratory study. *J Affect Disord* 2013; **146**: 290-294 [PMID: 23122530 DOI: 10.1016/j.jad.2012.07.034]
7   **Loo CK**, Mahon M, Katalinic N, Lyndon B, Hadzi-Pavlovic D. Predictors of response to ultrabrief right unilateral electroconvulsive therapy. *J Affect Disord* 2011; **130**: 192-197 [PMID: 20961620 DOI: 10.1016/j.jad.2010.09.016]
8   **Wade BS**, Joshi SH, Njau S, Leaver AM, Vasavada M, Woods RP, Gutman BA, Thompson PM, Espinoza R, Narr KL. Effect of Electroconvulsive Therapy on Striatal Morphometry in Major Depressive Disorder. *Neuropsychopharmacology* 2016; **41**: 2481-2491 [PMID: 27067127 DOI: 10.1038/npp.2016.48]
9   **Coffey CE**, Figiel GS, Djang WT, Sullivan DC, Herfkens RJ, Weiner RD. Effects of ECT on brain

structure: a pilot prospective magnetic resonance imaging study. *Am J Psychiatry* 1988; **145**: 701-706 [PMID: 3369556 DOI: 10.1176/ajp.145.6.701]

10   **Figiel GS**, Coffey CE, Weiner RD. Brain Magnetic Resonance Imaging in Elderly Depressed Patients Receiving Electroconvulsive Therapy. *Convuls Ther* 1989; **5**: 26-34 [PMID: 11940991]

11   **Oltedal L**, Bartsch H, Sørhaug OJ, Kessler U, Abbott C, Dols A, Stek ML, Ersland L, Emsell L, van Eijndhoven P, Argyelan M, Tendolkar I, Nordanskog P, Hamilton P, Jorgensen MB, Sommer IE, Heringa SM, Draganski B, Redlich R, Dannlowski U, Kugel H, Bouckaert F, Sienaert P, Anand A, Espinoza R, Narr KL, Holland D, Dale AM, Oedegaard KJ. The Global ECT-MRI Research Collaboration (GEMRIC): Establishing a multi-site investigation of the neural mechanisms underlying response to electroconvulsive therapy. *Neuroimage Clin* 2017; **14**: 422-432 [PMID: 28275543 DOI: 10.1016/j.nicl.2017.02.009]

12   **Nordanskog P**, Dahlstrand U, Larsson MR, Larsson EM, Knutsson L, Johanson A. Increase in hippocampal volume after electroconvulsive therapy in patients with depression: a volumetric magnetic resonance imaging study. *J ECT* 2010; **26**: 62-67 [PMID: 20190603 DOI: 10.1097/YCT.0b013e3181a95da8]

13   **Abbott CC**, Jones T, Lemke NT, Gallegos P, McClintock SM, Mayer AR, Bustillo J, Calhoun VD. Hippocampal structural and functional changes associated with electroconvulsive therapy response. *Transl Psychiatry* 2014; **4**: e483 [PMID: 25405780 DOI: 10.1038/tp.2014.124]

14   **Bouckaert F**, De Winter FL, Emsell L, Dols A, Rheebergen D, Wampers M, Sunaert S, Stek M, Sienaert P, Vandenbulcke M. Grey matter volume increase following electroconvulsive therapy in patients with late life depression: a longitudinal MRI study. *J Psychiatry Neurosci* 2016; **41**: 105-114 [PMID: 26395813 DOI: 10.1503/jpn.140322]

15   **Oudega ML**, van Exel E, Stek ML, Wattjes MP, van der Flier WM, Comijs HC, Dols A, Scheltens P, Barkhof F, Eikelenboom P, van den Heuvel OA. The structure of the geriatric depressed brain and response to electroconvulsive therapy. *Psychiatry Res* 2014; **222**: 1-9 [PMID: 24686000 DOI: 10.1016/j.pscychresns.2014.03.002]

16   **Sartorius A**, Demirakca T, Böhringer A, Clemm von Hohenberg C, Aksay SS, Bumb JM, Kranaster L, Ende G. Electroconvulsive therapy increases temporal gray matter volume and cortical thickness. *Eur Neuropsychopharmacol* 2016; **26**: 506-517 [PMID: 26792445 DOI: 10.1016/j.euroneuro.2015.12.036]

17   **Redlich R**, Opel N, Grotegerd D, Dohm K, Zaremba D, Bürger C, Münker S, Mühlmann L, Wahl P, Heindel W, Arolt V, Alferink J, Zwanzger P, Zavorotnyy M, Kugel H, Dannlowski U. Prediction of Individual Response to Electroconvulsive Therapy *via* Machine Learning on Structural Magnetic Resonance Imaging Data. *JAMA Psychiatry* 2016; **73**: 557-564 [PMID: 27145449 DOI: 10.1001/jamapsychiatry.2016.0316]

18   **van Waarde JA**, Scholte HS, van Oudheusden LJ, Verwey B, Denys D, van Wingen GA. A functional MRI marker may predict the outcome of electroconvulsive therapy in severe and treatment-resistant depression. *Mol Psychiatry* 2015; **20**: 609-614 [PMID: 25092248 DOI: 10.1038/mp.2014.78]

19   **Gusnard DA**, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. *Nat Rev Neurosci* 2001; **2**: 685-694 [PMID: 11584306 DOI: 10.1038/35094500]

20   **Qiu H**, Li X, Luo Q, Li Y, Zhou X, Cao H, Zhong Y, Sun M. Alterations in patients with major depressive disorder before and after electroconvulsive therapy measured by fractional amplitude of low-frequency fluctuations (fALFF). *J Affect Disord* 2019; **244**: 92-99 [PMID: 30326347 DOI: 10.1016/j.jad.2018.10.099]

21   **Sinha P**, Joshi H, Ithal D. Resting State Functional Connectivity of Brain With Electroconvulsive Therapy in Depression: Meta-Analysis to Understand Its Mechanisms. *Front Hum Neurosci* 2020; **14**: 616054 [PMID: 33551779 DOI: 10.3389/fnhum.2020.616054]

22   **Wei Q**, Bai T, Chen Y, Ji G, Hu X, Xie W, Xiong Z, Zhu D, Wei L, Hu P, Yu Y, Wang K, Tian Y. The Changes of Functional Connectivity Strength in Electroconvulsive Therapy for Depression: A Longitudinal Study. *Front Neurosci* 2018; **12**: 661 [PMID: 30319341 DOI: 10.3389/fnins.2018.00661]

23   **Mo Y**, Wei Q, Bai T, Zhang T, Lv H, Zhang L, Ji G, Yu F, Tian Y, Wang K. Bifrontal electroconvulsive therapy changed regional homogeneity and functional connectivity of left angular gyrus in major depressive disorder. *Psychiatry Res* 2020; **294**: 113461 [PMID: 33038791 DOI: 10.1016/j.psychres.2020.113461]

24   **Sun H**, Jiang R, Qi S, Narr KL, Wade BS, Upston J, Espinoza R, Jones T, Calhoun VD, Abbott CC, Sui J. Preliminary prediction of individual response to electroconvulsive therapy using whole-brain functional magnetic resonance imaging data. *Neuroimage Clin* 2020; **26**: 102080 [PMID: 31735637 DOI: 10.1016/j.nicl.2019.102080]

25   **Liu Y**, Du L, Li Y, Liu H, Zhao W, Liu D, Zeng J, Li X, Fu Y, Qiu H, Qiu T, Hu H, Meng H, Luo Q. Antidepressant Effects of Electroconvulsive Therapy Correlate With Subgenual Anterior Cingulate Activity and Connectivity in Depression. *Medicine (Baltimore)* 2015; **94**: e2033 [PMID: 26559309 DOI: 10.1097/MD.0000000000002033]

26   **Cano M**, Cardoner N, Urretavizcaya M, Martínez-Zalacaín I, Goldberg X, Via E, Contreras-Rodríguez O, Camprodon J, de Arriba-Arnau A, Hernández-Ribas R, Pujol J, Soriano-Mas C, Menchón JM. Modulation of Limbic and Prefrontal Connectivity by Electroconvulsive Therapy in Treatment-resistant Depression: A Preliminary Study. *Brain Stimul* 2016; **9**: 65-71 [PMID: 26440406 DOI: 10.1016/j.brs.2015.08.016]

27   **Leaver AM**, Wade B, Vasavada M, Hellemann G, Joshi SH, Espinoza R, Narr KL. Fronto-Temporal

Connectivity Predicts ECT Outcome in Major Depression. *Front Psychiatry* 2018; **9**: 92 [PMID: 29618992 DOI: 10.3389/fpsyt.2018.00092]

28   **Qiu H**, Li X, Zhao W, Du L, Huang P, Fu Y, Qiu T, Xie P, Meng H, Luo Q. Electroconvulsive Therapy-Induced Brain Structural and Functional Changes in Major Depressive Disorders: A Longitudinal Study. *Med Sci Monit* 2016; **22**: 4577-4586 [PMID: 27888657 DOI: 10.12659/msm.898081]

29   **Argyelan M**, Lencz T, Kaliora S, Sarpal DK, Weissman N, Kingsley PB, Malhotra AK, Petrides G. Subgenual cingulate cortical activity predicts the efficacy of electroconvulsive therapy. *Transl Psychiatry* 2016; **6**: e789 [PMID: 27115120 DOI: 10.1038/tp.2016.54]

30   **Bai T**, Wei Q, Zu M, Xie W, Wang J, Gong-Jun J, Yu F, Tian Y, Wang K. Functional plasticity of the dorsomedial prefrontal cortex in depression reorganized by electroconvulsive therapy: Validation in two independent samples. *Hum Brain Mapp* 2019; **40**: 465-473 [PMID: 30240504 DOI: 10.1002/hbm.24387]

31   **Miskowiak KW**, Macoveanu J, Jørgensen MB, Ott CV, Støttrup MM, Jensen HM, Jørgensen A, Harmer CJ, Paulson OB, Siebner HR, Kessing LV. Effect of electroconvulsive therapy on neural response to affective pictures: A randomized, sham-controlled fMRI study. *Eur Neuropsychopharmacol* 2018; **28**: 915-924 [PMID: 29891215 DOI: 10.1016/j.euroneuro.2018.05.013]

32   **Redlich R**, Bürger C, Dohm K, Grotegerd D, Opel N, Zaremba D, Meinert S, Förster K, Repple J, Schnelle R, Wagenknecht C, Zavorotnyy M, Heindel W, Kugel H, Gerbaulet M, Alferink J, Arolt V, Zwanzger P, Dannlowski U. Effects of electroconvulsive therapy on amygdala function in major depression - a longitudinal functional magnetic resonance imaging study. *Psychol Med* 2017; **47**: 2166-2176 [PMID: 28397635 DOI: 10.1017/S0033291717000605]

33   **Masuoka T**, Tateno A, Sakayori T, Tiger M, Kim W, Moriya H, Ueda S, Arakawa R, Okubo Y. Electroconvulsive therapy decreases striatal dopamine transporter binding in patients with depression: A positron emission tomography study with [^{18}F]FE-PE2I. *Psychiatry Res Neuroimaging* 2020; **301**: 111086 [PMID: 32464340 DOI: 10.1016/j.pscychresns.2020.111086]

34   **Tiger M**, Svensson J, Liberg B, Saijo T, Schain M, Halldin C, Farde L, Lundberg J. [^{11}C]raclopride positron emission tomography study of dopamine-D$_{2/3}$ receptor binding in patients with severe major depressive episodes before and after electroconvulsive therapy and compared to control subjects. *Psychiatry Clin Neurosci* 2020; **74**: 263-269 [PMID: 31943514 DOI: 10.1111/pcn.12980]

35   **Baldinger-Melich P**, Gryglewski G, Philippe C, James GM, Vraka C, Silberbauer L, Balber T, Vanicek T, Pichler V, Unterholzner J, Kranz GS, Hahn A, Winkler D, Mitterhauser M, Wadsak W, Hacker M, Kasper S, Frey R, Lanzenberger R. The effect of electroconvulsive therapy on cerebral monoamine oxidase A expression in treatment-resistant depression investigated using positron emission tomography. *Brain Stimul* 2019; **12**: 714-723 [PMID: 30635228 DOI: 10.1016/j.brs.2018.12.976]

36   **Yatham LN**, Liddle PF, Lam RW, Zis AP, Stoessl AJ, Sossi V, Adam MJ, Ruth TJ. Effect of electroconvulsive therapy on brain 5-HT(2) receptors in major depression. *Br J Psychiatry* 2010; **196**: 474-479 [PMID: 20513859 DOI: 10.1192/bjp.bp.109.069567]

37   **Meyer JH**, Kapur S, Eisfeld B, Brown GM, Houle S, DaSilva J, Wilson AA, Rafi-Tari S, Mayberg HS, Kennedy SH. The effect of paroxetine on 5-HT(2A) receptors in depression: an [(18)F]setoperone PET imaging study. *Am J Psychiatry* 2001; **158**: 78-85 [PMID: 11136637 DOI: 10.1176/appi.ajp.158.1.78]

38   **Mischoulon D**, Dougherty DD, Bottonari KA, Gresham RL, Sonawalla SB, Fischman AJ, Fava M. An open pilot study of nefazodone in depression with anger attacks: relationship between clinical response and receptor binding. *Psychiat Res-Neuroim* 2002; **116**: 151-161 [DOI: 10.1016/S0925-4927(02)00082-3]

39   **Yatham LN**, Liddle PF, Dennie J, Shiah IS, Adam MJ, Lane CJ, Lam RW, Ruth TJ. Decrease in brain serotonin 2 receptor binding in patients with major depression following desipramine treatment: a positron emission tomography study with fluorine-18-labeled setoperone. *Arch Gen Psychiatry* 1999; **56**: 705-711 [PMID: 10435604 DOI: 10.1001/archpsyc.56.8.705]

40   **Lanzenberger R**, Baldinger P, Hahn A, Ungersboeck J, Mitterhauser M, Winkler D, Micskei Z, Stein P, Karanikas G, Wadsak W, Kasper S, Frey R. Global decrease of serotonin-1A receptor binding after electroconvulsive therapy in major depression measured by PET. *Mol Psychiatry* 2013; **18**: 93-100 [PMID: 22751491 DOI: 10.1038/mp.2012.93]

41   **Abbott CC**, Gallegos P, Rediske N, Lemke NT, Quinn DK. A review of longitudinal electroconvulsive therapy: neuroimaging investigations. *J Geriatr Psychiatry Neurol* 2014; **27**: 33-46 [PMID: 24381234 DOI: 10.1177/0891988713516542]

42   **Bak J**, Lee SM, Kwon YJ, Shim SH, Kim JI. The Normalization of Brain ^{18}F-fluorodeoxy-D-glucose Positron Emission Tomography Hypometabolism following Electroconvulsive Therapy in a 55-year-old Woman with Treatment-resistant Late Onset Depression: A Case Report. *Clin Psychopharmacol Neurosci* 2017; **15**: 82-86 [PMID: 28138119 DOI: 10.9758/cpn.2017.15.1.82]

43   **Hassamal S**, Jolles P, Pandurangi A. Reversal of cerebral glucose hypometabolism on positron emission tomography with electroconvulsive therapy in an elderly patient with a psychotic episode. *Psychogeriatrics* 2016; **16**: 376-381 [PMID: 26756319 DOI: 10.1111/psyg.12174]

44   **Sanacora G**, Treccani G, Popoli M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. *Neuropharmacology* 2012; **62**: 63-77 [PMID: 21827775 DOI: 10.1016/j.neuropharm.2011.07.036]

45 **Walter M**, Henning A, Grimm S, Schulte RF, Beck J, Dydak U, Schnepf B, Boeker H, Boesiger P, Northoff G. The relationship between aberrant neuronal activation in the pregenual anterior cingulate, altered glutamatergic metabolism, and anhedonia in major depression. *Arch Gen Psychiatry* 2009; **66**: 478-486 [PMID: 19414707 DOI: 10.1001/archgenpsychiatry.2009.39]

46 **Arnone D**, Mumuni AN, Jauhar S, Condon B, Cavanagh J. Indirect evidence of selective glial involvement in glutamate-based mechanisms of mood regulation in depression: meta-analysis of absolute prefrontal neuro-metabolic concentrations. *Eur Neuropsychopharmacol* 2015; **25**: 1109-1117 [PMID: 26028038 DOI: 10.1016/j.euroneuro.2015.04.016]

47 **Grimm S**, Ernst J, Boesiger P, Schuepbach D, Boeker H, Northoff G. Reduced negative BOLD responses in the default-mode network and increased self-focus in depression. *World J Biol Psychiatry* 2011; **12**: 627-637 [PMID: 21247256 DOI: 10.3109/15622975.2010.545145]

48 **Merkl A**, Schubert F, Quante A, Luborzewski A, Brakemeier EL, Grimm S, Heuser I, Bajbouj M. Abnormal cingulate and prefrontal cortical neurochemistry in major depression after electroconvulsive therapy. *Biol Psychiatry* 2011; **69**: 772-779 [PMID: 20951980 DOI: 10.1016/j.biopsych.2010.08.009]

49 **Pfleiderer B**, Michael N, Erfurth A, Ohrmann P, Hohmann U, Wolgast M, Fiebich M, Arolt V, Heindel W. Effective electroconvulsive therapy reverses glutamate/glutamine deficit in the left anterior cingulum of unipolar depressed patients. *Psychiat Res-Neuroim* 2003; **122**: 185-192 [DOI: 10.1016/s0925-4927(03)00003-9]

50 **Baldinger P**, Lotan A, Frey R, Kasper S, Lerer B, Lanzenberger R. Neurotransmitters and electroconvulsive therapy. *J ECT* 2014; **30**: 116-121 [PMID: 24820941 DOI: 10.1097/YCT.0000000000000138]

51 **Njau S**, Joshi SH, Espinoza R, Leaver AM, Vasavada M, Marquina A, Woods RP, Narr KL. Neurochemical correlates of rapid treatment response to electroconvulsive therapy in patients with major depression. *J Psychiatry Neurosci* 2017; **42**: 6-16 [PMID: 27327561 DOI: 10.1503/jpn.150177]

52 **Michael N**, Erfurth A, Ohrmann P, Arolt V, Heindel W, Pfleiderer B. Metabolic changes within the left dorsolateral prefrontal cortex occurring with electroconvulsive therapy in patients with treatment resistant unipolar depression. *Psychol Med* 2003; **33**: 1277-1284 [PMID: 14580081 DOI: 10.1017/s0033291703007931]

53 **Kobayashi K**, Imoto Y, Yamamoto F, Kawasaki M, Ueno M, Segi-Nishida E, Suzuki H. Rapid and lasting enhancement of dopaminergic modulation at the hippocampal mossy fiber synapse by electroconvulsive treatment. *J Neurophysiol* 2017; **117**: 284-289 [PMID: 27784811 DOI: 10.1152/jn.00740.2016]

54 **Jorgensen A**, Magnusson P, Hanson LG, Kirkegaard T, Benveniste H, Lee H, Svarer C, Mikkelsen JD, Fink-Jensen A, Knudsen GM, Paulson OB, Bolwig TG, Jorgensen MB. Regional brain volumes, diffusivity, and metabolite changes after electroconvulsive therapy for severe depression. *Acta Psychiatr Scand* 2016; **133**: 154-164 [PMID: 26138003 DOI: 10.1111/acps.12462]

55 **Lloyd KG**, Morselli PL, Bartholini G. GABA and affective disorders. *Med Biol* 1987; **65**: 159-165 [PMID: 2821330]

56 **Esel E**, Kose K, Hacimusalar Y, Ozsoy S, Kula M, Candan Z, Turan T. The effects of electroconvulsive therapy on GABAergic function in major depressive patients. *J ECT* 2008; **24**: 224-228 [PMID: 18562944 DOI: 10.1097/YCT.0b013e31815cbaa1]

57 **Sanacora G**, Mason GF, Rothman DL, Hyder F, Ciarcia JJ, Ostroff RB, Berman RM, Krystal JH. Increased cortical GABA concentrations in depressed patients receiving ECT. *Am J Psychiatry* 2003; **160**: 577-579 [PMID: 12611844 DOI: 10.1176/appi.ajp.160.3.577]

58 **Knudsen MK**, Near J, Blicher AB, Videbech P, Blicher JU. Magnetic resonance (MR) spectroscopic measurement of γ-aminobutyric acid (GABA) in major depression before and after electroconvulsive therapy. *Acta Neuropsychiatr* 2019; **31**: 17-26 [PMID: 30079857 DOI: 10.1017/neu.2018.22]

59 **Tosun Ş**, Tosun M, Akansel G, Gökbakan AM, Ünver H, Tural Ü. Proton magnetic resonance spectroscopic analysis of changes in brain metabolites following electroconvulsive therapy in patients with major depressive disorder. *Int J Psychiatry Clin Pract* 2020; **24**: 96-101 [PMID: 31825726 DOI: 10.1080/13651501.2019.1699118]

60 **Ende G**, Braus DF, Walter S, Weber-Fahr W, Henn FA. The hippocampus in patients treated with electroconvulsive therapy: a proton magnetic resonance spectroscopic imaging study. *Arch Gen Psychiatry* 2000; **57**: 937-943 [PMID: 11015811 DOI: 10.1001/archpsyc.57.10.937]

61 **Han KM**, Choi S, Jung J, Na KS, Yoon HK, Lee MS, Ham BJ. Cortical thickness, cortical and subcortical volume, and white matter integrity in patients with their first episode of major depression. *J Affect Disord* 2014; **155**: 42-48 [PMID: 24210630 DOI: 10.1016/j.jad.2013.10.021]

62 **Tendolkar I**, van Beek M, van Oostrom I, Mulder M, Janzing J, Voshaar RO, van Eijndhoven P. Electroconvulsive therapy increases hippocampal and amygdala volume in therapy refractory depression: a longitudinal pilot study. *Psychiatry Res* 2013; **214**: 197-203 [PMID: 24090511 DOI: 10.1016/j.pscychresns.2013.09.004]

63 **Nordanskog P**, Larsson MR, Larsson EM, Johanson A. Hippocampal volume in relation to clinical and cognitive outcome after electroconvulsive therapy in depression. *Acta Psychiatr Scand* 2014; **129**: 303-311 [PMID: 23745780 DOI: 10.1111/acps.12150]

64 **Gyger L**, Ramponi C, Mall JF, Swierkosz-Lenart K, Stoyanov D, Lutti A, von Gunten A, Kherif F, Draganski B. Temporal trajectory of brain tissue property changes induced by electroconvulsive therapy. *Neuroimage* 2021; **232**: 117895 [PMID: 33617994 DOI: 10.1016/j.neuroimage.2021.117895]

65   **Enneking V**, Dzvonyar F, Dück K, Dohm K, Grotegerd D, Förster K, Meinert S, Lemke H, Klug M, Waltemate L, Goltermann J, Hülsmann C, Borgers T, Böhnlein J, Sindermann L, Richter M, Leehr EJ, Repple J, Opel N, Baune BT, Dannlowski U, Redlich R. Brain functional effects of electroconvulsive therapy during emotional processing in major depressive disorder. *Brain Stimul* 2020; **13**: 1051-1058 [PMID: 32388195 DOI: 10.1016/j.brs.2020.03.018]

66   **Machino A**, Kunisato Y, Matsumoto T, Yoshimura S, Ueda K, Yamawaki Y, Okada G, Okamoto Y, Yamawaki S. Possible involvement of rumination in gray matter abnormalities in persistent symptoms of major depression: an exploratory magnetic resonance imaging voxel-based morphometry study. *J Affect Disord* 2014; **168**: 229-235 [PMID: 25064808 DOI: 10.1016/j.jad.2014.06.030]

67   **Depping MS**, Wolf ND, Vasic N, Sambataro F, Thomann PA, Christian Wolf R. Specificity of abnormal brain volume in major depressive disorder: a comparison with borderline personality disorder. *J Affect Disord* 2015; **174**: 650-657 [PMID: 25577159 DOI: 10.1016/j.jad.2014.11.059]

68   **Gryglewski G**, Baldinger-Melich P, Seiger R, Godbersen GM, Michenthaler P, Klöbl M, Spurny B, Kautzky A, Vanicek T, Kasper S, Frey R, Lanzenberger R. Structural changes in amygdala nuclei, hippocampal subfields and cortical thickness following electroconvulsive therapy in treatment-resistant depression: longitudinal analysis. *Br J Psychiatry* 2019; **214**: 159-167 [PMID: 30442205 DOI: 10.1192/bjp.2018.224]

69   **Cao B**, Luo Q, Fu Y, Du L, Qiu T, Yang X, Chen X, Chen Q, Soares JC, Cho RY, Zhang XY, Qiu H. Predicting individual responses to the electroconvulsive therapy with hippocampal subfield volumes in major depression disorder. *Sci Rep* 2018; **8**: 5434 [PMID: 29615675 DOI: 10.1038/s41598-018-23685-9]

70   **Joshi SH**, Espinoza RT, Pirnia T, Shi J, Wang Y, Ayers B, Leaver A, Woods RP, Narr KL. Structural Plasticity of the Hippocampus and Amygdala Induced by Electroconvulsive Therapy in Major Depression. *Biol Psychiatry* 2016; **79**: 282-292 [PMID: 25842202 DOI: 10.1016/j.biopsych.2015.02.029]

71   **Ota M**, Noda T, Sato N, Okazaki M, Ishikawa M, Hattori K, Hori H, Sasayama D, Teraishi T, Sone D, Kunugi H. Effect of electroconvulsive therapy on gray matter volume in major depressive disorder. *J Affect Disord* 2015; **186**: 186-191 [PMID: 26247910 DOI: 10.1016/j.jad.2015.06.051]

72   **van Eijndhoven P**, Mulders P, Kwekkeboom L, van Oostrom I, van Beek M, Janzing J, Schene A, Tendolkar I. Bilateral ECT induces bilateral increases in regional cortical thickness. *Transl Psychiatry* 2016; **6**: e874 [PMID: 27552587 DOI: 10.1038/tp.2016.139]

73   **Jiang R**, Abbott CC, Jiang T, Du Y, Espinoza R, Narr KL, Wade B, Yu Q, Song M, Lin D, Chen J, Jones T, Argyelan M, Petrides G, Sui J, Calhoun VD. SMRI Biomarkers Predict Electroconvulsive Treatment Outcomes: Accuracy with Independent Data Sets. *Neuropsychopharmacology* 2018; **43**: 1078-1087 [PMID: 28758644 DOI: 10.1038/npp.2017.165]

74   **Pirnia T**, Joshi SH, Leaver AM, Vasavada M, Njau S, Woods RP, Espinoza R, Narr KL. Electroconvulsive therapy and structural neuroplasticity in neocortical, limbic and paralimbic cortex. *Transl Psychiatry* 2016; **6**: e832 [PMID: 27271858 DOI: 10.1038/tp.2016.102]

75   **Gbyl K**, Videbech P. Electroconvulsive therapy increases brain volume in major depression: a systematic review and meta-analysis. *Acta Psychiatr Scand* 2018; **138**: 180-195 [PMID: 29707778 DOI: 10.1111/acps.12884]

76   **Chen G**, Guo Y, Zhu H, Kuang W, Bi F, Ai H, Gu Z, Huang X, Lui S, Gong Q. Intrinsic disruption of white matter microarchitecture in first-episode, drug-naive major depressive disorder: A voxel-based meta-analysis of diffusion tensor imaging. *Prog Neuropsychopharmacol Biol Psychiatry* 2017; **76**: 179-187 [PMID: 28336497 DOI: 10.1016/j.pnpbp.2017.03.011]

77   **Yrondi A**, Nemmi F, Billoux S, Giron A, Sporer M, Taib S, Salles J, Pierre D, Thalamas C, Schmitt L, Péran P, Arbus C. Significant Decrease in Hippocampus and Amygdala Mean Diffusivity in Treatment-Resistant Depression Patients Who Respond to Electroconvulsive Therapy. *Front Psychiatry* 2019; **10**: 694 [PMID: 31607967 DOI: 10.3389/fpsyt.2019.00694]

78   **Gryglewski G**, Seiger R, Baldinger-Melich P, Unterholzner J, Spurny B, Vanicek T, Hahn A, Kasper S, Frey R, Lanzenberger R. Changes in White Matter Microstructure After Electroconvulsive Therapy for Treatment-Resistant Depression. *Int J Neuropsychopharmacol* 2020; **23**: 20-25 [PMID: 31740958 DOI: 10.1093/ijnp/pyz059]

79   **Repple J**, Meinert S, Bollettini I, Grotegerd D, Redlich R, Zaremba D, Bürger C, Förster K, Dohm K, Stahl F, Opel N, Hahn T, Enneking V, Leehr EJ, Böhnlein J, Leenings R, Kaehler C, Emden D, Winter NR, Heindel W, Kugel H, Bauer J, Arolt V, Benedetti F, Dannlowski U. Influence of electroconvulsive therapy on white matter structure in a diffusion tensor imaging study. *Psychol Med* 2020; **50**: 849-856 [PMID: 31010441 DOI: 10.1017/S0033291719000758]

80   **Kubicki A**, Leaver AM, Vasavada M, Njau S, Wade B, Joshi SH, Loureiro J, Hellemann G, Woods RP, Espinoza R, Narr KL. Variations in Hippocampal White Matter Diffusivity Differentiate Response to Electroconvulsive Therapy in Major Depression. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2019; **4**: 300-309 [PMID: 30658916 DOI: 10.1016/j.bpsc.2018.11.003]

81   **Lyden H**, Espinoza RT, Pirnia T, Clark K, Joshi SH, Leaver AM, Woods RP, Narr KL. Electroconvulsive therapy mediates neuroplasticity of white matter microstructure in major depression. *Transl Psychiatry* 2014; **4**: e380 [PMID: 24713861 DOI: 10.1038/tp.2014.21]

Observational Study

Prevalence and clinical characteristics of COVID-19 in inpatients with schizophrenia in Wuhan, China

Hong-Wei Sheng, Hong-Gang Wang, Chun-Zhi Wang, Jiang Wu, Li-Jian Huo, Ruo-Xi Wang, Yong-Jie Zhou, Xiang-Yang Zhang

ORCID number: Hong-Wei Sheng 0000-0001-6440-5611; Hong-Gang Wang 0000-0001-5714-6463; Chun-Zhi Wang 0000-0003-1005-1461; Jiang Wu 0000-0001-9166-8222; Li-Jian Huo 0000-0003-1756-5967; Ruo-Xi Wang 0000-0002-9695-0582; Yong-Jie Zhou 0000-0001-6384-2684; Xiang-Yang Zhang 0000-0003-3326-382X.

Author contributions: Zhang XY, Zhou YJ, and Sheng HW designed the study; Sheng HY, Wu J, Huo LJ, and Huang W were responsible for collecting the clinical data; Wang HG and Wang CZ collected the literature and cleaned the data; Zhou YJ and Zeng LY did statistical analysis; Zhou YJ and Sheng HW wrote the manuscript; Zhang XY reviewed and revised the manuscript.

Institutional review board statement: The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The Wuhan Youfu Hospital received approval for this study from the institutional review board of the Institute of Psychology, Chinese Academy of Sciences. Given the urgent need for data collection and retrospective research, no written informed consent was required for these

Hong-Wei Sheng, Jiang Wu, Department of Psychiatry, Wuhan Youfu Hospital, Wuhan 430070, Hubei Province, China

Hong-Gang Wang, Chun-Zhi Wang, Qingdao Mental Health Center, Qingdao University, Qingdao 266000, Shandong Province, China

Li-Jian Huo, Xiang-Yang Zhang, CAS Key Laboratory of Mental Health, Chinese Academy of Sciences, Beijing 10000, China

Ruo-Xi Wang, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430070, Hubei Province, China

Yong-Jie Zhou, Department of Psychiatric Rehabilitation, Shenzhen Kangning Hospital, Shenzhen 510810, Guangdong Province, China

Corresponding author: Xiang-Yang Zhang, MD, PhD, CAS Key Laboratory of Mental Health, Chinese Academy of Sciences, 16 Lincui Road, Chaoyang District, Beijing 10000, China. zhangxy@psych.ac.cn

Abstract

BACKGROUND
In contrast to many Western countries, China has maintained its large psychiatric hospitals. The prevalence and clinical characteristics of coronavirus disease 2019 (COVID-19) in inpatients with schizophrenia (SCZ) are unclear.

AIM
To assess the prevalence of COVID-19 among inpatients with SCZ and compare the infected to uninfected SCZ patients in a Wuhan psychiatric hospital.

METHODS
We retrospectively collected demographic characteristics and clinical profiles of all SCZ patients with COVID-19 at Wuhan's Youfu Hospital.

RESULTS
Among the 504 SCZ patients, 84 had COVID-19, and we randomly sampled 174 who were uninfected as a comparison group. The overall prevalence of COVID-19 in SCZ patients was 16.7%. Among the 84 SCZ patients with confirmed COVID-19, the median age was 54 years and 76.2% were male. The most common

symptom was fever (82%), and less common symptoms were cough (31%), poor appetite (20%), and fatigue (16%). Compared with SCZ patients without COVID-19, those with COVID-19 were older (P = 0.006) and significantly lighter (P = 0.002), and had more comorbid physical diseases (P = 0.001). Surprisingly, those infected were less likely to be smokers (< 0.001) or to be treated with clozapine (P = 0.03). Further logistic regression showed that smoking [odds ratio (OR) = 5.61], clozapine treated (OR = 2.95), and male (OR = 3.48) patients with relatively fewer comorbid physical diseases (OR = 0.098) were at a lower risk for COVID-19. SCZ patients with COVID-19 presented primarily with fever, but only one-third had a cough, which might otherwise be the most common mode of transmission between individuals.

CONCLUSION
Two unexpected protective factors for COVID-19 among SCZ inpatients are smoking and clozapine treatment.

Key Words: Mental health; Schizophrenia; Inpatient; Epidemiology

Core Tip: In contrast to many Western countries, China has maintained its large psychiatric hospitals. The prevalence and clinical characteristics of coronavirus disease 2019 (COVID-19) in inpatients with schizophrenia (SCZ) are unclear. Our aim was to assess the prevalence of COVID-19 among inpatients with SCZ and compare the infected to uninfected SCZ patients in a Wuhan psychiatric hospital. Two unexpected protective factors for COVID-19 among SCZ inpatients are smoking and clozapine treatment.

INTRODUCTION

On December 8, 2019, several cases of acute respiratory illness with unknown etiology were reported in Wuhan, Hubei Province, China[1-4], which is now well-known as coronavirus disease 2019 (COVID-19) pneumonia (CP)[4-6]. By early January, 2020, the Chinese Center for Disease Control and Prevention (CDC) identified the coronavirus from samples of bronchoalveolar lavage fluid of a patient in Wuhan[2]. Among the initially identified COVID-19 patients, most (73%) were men, and their clinical symptoms included fever (98%), cough (76%), dyspnoea (55%), and myalgia or fatigue (44%) with less common symptoms being secretion of sputum, headache, and diarrhea. All CP patients had abnormal chest CT manifestations, and 63% had lymphopenia. Some CP patients had complications such as acute respiratory distress syndrome (ARDS), acute cardiac injury, and secondary infection. Six (15%) of the 41 hospitalized CP cases died[1]. A subsequent study of COVID-19 patients confirmed the association in older men with medical comorbidities[3]. Common symptoms included fever (99%), fatigue (70%), and dry cough (59%). Laboratory tests showed that 70% had lymphopenia, and chest CT displayed bilateral patchy shadows or ground glass opacity in the lungs of all patients. As of February 3, the overall mortality was 4.3%[4]. The most recent report from the Chinese CDC on the initially confirmed 425 CP patients in Wuhan found a slightly higher percentage of men (56%) and a median age of 59 years. The estimated contagion number was 2.2 with a 95% confidence interval (CI) of 1.4-3.9[5], which is substantially greater than that of influenza or severe acute respiratory syndrome (SARS), and predicts robust human to human transmission through respiratory spread[7-8].

Schizophrenia (SCZ) is one of the most common severe mental disorders, characterized by positive and negative symptoms and cognitive impairment, affecting about 1% of the world's population[9-10]. In China, the prevalence of SCZ is similar, suggesting that genetic factors may play a critical role in the occurrence of this disease [11-12]. Given the huge population of 1.3 billion in China, the number of SCZ individuals is very large. Compared with the number of 20000 psychiatrists in China, the number of SCZ patients is much larger. Therefore, in the large mental health hospitals in China, the resources for managing this COVID-19 epidemic are very limited, and these SCZ inpatients are expected to be highly contagious.

Therefore, we investigated the CP situation among SCZ inpatients in one of the major psychiatric hospitals in Wuhan during this COVID-19 pandemic with several major objectives. First, we sought to estimate the prevalence and clinical characteristics of the hospitalized SCZ patients with confirmed CP in Wuhan's public psychiatric hospitals. Second, we compared the clinical profiles, especially the potential risk and protective factors, among SCZ patients with *vs* without symptomatic COVID-19, some of whom went on to develop CP and a smaller percentage died from CP.

MATERIALS AND METHODS

Subjects

The Wuhan Youfu Hospital (Wuhan, Hubei Province, China) housed 586 psychiatric inpatients during the COVID epidemic. The first confirmed case of CP at this hospital occurred on January 8, 2020. As of February 29, 2020, there were 84 confirmed SCZ cases with CP at the hospital, and we included all CP cases in this study. After the first case emerged, the hospital set up isolation wards for COVID-19 patients, with airborne preventive measures, and immediately transferred all confirmed patients to these special wards.

There were eight wards in the hospital. In one ward, there were ten rooms with 60-80 hospitalized patients. The patients met each other among rooms in one ward. If one patient had COVID-19, he or she had an equal opportunity to make all other patients in the same room or at the same ward infected. Once a patient was found to have symptoms of fever or infection, the entire room was isolated on the spot. Then, the fever patient was transferred to a separate ward for isolation treatment, and other patients in the ward where the fever patient was located were isolated and observed in the room for 14 d.

Just 3 to 4 mo before the outbreak of COVID-19 in September, 2019, the Institute of Psychology, Chinese Academy of Sciences randomly recruited 174 patients with SCZ from Wuhan Youfu Hospital to conduct another study, which we used as an approximately two to one control group for comparison to the 84 schizophrenics with COVID-19 in this study.

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The Wuhan Youfu Hospital received approval for this study from the institutional review board of the Institute of Psychology, Chinese Academy of Sciences. Given the urgent need for data collection and retrospective research, no written informed consent was required for these current analyses.

Data collection

We designed a special Case Record Form to collect general information, sociodemographic data, and clinical, laboratory, radiological, and treatment data from electronic medical records for all psychiatric patients with and without confirmed COVID-19. Two researchers independently reviewed the data collection forms to confirm the accuracy of the data collected. If there were any ambiguous data related to COVID-19, such as epidemiological data, we made additional interviews with patients or their family members.

COVID-19 was diagnosed according to the World Health Organization (WHO) interim guidelines[13], and was confirmed by real-time reverse transcription-polymerase chain reaction (RT-PCR) or next-generation sequencing assay of throat swab specimens[1]. The Wuhan CDC Laboratory confirmed COVID-19 before January 23, 2020, and the diagnosis was subsequently confirmed in certified tertiary care hospitals. RT-PCR testing followed the protocol set up by the WHO. Of 84 SCZ cases, 58 were laboratory-confirmed and the others were confirmed by chest radiography or computed tomography (CT) plus clinical symptoms. In addition, we defined the degree of severity of COVID-19 (severe *vs* non-severe) at the time of admission using the American Thoracic Society guidelines for community-acquired pneumonia[14].

We extracted additional data related to novel coronavirus from electronic medical records: History of exposure to novel coronavirus and possible pathway, clinical symptoms or signs, laboratory results, and chest radiologic assessments. Laboratory assessments included whole blood cell count, coagulation profile, and blood biochemical analysis (such as C-reactive protein, albumin/globulin ratio, creatinine kinase, myocardial enzymes, liver and renal function, blood glucose and lipid profiles, and electrolytes). In addition, we tested for seven types of common viruses (including influenza, avian influenza, respiratory syncytial virus, adenovirus, parainfluenza virus, SARS-CoV, and MERS-CoV) in throat swab specimens using real-time RT-PCR methods. Finally, most patients underwent chest CT or radiography as well as electro-cardiograms when their physical condition indicated such testing.

Study outcomes

The main endpoints were transfer to a designated COVID-19 hospital due to development of a serious condition requiring a ventilator, or death. The secondary endpoints were the rate of death and the time from symptom onset to the main endpoints[6].

We defined ARDS and shock according to the WHO interim guidelines.

Statistical analysis

We express continuous variables as medians and interquartile ranges or simple ranges, as appropriate, and categorical variables as the number and percentages. Since all the demographic and clinical data are normally distributed (Kolmogorov-Smirnov one-sample test, $P > 0.05$), comparisons of demographic and clinical variables between different groups were performed using analysis of variance for continuous variables and chi-square test for categorical variables. We used analysis of covariance to control for confounding factors. We describe the prevalence of COVID-19 in both sexes with percentages and analyzed them by chi-square tests. A binary logistic regression analysis was performed to assess which factors were independently associated with COVID-19. We applied Bonferroni corrections to each test to adjust for multiple testing, and used SPSS (version 18.0, Chicago, IL, United States) to do all statistical analyses with a two-tailed significance level at 0.05.

RESULTS

Demographic and clinical features

By February 29, 2020, we identified 84 SCZ inpatients with COVID-19 at Wuhan Youfu Hospital. Of the 84 cases, 58 were laboratory-confirmed and the other 26 were confirmed by chest radiography or CT plus clinical symptoms. The prevalence of COVID-19 among the SCZ inpatients was 16.7% (84/504). The first two SCZ patients were diagnosed with COVID-19 on January 8, 2020. Table 1 shows the data for all 101 psychiatric patients with COVID-19.

Among all the 84 SCZ patients, 64 were male, and the age ranged from 19 to 81 years with a median age of 54 years. Besides their SCZ disorders, more than half (*n* = 44) of the patients with COVID-19 had comorbid physical diseases before they had COVID-19, including hypertension (*n* = 22), diabetes (*n* = 8), anemia (*n* = 7), leukopenia (*n* = 7), and cerebral infarction (*n* = 2).

The most common symptoms of the COVID-19 patients were fever (82%; the highest temperature of 40.5 °C, with 4 patients having a temperature ≥ 40 °C), cough (31%), poor appetite (20%), and fatigue (16%). Their fewer common symptoms were chest tightness (15%) and shortness of breath (11%); however, no patients reported nausea, vomiting, or diarrhea.

Radiologic and laboratory measurements

Among the 84 patients, 58 had CT scans, with 50 (86%) having abnormal manifest-ations. Among the 58 patients with CT scans, 38 (66%) had bilateral lung involvement. The most common manifestations of chest CT were ground-glass opacity (51%) and bilateral patchy shadowing (46%).

Blood samples were available from 81 patients and 46% had lymphocytopenia, 36% had neutropenia, 34% had leukopenia, and 12% had thrombocytopenia. In addition, 68% of patients had elevated C-reactive protein levels.

Table 1 Clinical characteristics of psychiatric inpatients with coronavirus disease 2019 based on disease severity

	All patients (*n* = 101)	Severe (*n* = 17)	Non-severe (*n* = 84)	F/χ^2	*P*
Age	54.8 ± 12.0	61.3 ± 14.1	53.4 ± 11.2	9.63	0.003
Median (IQR), years	56 (48-63)	65 (57-70)	55 (47-61)		
Distribution, years (%)				14.50	0.001
20-49	30 (29.7%)	2 (11.8%)	28 (33.3%)		
50-64	51 (50.5%)	6 (35.3%)	45 (53.6%)		
≥ 65	20 (19.8%)	9 (52.9%)	11 (13.1%)		
Male/female	72/29 (71.3%/28.7%)	10/7 (58.8%/41.2%)	62/22 (73.8%/26.2%)	1.55	0.21
Blood pressure					
Systolic pressure	122.2 ± 7.2	119.6 ± 6.8	122.8 ± 7.2	2.80	0.09
Diastolic pressure	77.2 ± 5.5	76.9 ± 4.4	77.2 ± 5.7	0.06	0.81
Diagnosis					
Schizophrenia	84	10	74		
Bipolar disorder	4	1	3		
Alzheimer's Disease	4	4	0		
Mental retardation	3	1	2		
Epileptic psychosis	3	0	3		
Organic mental disorder	3	1	2		
Weight (kg)	62.1 ± 10.3	55.8 ± 7.7	63.2 ± 10.4	1.62	0.21
Smoker/non-smoker	14/76	1/10	13/66	0.40	0.53
Duration of illness (yr)	27.9 ± 11.8	31.7 ± 14.4	27.4 ± 11.4	1.41	0.24
Age of onset (yr)	26.9 ± 11.0	34.3 ± 17.5	25.8 ± 9.4	2.56	0.11
Comorbid physical diseases	43 (48.8%)	13 (76.5%)	40 (47.6%)	4.72	0.03
Antipsychotics					
Clozapine	14 (13.9%)	3 (17.6%)	11 (13.1%)	0.25	0.62
Non-clozapine	87 (86.1%)	14 (82.4%)	73 (86.9%)		
Antipsychotic dose (mg) (chlorpromazine equivalents)	239.2 ± 156.2	191.0 ± 164.1	264.4 ± 160.8	3.16	0.08

COVID-19: Coronavirus disease 2019; IQR: The interquartile range.

Treatment

The hospital established isolation wards and once a patient showed suspicious symptoms of COVID-19, he/she received laboratory or radiological confirmation, and was transferred to these isolation wards. Among all the 84 patients, 70 received intravenous or oral antibiotic therapy; 55 took oseltamivir at 75 mg-150 mg/d, and 10 took umifenovir at 0.3-0.6 g/d. In addition, 14 and 3 patients received cephalosporin antibiotics and azithromycin, respectively, in combination with oseltamivir or alone. Finally, 17 patients received oxygen therapy and 3 received glucocorticoids.

Among all 84 patients, 13 developed respiratory distress syndrome (RDS), and the median duration from onset of COVID to RDS was 8 d (interquartile range, 5-13). Finally, 11 patients (13.1%) were admitted to an ICU at another hospital and 8 (9.5%) died.

Comparison of SCZ patients with and without COVID-19

Table 1 shows the demographic and clinical characteristics of the SCZ patients with and without COVID-19. Compared to patients without COVID-19, patients with COVID-19 were older (*P* = 0.006), had significantly lower weight (*P* = 0.002) and lower systolic pressure (*P* = 0.005), had more comorbid physical diseases (*P* = 0.001), and were less likely to be smokers (*P* < 0.001). Since there was a significant difference in

antipsychotic treatment between the two groups (F = 14.1, DF = 6, P = 0.03), we further divided the patients into a clozapine and non-clozapine treated group, and found a significant difference in the infection rates between the two groups (32% in non-COVID-19 *vs* 18% in COVID-19; χ^2 = 5.42, P = 0.02). All these significant differences passed the Bonferroni corrections (P < 0.05) except for clozapine treatment (P > 0.05). In addition, there was a trend towards a higher proportion of female patients with COVID-19 (P = 0.07).

Table 2 shows results using logistic regression to adjust for these several significant characteristics distinguishing those with and without COVID-19. The following differences remained significant independent predictors: Comorbid physical diseases, smoking, clozapine treatment, and sex. As indicated by the odds ratios and beta weights, the schizophrenic patients with a lower risk for COVID-19 were clozapine treated males who smoked and had fewer comorbid physical diseases.

DISCUSSION

This first report about COVID-19 among SCZ inpatients contains three key findings. First, and most importantly, the mortality rate from CP of 9.5% among these SCZ inpatients is remarkably higher than that from COVID-19 found in the general population of this epidemic region[5-6]. Second, the most common symptom of COVID-19 in these patients was fever (82%) and the less common symptoms included cough (31%), poor appetite (20%), and fatigue (16%). Third, some unusual and relatively unexpected protective factors for lower rates of COVID-19 included being male and treatment with clozapine, as well as more smoking among these SCZ patients. In contrast to men and smokers, the general population is at a greater risk of contracting COVID-19 and its complications. The other association of risk for COVID-19 with more comorbid physical diseases is consistent with the general population during this epidemic.

The death rate of 9.5% in these SCZ patients with COVID-19 was much higher than the death rate of 1.4%-3.2% in the general Wuhan population with COVID-19[6]. These striking 3 to 7 fold differences in death rates and failure to survive severe complications with 62% (8/13) dying once they developed severe complications suggest that these SCZ patients may be more vulnerable to more direct progression from severe complications to death from COVID-19 and overall less responsive to attempts at treating this infection. A large number of epidemiological studies have shown that high rates of smoking[14-16], obesity[17-18], diabetes[19-20], and cardiovascular diseases[21] occur in SCZ patients, especially in those chronic and medicated patients, and that these comorbid disorders may contribute to a 15%-20% reduction in life expectancy reported in this population[15-21]. Therefore, the chronic SCZ patients in this study may have been vulnerable to higher mortality from COVID-19 based primarily on these other illnesses.

Another remarkable feature in our patients with COVID-19 is the relatively low contagion rate, in spite of almost all patients having clear and repeated contacts with infected patients before these infected patients showed clinical symptoms. We did not test for COVID-19 in all 504 patients so we do not know the actual rate of infection in this group, but relatively few (17%) showed any signs of COVID-19. This low disease rate was remarkable in spite of obvious potential for human-to-human transmission in the hospital with its densely populated wards that had 4-6 people in one room. COVID-19 may be spread through the respiratory or gastrointestinal tract, but gastrointestinal tract symptoms, such as nausea, vomiting, or diarrhea were uncommon in these patients, making upper respiratory tract contagion most likely.

While the most common symptom of fever in 82% of our CP patients was consistent with the 89% community rate, cough frequency (31%), which was much less than the community rate of 68%, might have contributed to the relatively lower contagion rate in these hospitalized patients[1-6]. Moreover, the cough frequency may have been low because of the sedative influence of antipsychotic medication. Additionally, fewer of our patients had gastrointestinal symptoms like nausea or vomiting (5%) and diarrhea (4%) than found in the community[6]. Reasons for these symptom differences may include biological differences in the disease of SCZ and specific medication effects. For example, antipsychotic agents can reduce nausea, vomiting, and diarrhea[22], masking these symptoms in COVID-19, and we found a specific effect of clozapine in reducing risk of COVID-19 induced symptoms and possibly infection itself. From another perspective, we found that nearly half of our patients with COVID-19 exhibited reduced white cell counts, including 46% with lymphocytopenia, 36% with leuko-

Table 2 Characteristics of schizophrenia patients with or without coronavirus disease 2019

	COVID-19 patients (*n* = 84)	Non-COVID-19 patients (*n* = 174)	*F, Z* or χ	*P*
Age (yr)	54.6 ± 9.5	51.1 ± 9.5	7.65	0.006
Gender (Male/ Female)	64/20 (76.2%/23.8%)	137/31 (78.7%/17.8%)	3.36	0.07
Marital status			1.06	0.59
Single	45/75 (60.0%)	104/160 (65.0%)		
Married	9/75 (12.0%)	21/160 (13.1%)		
Divorced	21/75 (28.0%)	35/160 (21.9%)		
Weight (kg)	62.0 ± 10.3	67.8 ± 16.6	9.40	0.002
Blood pressure				
Systolic pressure	122.5 ± 7.2	125.5 ± 8.0	7.98	0.005
Diastolic pressure	77.3 ± 5.7	76.6 ± 6.0	0.81	0.37
Smoker/non-smoker	11/65	92/74	35.8	0.000
Duration of illness (years)	29.4 ± 11.0	27.4 ± 10.3	2.09	0.14
Age of onset (years)	25.4 ± 7.9	23.8 ± 7.3	2.06	0.15
Comorbid physical diseases	43 (48.8%)	44/164 (26.8%)	11.9	0.001
Antipsychotics			14.1	0.03
Olanzapine	18 (21.4%)	16 (9.2%)		
Risperidone	16 (19.0%)	45 (25.9%)		
Clozapine	15 (17.9%)	55 (31.6%)		
Quetiapine	13 (15.5%)	18 (10.3%)		
Aripiprazole	11 (13.1%)	17 (9.8%)		
Ziprasidone	4 (4.8%)	5 (2.9%)		
Typicals	7 (8.3%)	18 (10.3%)		
Antipsychotic dose (mg/d) (chlorpromazine equivalents)	264.4 ± 160.8	226.9 ± 152.8	3.16	0.08

COVID-19: Coronavirus disease 2019.

penia, and 34% with neutropenia, and 12% had thrombocytopenia and 68% had elevated C-reactive protein levels. While these findings are consistent with community patient reductions during COVID-19[1,3,6], antipsychotic drugs, especially clozapine, also are associated with low blood cell counts[23-25]. Therefore, protective effects of clozapine in our patients remain interesting, but in need of replication, while adverse factors in our SCZ patients, such as physical diseases, older age, and lower weight (caused by malnutrition), clearly appear to be risk factors for COVID-19 and its severe complications including death.

The three protective clinical factors of clozapine treatment, smoking, and being male have remarkable associations with COVID-19 among our SCZ inpatients. Moreover, the logistic analysis found significant independent contributions from these three factors for developing COVID-19 symptoms and complications. Biological mechanisms that might contribute to clozapine's association are its anti-inflammatory effects by inhibiting a NOD-like receptor family and the pyrin domain-containing protein-3 inflammasome[26]. Immunosuppression and anti-inflammatory effects of nicotine and smoking may also be a mechanism for the protective effects of smoking on COVID-19. We previously found that SCZ smokers had significantly decreased IL-2 and IL-6 levels, supporting that nicotine may cause immunosuppression in SCZ patients[27].

The association between smoking and COVID-19 has become a controversial topic in the world [28-29]. It is well known that smoking is harmful to health, and COVID-19 is just another example of how smoking may cause lung damage and makes a person at higher risk for COVID-19 and its complications. However, the most recent epidemiological survey demonstrates that current smoking status may protect against COVID-19[30], which may be based on the molecular biology of nicotinic receptor[31]. A recent

hypothesis has proposed that the nicotinic acetylcholine receptor may play a pivotal role in the pathophysiology of COVID-19, and nicotine and nicotinic agents may be a possible treatment for COVID-19[30]. Thus, our finding that smoking had a protective effect on COVID-19 among the SCZ inpatients appears to provide the new clinical support for this hypothesis. However, due to the limited sample size in this study, our finding should be replicated in a larger sample of smoking SCZ patients in further investigation. In addition, angiotensin-converting enzyme-2 (ACE2) receptor is a novel adhesion molecule through which SARS-CoV-2 can invade target cells causing COVID-19[32,33]. Interestingly, some recent studies found a connection between smoking and COVID-19[34]. Moreover, smokers had higher ACE2 gene expression than never-smokers, while nicotine may up-regulate ACE2 receptors, suggesting that smokers may be more susceptible to COVID-19, and smoking may exacerbates mortality[35]. Taken together, the relationship between smoking and COVID-19 is still contradictory, which deserves further study.

Our study has some limitations. First, a few cases had missing or incomplete symptom data due to the urgent situation in providing treatments. Second, about one-third of patients did not have COVID-19 laboratory tests to confirm their diagnosis due to restrictions in testing availability. Third, due to the much older age of the SCZ patients with COVID-19, some had unavoidable recall problems with some clinical data. Fourth, since many patients were still in the hospital when we extracted the data, and the outcome was unknown at the time of data cutoff, we were only able to use data about their clinical outcome at the time of data analysis. More patients may have died, for example, beyond the window of this study timeframe, and we did not have data on the prevalence of asymptomatic COVID-19 within this inpatient population to enable an accurate assessment of contagion among these inpatients. Fifth, there is a lack of the data on the possible change of mental clinical state in the infected patients. Hence, we did not know whether there was any change in their symptoms of SCZ at the time of their infection.

CONCLUSION

In summary, we have found a seemingly higher prevalence of COVID-19 among the SCZ inpatients than that in the general population in Wuhan. Moreover, the 9.5% mortality of these patients with CP is remarkably higher than that in the general population from this region. These findings suggest that these primarily SCZ patients may be more vulnerable to death from severe complications of COVID-19 and need rapid and intensive interventions once clinicians detect COVID-19. While some symptoms like fever occurred at similar rates in our patients and in the community, other symptoms like cough and gastrointestinal symptoms were less common, and other symptoms, such as poor appetite and fatigue, were substantially more common in our SCZ patients. Less coughing may have reduced contagion and lack of vomiting and diarrhea may have limited fecal spread. Finally, our SCZ patients with COVID-19 had several high risk factors. These infected patients were older, had lower weight and more comorbid physical diseases, and unexpectedly, had a less smoking rate and less treatment with clozapine. It appears that clozapine treatment and smoking may be protective for COVID-19 among SCZ inpatients, perhaps related to nicotine and clozapine immunosuppression, which deserves further exploration.

ARTICLE HIGHLIGHTS

Research background

In contrast to many Western countries, China has maintained its large psychiatric hospitals. The prevalence and clinical characteristics of coronavirus disease 2019 (COVID-19) in inpatients with schizophrenia (SCZ) are unclear.

Research motivation

In the large mental health hospitals in China, the resources for managing this COVID-19 epidemic are very limited, and these SCZ inpatients are expected to be highly contagious.

Research objectives

To assess the prevalence of COVID-19 among inpatients with SCZ and compare the infected to uninfected SCZ patients in a Wuhan psychiatric hospital.

Research methods

We retrospectively collected demographic characteristics and clinical profiles of all SCZ patients with COVID-19 at Wuhan's Youfu Hospital.

Research results

Among the 504 SCZ patients, 84 had COVID-19, and we randomly sampled 174 who were uninfected as a comparison group. The overall prevalence of COVID-19 in SCZ inpatients was 16.7%. Among these 84 SCZ patients with confirmed COVID-19, the median age was 54 years and 76.2% were male. The most common symptom was fever (82%), and less common symptoms were cough (31%), poor appetite (20%), and fatigue (16%). Compared with SCZ patients without COVID-19, patients with COVID-19 were older ($P = 0.006$), significantly lighter ($P = 0.002$), and had more comorbid physical diseases ($P = 0.001$). Surprisingly, those infected were less likely to be smokers (< 0.001) or to be treated with clozapine ($P = 0.03$). Further logistic regression showed that smoking [odds ratio (OR) = 5.61], clozapine treated (OR = 2.95), and male (OR = 3.48) patients with relatively fewer comorbid physical diseases (OR = 0.098) were at lower risk of COVID-19. The SCZ patients with COVID-19 presented primarily with fever, but only one-third had a cough, which might otherwise be the most common mode of transmission between individuals.

Research conclusions

Two unexpected protective factors for COVID-19 among these SCZ inpatients are smoking and clozapine treatment.

Research perspectives

Clozapine treatment and smoking may be protective for COVID-19 among SCZ inpatients, perhaps related to nicotine and clozapine immunosuppression, which deserves further exploration.

REFERENCES

1　**Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]

2　**Zhu N**, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020; **382**: 727-733 [PMID: 31978945 DOI: 10.1056/NEJMoa2001017]

3　**Chen N**, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-513 [PMID: 32007143 DOI: 10.1016/S0140-6736(20)30211-7]

4　**Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]

5　**Li Q**, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Liu M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JT, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med* 2020; **382**: 1199-1207 [PMID: 31995857 DOI: 10.1056/NEJMoa2001316]

6　**Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020; **382**: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]

7　**Chan JF**, Yuan S, Kok KH, To KK, Chu H, Yang J, Xing F, Liu J, Yip CC, Poon RW, Tsoi HW, Lo SK, Chan KH, Poon VK, Chan WM, Ip JD, Cai JP, Cheng VC, Chen H, Hui CK, Yuen KY. A

familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020; **395**: 514-523 [PMID: 31986261 DOI: 10.1016/S0140-6736(20)30154-9]

8   **Phan LT**, Nguyen TV, Luong QC, Nguyen HT, Le HQ, Nguyen TT, Cao TM, Pham QD. Importation and Human-to-Human Transmission of a Novel Coronavirus in Vietnam. *N Engl J Med* 2020; **382**: 872-874 [PMID: 31991079 DOI: 10.1056/NEJMc2001272]

9   **Kahn RS**, Sommer IE, Murray RM, Meyer-Lindenberg A, Weinberger DR, Cannon TD, O'Donovan M, Correll CU, Kane JM, van Os J, Insel TR. Schizophrenia. *Nat Rev Dis Primers* 2015; **1**: 15067 [PMID: 27189524 DOI: 10.1038/nrdp.2015.67]

10   **Charlson FJ**, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG, McGrath JJ, Whiteford HA. Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016. *Schizophr Bull* 2018; **44**: 1195-1203 [PMID: 29762765 DOI: 10.1093/schbul/sby058]

11   **Phillips MR**, Zhang J, Shi Q, Song Z, Ding Z, Pang S, Li X, Zhang Y, Wang Z. Prevalence, treatment, and associated disability of mental disorders in four provinces in China during 2001-05: an epidemiological survey. *Lancet* 2009; **373**: 2041-2053 [PMID: 19524780 DOI: 10.1016/S0140-6736(09)60660-7]

12   **Huang Y**, Wang Y, Wang H, Liu Z, Yu X, Yan J, Yu Y, Kou C, Xu X, Lu J, Wang Z, He S, Xu Y, He Y, Li T, Guo W, Tian H, Xu G, Ma Y, Wang L, Yan Y, Wang B, Xiao S, Zhou L, Li L, Tan L, Zhang T, Ma C, Li Q, Ding H, Geng H, Jia F, Shi J, Wang S, Zhang N, Du X, Wu Y. Prevalence of mental disorders in China: a cross-sectional epidemiological study. *Lancet Psychiatry* 2019; **6**: 211-224 [PMID: 30792114 DOI: 10.1016/S2215-0366(18)30511-X]

13   **World Health Organization**.   Coronavirus disease (COVID-19) outbreak 2020. [cited 13 February 2021]. Available from: https://www.who.int/health-topics/coronavirus#tab=tab_1

14   **Metlay JP**, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, Cooley LA, Dean NC, Fine MJ, Flanders SA, Griffin MR, Metersky ML, Musher DM, Restrepo MI, Whitney CG. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* 2019; **200**: e45-e67 [PMID: 31573350 DOI: 10.1164/rccm.201908-1581ST]

15   **Zhang XY**, Liang J, Chen DC, Xiu MH, He J, Cheng W, Wu Z, Yang FD, Haile CN, Sun H, Lu L, Kosten TA, Kosten TR. Cigarette smoking in male patients with chronic schizophrenia in a Chinese population: prevalence and relationship to clinical phenotypes. *PLoS One* 2012; **7**: e30937 [PMID: 22347412 DOI: 10.1371/journal.pone.0030937]

16   **King M**, Jones R, Petersen I, Hamilton F, Nazareth I. Cigarette smoking as a risk factor for schizophrenia or all non-affective psychoses. *Psychol Med* 2020; 1-9 [PMID: 32148211 DOI: 10.1017/S0033291720000136]

17   **Tian Y**, Liu D, Wang D, Wang J, Xu H, Dai Q, Andriescue EC, Wu HE, Xiu M, Chen D, Wang L, Chen Y, Yang R, Wu A, Wei CW, Zhang X. Obesity in Chinese patients with chronic schizophrenia: Prevalence, clinical correlates and relationship with cognitive deficits. *Schizophr Res* 2020; **215**: 270-276 [PMID: 31653580 DOI: 10.1016/j.schres.2019.10.017]

18   **Manu P**, Dima L, Shulman M, Vancampfort D, De Hert M, Correll CU. Weight gain and obesity in schizophrenia: epidemiology, pathobiology, and management. *Acta Psychiatr Scand* 2015; **132**: 97-108 [PMID: 26016380 DOI: 10.1111/acps.12445]

19   **Suvisaari J**, Keinänen J, Eskelinen S, Mantere O. Diabetes and Schizophrenia. *Curr Diab Rep* 2016; **16**: 16 [PMID: 26803652 DOI: 10.1007/s11892-015-0704-4]

20   **Hoffman RP**. The Complex Inter-Relationship Between Diabetes and Schizophrenia. *Curr Diabetes Rev* 2017; **13**: 528-532 [PMID: 28000544 DOI: 10.2174/1573399812666161201205322]

21   **Kritharides L**, Chow V, Lambert TJ. Cardiovascular disease in patients with schizophrenia. *Med J Aust* 2017; **206**: 91-95 [PMID: 28152356 DOI: 10.5694/mja16.00650]

22   **Sutherland A**, Naessens K, Plugge E, Ware L, Head K, Burton MJ, Wee B. Olanzapine for the prevention and treatment of cancer-related nausea and vomiting in adults. *Cochrane Database Syst Rev* 2018; **9**: CD012555 [PMID: 30246876 DOI: 10.1002/14651858.CD012555.pub2]

23   **Hollingworth SA**, Winckel K, Saiepour N, Wheeler AJ, Myles N, Siskind D. Clozapine-related neutropenia, myocarditis and cardiomyopathy adverse event reports in Australia 1993-2014. *Psychopharmacology (Berl)* 2018; **235**: 1915-1921 [PMID: 29589067 DOI: 10.1007/s00213-018-4881-0]

24   **Manu P**, Lapitskaya Y, Shaikh A, Nielsen J. Clozapine Rechallenge After Major Adverse Effects: Clinical Guidelines Based on 259 Cases. *Am J Ther* 2018; **25**: e218-e223 [PMID: 29505490 DOI: 10.1097/MJT.0000000000000715]

25   **Verdoux H**, Quiles C, de Leon J. Clinical determinants of fever in clozapine users and implications for treatment management: A narrative review. *Schizophr Res* 2019; **211**: 1-9 [PMID: 31378552 DOI: 10.1016/j.schres.2019.07.040]

26   **Giridharan VV**, Scaini G, Colpo GD, Doifode T, Pinjari OF, Teixeira AL, Petronilho F, Macêdo D, Quevedo J, Barichello T. Clozapine Prevents Poly (I:C) Induced Inflammation by Modulating NLRP3 Pathway in Microglial Cells. *Cells* 2020; **9** [PMID: 32121312 DOI: 10.3390/cells9030577]

27   **Zhang XY**, Cao LY, Song C, Wu GY, Chen DC, Qi LY, Wang F, Xiu MH, Chen S, Zhang Y, Lu L, Kosten TA, Kosten TR. Lower serum cytokine levels in smokers than nonsmokers with chronic schizophrenia on long-term treatment with antipsychotics. *Psychopharmacology (Berl)* 2008; **201**: 383-389 [PMID: 18719893 DOI: 10.1007/s00213-008-1295-4]

28   **Berlin I**, Thomas D, Le Faou AL, Cornuz J. COVID-19 and Smoking. *Nicotine Tob Res* 2020; **22**: 1650-1652 [PMID: 32242236 DOI: 10.1093/ntr/ntaa059]

29   **Vardavas CI**, Nikitara K. COVID-19 and smoking: A systematic review of the evidence. *Tob Induc Dis* 2020; **18**: 20 [PMID: 32206052 DOI: 10.18332/tid/119324]

30   **Miyara M**, Tubach F, Pourcher V, Morelot-Panzini C, Pernet J, Haroche J, Lebbah S, Morawiec E, Gorochov G, Caumes E, Hausfater P, Combes A, Similowski T, Amoura Z. Low incidence of daily active tobacco smoking in patients with symptomatic COVID-19. *Qeios* 2020 [DOI: 10.32388/WPP19W.3]

31   **Jean-Pierre Changeux**, Amoura Z, Rey F, Miyara M. A nicotinic hypothesis for Covid-19 with preventive and therapeutic implications. *Qeios* 2020 [DOI: 10.32388/FXGQSB.2]

32   **Zemlin AE**, Wiese OJ. Coronavirus disease 2019 (COVID-19) and the renin-angiotensin system: A closer look at angiotensin-converting enzyme 2 (ACE2). *Ann Clin Biochem* 2020; **57**: 339-350 [PMID: 32369402 DOI: 10.1177/0004563220928361]

33   **South AM**, Diz DI, Chappell MC. COVID-19, ACE2, and the cardiovascular consequences. *Am J Physiol Heart Circ Physiol* 2020; **318**: H1084-H1090 [PMID: 32228252 DOI: 10.1152/ajpheart.00217.2020]

34   **Wang J**, Luo Q, Chen R, Chen T, Li J.   Susceptibility Analysis of COVID-19 in Smokers Based on ACE2. 2020 Preprint. Available from: Preprints2020030078 [DOI: 10.20944/preprints202003.0078.v1]

35   **Brake SJ**, Barnsley K, Lu W, McAlinden KD, Eapen MS, Sohal SS. Smoking Upregulates Angiotensin-Converting Enzyme-2 Receptor: A Potential Adhesion Site for Novel Coronavirus SARS-CoV-2 (Covid-19). *J Clin Med* 2020; **9** [PMID: 32244852 DOI: 10.3390/jcm9030841]

Neurobiological mechanisms underlying delayed expression of posttraumatic stress disorder: A scoping review

Geert E Smid, Jonna Lind, Jens Peter Bonde

ORCID number: Geert E Smid 0000-0002-9616-5234; Jonna Lind 0000-0001-9739-9115; Jens Peter Bonde 0000-0002-8181-3673.

Geert E Smid, ARQ Centrum'45, ARQ National Psychotrauma Centre, Diemen 1112XE, Netherlands

Geert E Smid, Department of Humanist Chaplaincy Studies, University of Humanistic Studies, Utrecht 3512 HD, Netherlands

Jonna Lind, ARQ Centre of Excellence on War, Persecution and Violence, ARQ National Psychotrauma Centre, Diemen 1112XE, Netherlands

Jens Peter Bonde, Department of Occupational and Environmental Medicine, Frederiksberg and Bispebjerg Hospital, Copenhagen 2400, Denmark

Jens Peter Bonde, Department of Public Health, University of Copenhagen, Copenhagen 1014, Denmark

Corresponding author: Geert E Smid, MD, PhD, Professor, ARQ Centrum'45, ARQ National Psychotrauma Centre, Nienoord 5, Diemen 1112XE, Netherlands. g.smid@centrum45.nl

Abstract

BACKGROUND
The capacity of posttraumatic stress disorder (PTSD) to occur with delayed onset has been documented in several systematic reviews and meta-analyses. Neurobiological models of PTSD may provide insight into the mechanisms underlying the progressive increase in PTSD symptoms over time as well as into occasional occurrences of long-delayed PTSD with few prodromal symptoms.

AIM
To obtain an overview of key concepts explaining and types of evidence supporting neurobiological underpinnings of delayed PTSD.

METHODS
A scoping review of studies reporting neurobiological findings relevant to delayed PTSD was performed, which included 38 studies in the qualitative synthesis.

RESULTS
Neurobiological mechanisms underlying PTSD symptoms, onset, and course involve several interconnected systems. Neural mechanisms involve the neurocircuitry of fear, comprising several structures, such as the hippocampus, amygdala, and prefrontal cortex, that are amenable to time-dependent increases in activity

through sensitization and kindling. Neural network models explain generalization of the fear response. Neuroendocrine mechanisms consist of autonomic nervous system and hypothalamic-pituitary-adrenocortical axis responses, both of which may be involved in sensitization to stress. Neuroinflammatory mechanisms are characterized by immune activation, which is sometimes due to the effects of traumatic brain injury. Finally, neurobehavioral/contextual mechanisms involve the effects of intervening stressors and mental and physical disorder comorbidities, and these may be particularly relevant in cases of long-delayed PTSD.

CONCLUSION
Thus, delayed PTSD may result from multiple underlying neurobiological mechanisms that may influence the likelihood of developing prodromal symptoms preceding the onset of full-blown PTSD.

Key Words: Posttraumatic stress disorder; Delayed expression; Sensitization; Neurobiology; Neuroendocrine; Neuroinflammatory

Core Tip: Multiple neurobiological mechanisms underlying delayed expression of posttraumatic stress disorder contribute to sensitization, kindling, and generalization leading to increasing symptoms, through epigenetic, neuroinflammatory, neuroendocrine, and neural interactions.

INTRODUCTION

Posttraumatic stress disorder (PTSD) with delayed expression (also known as delayed PTSD or delayed-onset PTSD) is a diagnostic category that applies to people who first meet the criteria for a PTSD diagnosis at least 6 mo following exposure to a traumatic event[1]. While the majority of people who develop PTSD do so within the first wk or mo following the traumatic encounter, a significant minority of people with PTSD present delayed expression of the disorder[2-4]. Since the inclusion of the PTSD diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) in 1980, a delayed category has been discerned[5]. Subsequently, the capacity of PTSD to occur with delayed expression has been documented in several systematic reviews and meta-analyses[2-4]. A proper understanding of the neurobiological basis for delayed expression of PTSD is clinically useful since it has implications for diagnostic assessment in both treatment and forensic settings and in the context of litigation. Specifically, neurobiological models of PTSD may explain variability in the progressive increase in PTSD symptoms over time following exposure to trauma that characterizes PTSD with delayed expression. Neurobiological mechanisms and systems are likely to play a central role in determining the duration of the prodromal phase, the presence of prodromal symptoms and mental and physical disorder comorbidities.

Because delayed expression is the exception rather than the rule, neurobiological mechanisms underlying delayed PTSD have received limited research attention. We therefore conducted a scoping review to obtain an overview of key concepts explaining and types of evidence supporting neurobiological underpinnings of delayed PTSD. The research questions were to determine what role neurobiological mechanisms have in the delayed expression of PTSD, and how neurobiological mechanisms contribute to explaining the occurrence of delayed PTSD following a long asymptomatic interval.

MATERIALS AND METHODS

Search strategy

Since our aim was to provide an overview of key concepts and types of evidence, we performed a scoping review[6]. We searched for publications examining the role of neurobiological mechanisms in developing delayed PTSD. The PRISMA scoping reviews checklist[7] was used to ensure correct reporting. We did not register the review protocol. The search was performed in early December 2020 in the following databases (all in the Ovid platform): PsycINFO; Ovid Medline ALL, Ovid Evidence Based Medicine Reviews (EBM Reviews - Cochrane Database of Systematic Reviews and EBM Reviews - Database of Abstracts of Reviews of Effects) and Embase. We based the search strategy on the two research questions and several lead articles (which we presented to Ovid Citation Analyzer to harvest search terms). We built a search strategy in PsycINFO (Ovid), which we then adapted to the other databases. The full search strategy for PsycINFO can be found in Supplementary Table 1. The search terms were grouped into clusters. For Question 1 (the role of neurobiological mechanisms in developing delayed PTSD), we had these clusters: etiology and neurobiological factors (sets 1 through 5), late-onset PTSD (set 6), and study types (sets 8 through 11). For Question 2 (delayed PTSD with a long-term asymptomatic interval), we used the following clusters: late-onset PTSD (set 6), remission and asymptomatic periods (set 7) and study types (sets 8 through 11). These clusters were combined using Boolean operators, and the combined clusters for question 1 (set 12) and question 2 (set 13) were combined. The search results were imported into Endnote and deduplicated using the method outlined elsewhere[8]. Supplementary Table 2 shows the number of items retrieved in each search system, the number of duplicates and thus the new articles collected. These articles were then screened for inclusion in this review.

Study selection

To screen and select articles, we used Rayyan, a web-based program for systematic reviews[9]. The screening process consisted of three phases: (1) Stepwise inclusion of records based on titles and abstracts with the aid of automatic Rayyan keywords for inclusion; (2) Manual inclusion and exclusion of records based on the inclusion and exclusion criteria; and (3) Manual exclusion of articles based on the full text. Records were eligible if they were: (1) About trauma and PTSD; (2) About delayed onset; (3) About neurobiology; and (4) About causal mechanisms or risk factors. Therefore, records were excluded if they reported studies that were: (1) Not about trauma and PTSD; (2) Not about delayed onset; (3) Not about neurobiology; or (4) Not about causal mechanisms or risk factors. Additionally, duplicate items were excluded. During the first phase, the references including the keywords in Table 1 were retained. In the second phase, two researchers (GS and JL) independently reviewed the titles and abstracts of the remaining 438 items, which had been preselected based on the keywords. In this phase, we used the same criteria as earlier, as outlined in Table 2. After this phase, 60 articles were screened based on the full text by the first author. Twenty-two articles were excluded, thus arriving at a final selection of 38 articles. Figure 1 shows a PRISMA diagram for an overview of the process.

Statistical analysis

The selected articles were divided into human studies (n = 22), animal studies (n = 4), and review studies (n = 12). From human studies, we abstracted the following data: population (N), the type of trauma or stressor, assessment times, type of PTSD assessment, prevalence of PTSD and delayed PTSD, and neurobiological observation methods. From animal studies, we abstracted the following data: types of animals (N), type of trauma or stressor, assessment times, observed anxiety and delayed effects, and neurobiological observation methods. From review studies, we abstracted the included study types (human and/or animal) and summarized the review focus. An overview of the included human, animal, and review studies is presented in Tables 3, 4 and 5, respectively. A detailed overview of human studies is provided in Supplementary Table 3.

RESULTS

The included studies reported three types of neurobiological mechanisms, specifically neural, neuroendocrine and neuroinflammatory mechanisms. In addition, included

Table 1 Study Selection Phase 1: Keywords used for stepwise including (and thus excluding) items

Criterion	Input for this criterion	Automatic keyword screening (Rayyan): Used keywords for include	Included	Thus excluded
1	5659	Trauma; traumas; traumatic; traumatized; traumatised; posttraumatic; PTSD	5194	465
2	5194	Asymptomatic; bridging; delayed; dormant; emerge; emerges; emerging; increase; increases; increasing; interval; late; latency; latent; onset; progression; progressive; symptom-free	2287	2907
3	2287	Adrenal; adrenalin; allostatic; ANS; autonomous; biochemical; biological; biology; biomarker; biomarkers; brain; cell; ceruleus; chemokine; coeruleus; cortex; cortisol; corticosteroids; corticosteroid; CT; cytokine; cytokines; DNA; epicortisol; epigenetic; epigenomic; epinephrine; frontal; genetic; hippocampus; hippocampal; HPA; hydrocortisone; hypothalamic; hypothalamus; imaging; immune; immunological; inflammation; LC; marker; markers; MRI; NE; nervous; neurobiological; neurobiology; neuroimaging; noradrenalin; norepinephrine; parasympathetic; PET; phenotype; phenotypical; pituitary; PNS; prefrontal; psychobiological; psychobiology; SNS; SPECT; stem; sympathetic	716	1571
4	716	Amnesia; amnesic; amnestic; cause; causal; dissociation; dissociative; factor; mechanism; mechanisms; predictor; protective; risk; sensitisation; sensitised; sensitization; sensitized; stage; staging; susceptibility; trigger; vulnerability	455	261
	455	Deduplication	438	17

ANS: Autonomous nervous system; CT: Computed tomography; HPA: Hypothalamic-pituitary axis; LC: Locus coeruleus; MRI: Magnetic resonance imaging; NE: Norepinephrine; PET: Positron emission tomography; PNS: Parasympathetic nervous system; SNS: Sympathetic nervous system; SPECT: Single photon emission computed tomography; PTSD: Posttraumatic stress disorder.

Table 2 Study Selection Phase 2: Manual title and abstract screening, inclusion and exclusion

Criterion	Input for this criterion	Manual title and abstract screening: Record refers to	Inclusion	Exclusion
1	438	Trauma and PTSD	308	130
2	308	Delayed onset	73	235
3	73	Neurobiology	62	11
4	62	Causal mechanisms or risk factors	60	2
	60	Full-text articles assessed for eligibility	60	

PTSD: Posttraumatic stress disorder.

studies reported neurobehavioral/contextual pathways. The following sections will summarize the findings for each of these types of mechanisms and pathways. An overview of the interconnected neural, neuroendocrine, neuroinflammatory, and neurobehavioral/contextual systems is presented in Figure 2.

Neural mechanisms
Studies of neural mechanisms of PTSD have focused on identifying brain structures involved in fear learning and modeling structural and functional characteristics underlying PTSD symptoms, onset, and course.

The neurocircuitry of fear
Animal research has identified the amygdala, medial prefrontal cortex (PFC), and hippocampus (the so-called limbofrontal neurocircuitry of fear) as the key regions involved in the acquisition, regulation, and extinction of conditioned fear[10].

Amygdala: The most consistent functional abnormality in human PTSD studies is increased amygdalar responsiveness to emotional stimuli, which may or may not be trauma specific. A hyperactive amygdala has been associated with the heightened fear and hyperarousal of patients with PTSD[11]. Consolidation of cued and contextual fear conditioning has been found to be mediated by epigenetic modifications in the amygdala[12].

In a study of healthy trauma-exposed rescue ambulance workers, an increased volume in the left amygdala was found. Left amygdalar volumes positively correlated with suppressed morning salivary cortisol concentrations[13], suggesting amygdalar

Table 3 Overview of Human Studies

Ref.	Population (*n*)	Trauma/stressor	Assessment times
Admon *et al*[14], 2013	Soldiers (33)	Treating a fellow soldier with severe combat injury	Pre-deployment and 18 mo later
Alway *et al*[30], 2016	TBI patients (85)	Motor vehicle accidents (76.5%), other accidents, assaults	6 mo, 1-, 2-, 3-, and 4-yr post-injury
Bryant *et al*[29], 2009	Traumatic injury patients with no (708) or mild TBI (459)	Transport accident, assault, fall, work injury, other injury	During hospital admission and at 3 mo post-injury
Bryant *et al*[28], 2013	Road traffic accident survivors admitted to trauma hospital (1084)	Transport accident, assault, fall, work injury, other injury	During hospital admission and at 3-, 12-, and 24 mos post-injury
Busso *et al*[21], 2014	Adolescents exposed to bombing (78)	Terrorist attack at the 2013 Boston marathon	1 year prior to trauma (*n* = 44), 4-6 wk posttrauma (*n* = 78)
Cacciaglia *et al* [13], 2017	Healthy rescue ambulance workers (18), non-exposed matched controls (18)	Exposed group: vehicle accident (41%), traumatic loss of a loved one, domestic violence, childhood abuse	Cross-sectional; trauma occurred a mean of 7.41 yr ago
Chase *et al*[39], 2015	Help-seeking veterans (16) and family members (10)	Exposure to blast during employment to combat-intense settings	Cross-sectional; > 7 yr after exposure
Do Prado *et al*[31], 2017	Adolescents with childhood trauma (30), controls without history of early life stress (27)	Sexual abuse, physical abuse, emotional abuse, physical neglect, emotional neglect	Cross-sectional; maltreatment ended > 12 mo ago
Gandubert *et al* [19], 2016	Emergency room patients (123)	Physical assault, sexual assault, serious accident, other	During the first week and at 1-, 4-, and 12 mos post-trauma
Gil *et al*[35], 2005	Traumatic brain injury patients (120)	Traffic accident	< 1 week, 3 mo, and 6 mo later
Glenn *et al*[27], 2017	Soldiers deployed to Afghanistan (852)	Combat experience, difficult living and working environment	4 wk before and 22 wk after deployment
Jung *et al*[47], 2019	Community-dwelling women (nurses) (50020)	Various self-reported on Brief Trauma Questionnaire	Biennial from enrollment
Monfort and Trehel[44], 2017	93-year-old veteran (1)	WW II combat experiences	65 years later
Roy *et al*[36], 2015	Combat veterans without PTSD, depression, or post-concussive syndrome < 2 mo after return (81)	Deployment to Iraq or Afghanistan > 3 mo	< 2 mo after return, 3, 6, and 12 mo
Smid *et al*[26], 2015	Deployed soldiers (693)	4 mo deployment to Afghanistan	2 mo prior to deployment and 1-, 6-, 12-, and 24 mo following deployment
Solomon and Mikulincer[42], 2006	Combat veterans with combat stress reaction (CSR) (131) or without (83)	1982 Lebanon War	1, 2, 3, and 20 yr after the war
Solomon *et al*[41], 2017	Ex-prisoners of war (101), combat controls (15)	1973 Yom Kippur War	18, 30, 35, 42 yr after the war
Stein *et al*[43], 2013	Community-dwelling (25,018)	Lifetime exposure to 27 traumatic events	Cross-sectional
Uddin *et al*[32], 2010	PTSD-affected (23) and -unaffected individuals (77) from large sample	Lifetime exposure to 19 traumatic events	Cross-sectional
Vaiva *et al*[20], 2005	Hospitalized traumatology patients (78)	Road traffic accident	1 and 6 wk, 12 mo
Wang *et al*[33], 2015	Blunt chest trauma patients (57)	Motor vehicle accidents (61.4%), falls, other accidents	1, 3, 6 mo
Waszczuk *et al* [46], 2020	First responders (1490)	Working at the World Trade Center site, New York following the 9/11, 2001 terrorist attacks	Mean = 7.75 monitoring visits per 1.49 yr, PTSD diagnosis at 12 yr

involvement in sensitized neuroendocrine responses (see below).

Hippocampus: Guided by evidence from animal studies demonstrating how stress can have a destructive effect on the hippocampus, a brain structure critical for learning and memory, studies in humans have frequently reported reduced hippocampal volume in patients with PTSD[11]. An abnormal hippocampus has been suggested to mediate PTSD-related deficits in the appreciation of safe contexts and contextual memory[11]. Indeed, epigenetic modifications in the hippocampus have been shown

Table 4 Overview of animal studies

Ref.	Animals (*n*)	Trauma/stressor	Assessment times	Anxiety and delayed effects	Neurobiological observation methods
Ardi *et al*[15], 2014	Rats: naïve (12), swim (12), swim + reminder (R) (12), UWT (12), UWT + R (12)	Rats were given daily 1-minute swim trials for 5 days. On day 6, 'swim' rats had an additional swim trial, and 'UWT' rats were swimming and then held underwater for 30 s using a net. On day 7, rats from the 'reminder' groups were exposed to 30 s of swimming	Following the 'reminder', rats were tested after 30 min.; 'swim' and 'UWT' rats were tested on day 7	Undergoing UWT results in reduced exploration in the open field even 24 h after the trauma compared to 'swim' and 'naïve' groups. Exposure to the reminder resulted in significantly enhanced anxiety behavior	electrophysiological recordings of hippocampal dentate gyrus GABA-ergic local circuit activity: paired-pulse inhibition (reflecting feedback inhibition), frequency-dependent inhibition (reflecting feed-forward inhibition), long-term potentiation; biochemical analysis: amygdala extracellular-signal-regulated kinase activity
Justice *et al* [45], 2015	Mice: wild type controls (43) and PTSD-group (65), Alzheimer's Disease model controls (76) and PTSD-group (145)	Mice in the PTSD group were immobilized for 2h on boards with tape in a brightly lit area. For the reminder, the procedure was repeated during 15 min.	2–3 mo and 6–12 mo	Animals displayed elevated anxiety and slightly elevated startle amplitudes	resting and peak plasma corticosteroid levels, cerebrospinal fluid beta-amyloid levels
Serova *et al* [25], 2019	Rats: 1 wk following stress (57), 2 wk following stress (42), controls (56)	Rats were immobilized for 2 h on a board by taping the limbs and restricting motion of the head, then subjected to forced swim for 20 min.	1 or 2 wk following stress	At 1 week, 17.5%, and at 2 wk, 57.1% of animals displayed severe anxiety	Gene expression in the mediobasal hypothalamus and locus coeruleus (LC), immunohistochemistry
Wilson *et al* [34], 2013	Rats: PTSD-group (10), controls (10)	PTSD group rats were secured in plexiglas cylinders and placed in a cage with a cat for one hour on days 1 and 11 of a 31-day stress regimen, and their cage cohort was changed daily	day 0, day 12, day 31	The PTSD group displayed significantly higher anxiety than the control group, and significantly diminished growthrate over the 31-day stress period	Growth, plasma (corticosterone), adrenal glands (weight, oxidative stress), and hippocampus, amygdala, and pre-frontal cortex (oxidative stress and inflammatory markers: interleukin-1β, NALP3-inflammosome, glyceraldehyde 3-phosphate dehydrogenase)

UWT: Underwater trauma; GABA: Gamma aminobutyric acid; NALP3: NACHT, LRR and PYD domains-containing protein 3 (also: nucleotide-binding domain, leucine-rich repeat family pyrin domain containing 3); PTSD: Posttraumatic stress disorder.

to be specifically involved in mediating contextual fear learning[12]. In deployed soldiers, reductions in hippocampal volume and connectivity with the ventromedial PFC from pre- to postdeployment were found to be related to concurrent increases in PTSD symptoms, whereas predeployment low hippocampal volume was not associated with outcomes in terms of PTSD symptoms[14]. However, this latter finding should not be regarded as contradicting prior evidence from homozygotic twins suggesting that smaller hippocampal volume is a predisposing risk factor for PTSD[11,14]. Probably, the effects of predisposing and acquired neural abnormalities are interrelated, such that reduced hippocampal volume may predispose to PTSD, yet at the same time development of PTSD can cause a secondary loss of hippocampal volume over time[11].

Animal research on hippocampal involvement in fear learning revealed time frames related to hippocampal fear memory processing. Consolidation of hippocampus-dependent fear memory can be evaluated 24 h after training, whereas consolidation of remote memory becomes evident at least 7 days after training, when memories from the hippocampus have been integrated for maintenance in the cortex[12]. In animal models of PTSD based on fear conditioning following shock exposure, exposure to a novel, neutral tone provides an index of fear sensitization[12]. Importantly, the expression of sensitized fear to a novel auditory cue has been found to increase with time after shock exposure[12].

A study in rats following underwater trauma exposure and subsequent exposure to a trauma reminder one week later[15] demonstrated the impact of trauma reminders on both the hippocampus and amygdala. While exposure to underwater trauma resulted in increased local circuit inhibitory feedback activity in the hippocampal dentate gyrus, exposure to the trauma reminder resulted in an additional increase in local circuit inhibitory feed-forward activity. Reminder exposure also resulted in impaired hippocampal dentate gyrus long-term potentiation and amygdalar extracellular-signal-regulated-kinase-2 (ERK2) activation, supporting the notion that under emotional conditions, the amygdala modulates stress-induced alterations in the dentate gyrus through the modulation of hippocampal ERK signaling[15].

Table 5 Overview of review studies

Ref.	Study types	Review focus
Admon *et al*[11], 2013	Human	Reviews predisposing and acquired neural abnormalities that can be discerned based on PTSD neuroimaging studies that include genetic, environmental, twin, and prospective data
Belda *et al*[22], 2015	Animal	Reviews sensitization: A phenomenon whereby exposure to a particular stimulus triggers a state of hyperresponsiveness
Kim *et al*[18], 2019	Human, animal	Reviews influences of chronic exposure to stress on the immune system, resulting in increased proinflammatory cytokine levels. Focuses on changes in the amygdala, hippocampus, PFC, and insula, that are particularly influenced by excess cytokines
McFarlane[17], 2000	Human	Focuses on people who develop PTSD de novo, *i.e.*, without preexisting disorder at the time of the traumatic event that may have acted as a risk factor to the onset of PTSD
McFarlane[23], 2010	Human	Examines the issue of the timing of the onset of PTSD following exposure to traumatic events
McFarlane *et al* [16], 2002	Human	Reviews the knowledge from neural networks to model a framework for exploring the relationship between neurobiology, cognition, and behavior in PTSD
McFarlane *et al* [40], 2017	Human	Argues that major advances in the biological treatments of PTSD depend on a more sophisticated classification of PTSD that acknowledges the heterogeneity of this condition
Michopoulos *et al* [24], 2015	Human	Reviews putative PTSD biomarkers with specific emphasis on the interaction between neurobiological influences on disease risk and symptom progression
Smid *et al*[38], 2003	Human	Reviews risk factors for delayed PTSD, including combat trauma, stressful events after the trauma and previous emotional problems
Soreq[37], 2010	Human, animal	Reviews effects that are often reported yr after prophylactic treatment with cholinesterase inhibitors for protection under threat of chemical warfare, *e.g.*, during the Gulf War, and their similarity to symptoms of PTSD
Wilker and Kolassa[10], 2013	Human, animal	Reviews genetic risk factors in PTSD etiology from the perspective of a psychobiological model, which proposes that intrusive memories, the core PTSD symptom, result from the formation of an associative neural fear network, which stores sensory-perceptual representations of traumatic memories
Zovkic *et al*[12], 2013	Human, animal	Discusses epigenetic regulation of PTSD in human studies and in animal models and ways in which these models can be expanded. Reviews the literature that directly addresses the involvement of epigenetics in PTSD and puts it into the broader context of epigenetics in stress and fear learning

PTSD: Posttraumatic stress disorder; PFC: Prefrontal cortex.

Prefrontal cortex: The PFC has been found to display abnormal function and structure in PTSD patients. Specifically, aspects of the medial sections of the medial PFC and anterior cingulate cortex (ACC) have been associated with patients' deficits in emotional regulation[11]. Connectivity studies, either functional or structural, have shown deficient connectivity between the amygdala and/or the hippocampus to the frontal lobe, which could contribute to difficulties that patients with PTSD have in integrating cognitive control over the emotional neural system[11]. Abnormal structure of the amygdala and dorsal ACC and their heightened responsivity to emotionally negative stimuli may represent predisposing neural abnormalities that increase the likelihood of developing PTSD following exposure to trauma[11]. Reduced volumes in medial PFC structures (specifically, the rostral ACC, ventromedial PFC, and orbitofrontal cortex), as well as reduced ventromedial PFC connectivity with the hippocampus, if acquired following exposure to trauma, may lead to PTSD susceptibility[11].

Neural network models

According to neural network models of PTSD, the structure of the neural networks involved in the processing of traumatic memories becomes progressively modified by the repeated replay of these memories through iterative learning, top-down activation and pruning[16]. Noradrenergic neurons play a central role in coordinating the interaction of multiple cortical regions, and functional alterations in the noradrenergic system leading to dysfunctional modulation of working memory in PTSD contribute to intrusive traumatic recollection[16]. Modifications of neural networks have a secondary effect of kindling in the hippocampus that further moderates the individual's sensitivity to a range of stressors[16]. The fear network model assumes that every new trauma activates the same memory structure, given that different
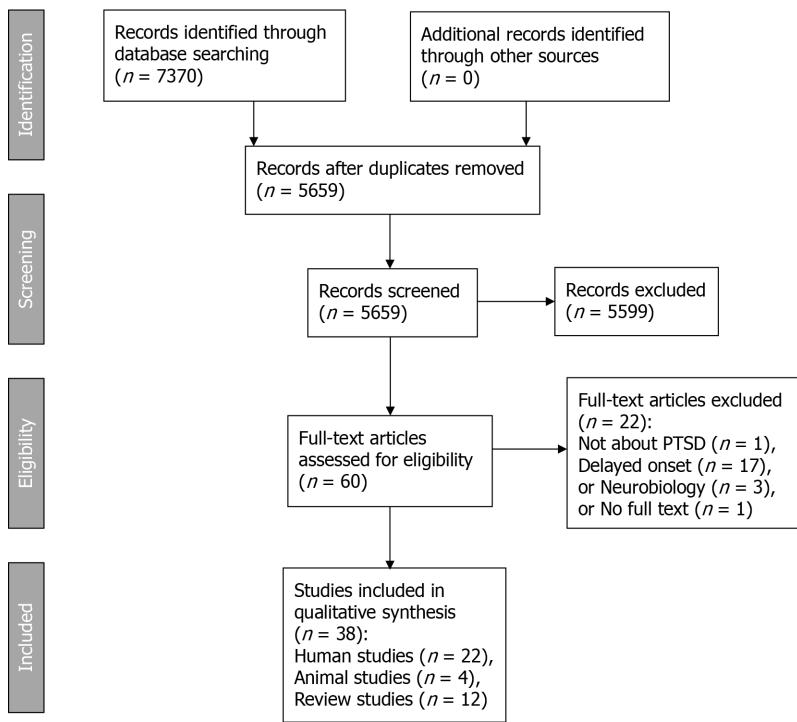
Figure 1 PRISMA flow chart. PTSD: Posttraumatic stress disorder.
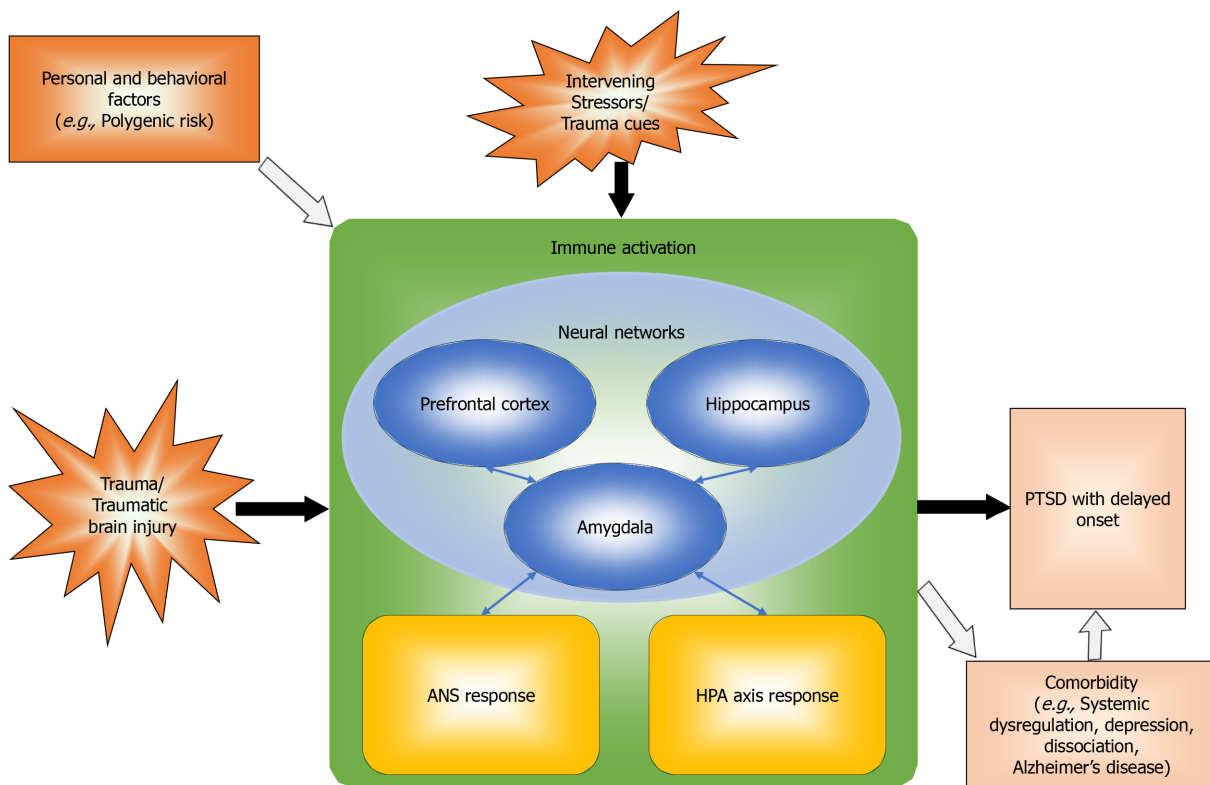
Figure 2 Neural, neuroendocrine, neuroinflammatory, and contextual mechanisms underlying delayed expression of posttraumatic stress disorder. Solid arrows indicate direct effects, open arrows indicate indirect effects. ANS: Autonomic nervous system; HPA: Hypothalamic-pituitary-adrenal; PTSD: Posttraumatic stress disorder.

traumatic experiences share important elements[10]. With each new traumatic event, sensory-perceptional elements are added, and the interconnections of the emerging fear network strengthen. With multiple traumatic events, the network will contain conflicting contextual information from different events. Hence, the memory for

context weakens with increasing traumatic load, followed by the emergence of intrusive symptoms[10]. An individual exposed to sequential trauma who has developed PTSD after a particular traumatic event may develop intrusive and distressing memories of previously experienced traumatic events that had not previously led to symptoms. Due to the pruning of dendrites, inappropriate fusion of memory networks occurs, which explains how a particular traumatic event can serve as an activator of previous traumatic memories[16]. Furthermore, the triggers for intrusive traumatic memories become increasingly more subtle and generalized[16].

Neuroendocrine mechanisms

Neuroendocrine mechanisms involve both neural and endocrine (hormonal) components. Two major neuroendocrine systems have been implicated in the stress response, one involving the autonomic nervous system and the other involving the hypothalamic-pituitary-adrenocortical (HPA) axis. Below, findings relevant to delayed PTSD regarding both neuroendocrine systems are summarized.

Autonomic nervous system responses

The autonomic nervous system responses to stressor exposure involves activation of neurons in the locus coeruleus (LC), the major noradrenergic (norepinephrinergic) nucleus of the brain involved in the regulation of arousal and autonomic activity, leading to adrenalin (epinephrine) release *via* the sympatho-adrenal medullary pathway. Autonomic hyperarousal is a risk factor predicting the course of PTSD[17]. Decreased activity of the parasympathetic nervous system, along with increased activity of the sympathetic nervous system, have been observed in PTSD[18]. In emergency room patients, the waist-to-hip ratio and systolic blood pressure were associated with PTSD 4 and 12 mo later; both measures are biomarkers of autonomic nervous system responses. A higher level of overnight urinary norepinephrine predicted PTSD at 4 mo, and body mass index at baseline was associated with a 12 mo PTSD diagnosis[19]. Gamma amino-butyric acid (GABA) is inversely associated with the intensity and duration of the central hyperadrenergic response in times of high stress. In hospitalized traumatology patients, lower GABA levels one week after hospitalization predicted PTSD 12 mo later. Among victims without PTSD at 6 wk, 80% of subjects with GABA levels below 0.20 nmol/mL developed delayed-onset PTSD[20]. Adolescents who were exposed to a terrorist bombing attack and who had had high levels of sympathetic reactivity during a Trier Social Stress Test (specifically, shorter preejection period on impedance cardiography) preceding the attack exhibited an elevated risk for PTSD symptoms compared to adolescents with low sympathetic reactivity in a context of low levels of exposure to media coverage of the attacks. In the context of high levels of media exposure, youth with high and low sympathetic reactivity exhibited equally high levels of PTSD symptoms. Thus, adolescents with low sympathetic reactivity developed PTSD symptoms only following high exposure to media coverage of the attack[21]. These results suggest that in the absence of pre-exposure vulnerability for PTSD, additional superimposed stress may be needed to trigger PTSD symptom onset.

HPA axis response

The HPA axis response to stressor exposure in humans involves activation of neurons in the hypothalamus that secrete releasing hormones, such as corticotrophin releasing hormone (CRH), that act on the pituitary to promote the secretion of adrenocortico-tropic hormone (ACTH), which in turn acts on the adrenal cortex to initiate the synthesis and release of glucocorticoid hormones, specifically cortisol. Exposure to systemic or high-intensity emotional stressors is followed by HPA axis sensitization. In some studies, with acute immune stressors, HPA sensitization appears to develop over time (incubation), but most studies find a strong initial sensitization that progressively declines over the days[22]. HPA axis cross-sensitization to heterotypic stressors is best observed with short duration (5-15 min) novel challenging stressors[22]. In addition to HPA axis (cross-) sensitization, behavioral sensitization, reflected in different types of animal tests related to fear conditioning and anxiety-like behavior, can be observed, especially following the imposition of a new, brief stressor. Behavioral sensitization appears to persist longer than that of the HPA axis, suggesting long-term latent effects of the initial exposure[22].

In the domain of the HPA axis, the process of sensitization explains why individuals with PTSD become unusually reactive to stress, which is manifested as exaggerated behavioral and biological responses to environmental challenge[23]. A study of healthy trauma-exposed rescue ambulance workers reported hyposuppression of

salivary cortisol in a dexamethasone challenge test. HPA axis sensitization appeared to be associated with amygdalar activity. Specifically, left amygdalar enlargement correlated with suppressed morning salivary cortisol[13]. These findings suggest that asymptomatic, trauma-exposed individuals develop neurobiological features similar to those in patients with PTSD. However, it is unclear whether and how prior trauma exposure affects the time of onset of PTSD symptoms following exposure to subsequent traumatic events.

Emerging genetic and epigenetic findings related to PTSD risk *vs* resilience have focused on modulators of HPA axis function prior to and following trauma[24]. In a study of gene expression in HPA axis-related brain regions in rats exposed to a single prolonged stressor, the percentage of animals displaying severe anxiety increased strongly from 17.5% at one week to 57.1% two wk after stress. This single prolonged stressor elicited time-dependent changes in gene expression for CRH and neuropeptide Y (NPY) systems in the locus coeruleus and hypothalamus. The locus coeruleus displayed prolonged activation, with enhanced gene expression for CRH receptor 1 and reduced gene expression for NPY and Y2 receptors. In the mediobasal hypothalamus, sustained increased CRH gene expression was found, but there was a flip in alterations of gene expression for glucocorticoid receptor (GR), FK506 binding protein 5 (FKBP5) and NPY receptor at two wk compared to one week. Although gene expression for GR and FKBP5 was increased over levels in unstressed rats at 1 wk, it was downregulated by 2 wk. Similarly, robust increases in Y2 receptor and Y5 receptor gene expression were observed at 1 wk, but after 2 wk, only the Y5 receptor differed from the unstressed levels and was downregulated to half the levels that were observed in unstressed rats[25]. These findings illustrate the cascade of neurobiological alterations underlying progressive symptom development following trauma.

Neuroinflammatory mechanisms

An accumulating body of evidence suggests that cytokines play a role in processes such as fear learning and memory that are involved in the pathogenesis of PTSD[18,26, 27]. High levels of proinflammatory cytokines associated with injury, inflammation, and severe psychological stress have been shown to exert direct detrimental effects on memory functioning and neural plasticity[18,26]. Studies of traumatic brain injury (TBI) survivors have yielded additional insights into PTSD progression over time[28-30].

Immune activation

Different mechanisms have been suggested to underlie immune activation following exposure to psychological trauma. In adolescents exposed to childhood maltreatment [31], evidence of immune activation and proinflammatory profiles was found, as well as more circulating lymphocyte subsets associated with cell activation and signs of early immunological aging. Underlying mechanisms included enhanced activation of both mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NFκB) signaling pathways and partial resistance to glucocorticoids, specifically, decreased lymphocyte sensitivity to dexamethasone[31]. In a cross-sectional study of PTSD-affected and PTSD-unaffected individuals, peripheral epigenomic and cytomegalovirus immune response profiles associated with PTSD were consistent with traumatic events inducing downstream alterations in immune function by reducing methylation levels of immune-related genes[32]. In hospitalized blunt chest trauma patients, transfusion, injury severity, and high-mobility group box 1 Levels, a key late mediator of systemic inflammation after one week, were predictive of PTSD at 6 mo, including delayed PTSD[33].

In soldiers reporting high combat stress exposure, both high mitogen-stimulated T-cell cytokine production and high innate cytokine production were associated with increases in PTSD symptoms in response to postdeployment stressful life events. In soldiers exposed to low combat stress and those with low cytokine production, postdeployment stressful life events were not associated with increases in PTSD symptoms. The effects of postdeployment stressful life events on the course of PTSD symptoms after a return from deployment largely depended on combat stress exposure as well as immune reactivity following return from deployment. High combat exposure does not by itself lead to increased sensitivity to postdeployment stressful life events but only in the presence of immune activation, as evidenced by high T-cell and innate cytokine production. Additionally, immune activation by itself is not sufficient to lead to increased reactivity to stressful life events, but only following high combat stress exposure. These findings suggest both beneficial and detrimental effects of high cytokine production, depending on the subsequent occurrence of stressful life events [26].

Heightened activity of the immune system may cause alterations in the structure and function of brain regions such as the amygdala, hippocampus, and PFC through changes in the levels of serotonin and kynurenine pathway metabolites and direct neurotoxic effects of cytokines[18]. Neurotoxic cytokine signaling may occur in conjunction with the production of reactive oxygen species (ROS). A study using a predator exposure/psychosocial stress animal model of PTSD found that proinflammatory cytokines and ROS were elevated in the amygdala, hippocampus, and PFC of the rat brain, indicating increased oxidative stress and inflammation. In addition, oxidative stress and inflammation were elevated systemically, as evidenced by increased ROS and proinflammatory cytokines in the adrenal glands and circulating blood. Importantly, within-group comparisons in the PTSD group of rats demonstrated that superoxide levels and total reactive oxygen species levels progressively increased during the stress regimen[34].

Traumatic brain injury

Studies of TBI survivors contradict the idea that TBI and PTSD are nonoverlapping conditions, as the loss of consciousness and amnesia associated with TBI have been shown not to protect against PTSD. In a study of hospitalized trauma survivors with mild TBI, of the 55 participants with memory of the traumatic event, 13 (23%) developed PTSD, and of the 65 participants without memory of the traumatic event, there were still 4 (6%) who developed PTSD[35]. In another study of TBI patients, the duration of posttraumatic amnesia (PTA) did not significantly differ between participants with acute and delayed-onset PTSD[30]. In a prospective cohort study of traumatic injury patients, mild TBI patients were even more likely to develop PTSD at 3 mo following injury than non-TBI patients. No associations were found between the duration of PTA and PTSD symptoms, but longer PTA was associated with less severe intrusive memories at baseline[29]. The absence of early intrusive symptoms may be associated with an increased likelihood of delayed PTSD. Indeed, in long-term prospective follow-up assessments in the same cohort, in the group with no PTSD at 3 mo, PTSD severity at 24 mo was predicted by PTSD severity during hospitalization, the presence of mild TBI, and the number of days spent in the hospital[28].

In soldiers deployed to Afghanistan, TBI was found to be associated with alterations in fear learning and extinction[27]. Experiencing multiple TBIs within a 2- to 3-year time frame exacerbated conditioned fear, and elevated learned fear contributed to the risk for PTSD after TBI[27]. In combat veterans who had been deployed to Iraq or Afghanistan for over 3 mo and who had no PTSD, depression, or postconcussive syndrome within 2 mo after return, independent predictors of PTSD after one year were single nucleotide polymorphisms in the genes coding for two proteins related to neuronal recovery: myelin basic protein and brain-derived neurotrophic factor; MBP and BDNF may work in concert to protect against or enhance recovery from brain injury, thereby mediating the risk of long-term mechanical and psychological injury [36]. Additional predictive factors were elevated resting state connectivity on functional MRI between the right amygdala and left superior temporal gyrus and reduced volume on MRI of the right superior longitudinal fasciculus tract, connecting the frontal lobe with the parieto-temporal brain regions[36]. Elevated resting activity in the auditory cortex, which is part of the superior temporal gyrus, may prime the brain for enhanced vulnerability to sensory impressions.

In addition to traumatic brain injury, exposure to noxious agents may accompany psychological trauma, particularly in combat-exposed soldiers. An example was the prophylactic treatment with cholinesterase inhibitors, *e.g.,* as prescribed during the Gulf War for protection of soldiers under threat of chemical warfare[37]. Robust elevations in acetylcholine levels occur in both PTSD and during treatment with cholinesterase inhibitors. Acetylcholine interactions with receptors induce, through a calcium-dependent mechanism, the early immediate transcription factor c-Fos. This parallels the immediate stress response, since the expression of c-Fos is drastically elevated within minutes under stress[37]. Long-term, persistent brain changes occur at a very slow pace, sometimes over years. The initial phase of the feedback response probably leads to delayed cascades of the transcription of relevant genes[37].

Intervening stressors

In a review of studies of delayed PTSD[38], several prospective studies provided evidence for stressful life events in the period following exposure to trauma to increase the risk of delayed PTSD. In a prospective cohort study of traumatic injury patients, in participants who had no PTSD at 3 mo, PTSD severity at 24 mo was predicted by the number of adverse life events after the 3 mo assessment, accounting for as much as 9% of the variance[28]. In deployed soldiers, the effects of postdeployment stressful life

events on the course of PTSD symptoms after return from deployment have been shown to depend on combat stress exposure as well as immune reactivity following return from deployment[26]. Postdeployment stressors occur in a context of readjustment to civilian life that may be complicated by a gradual unfolding of symptoms. In a study of veterans and their family members following deployment-relayed traumatic brain injury[39], participants reported that veterans "downplayed" their injuries and later "detached" themselves from friends, family, and communities and "denied" or were "oblivious" to their circumstances until a "wake-up call" pushed them to "get help." Most veterans said that they simply did not see that anything was wrong, while others usually attributed their issues, at least initially, to aging, stress, being tired or overworked or as a part of readjusting to civilian life[39].

Comorbidity

Mental and physical disorder comorbidities may need to be considered as potentially impacting the onset and course of PTSD.

Systemic dysregulation: Based on prospective studies providing substantial evidence about biological abnormalities that precede the full-blown disorder, PTSD has been conceptualized as a systemic disorder characterized by metabolic and immune dysregulations that are reflected in increased rates of cardiovascular and autoimmune disease [40]. A staging model of PTSD has been proposed[40] with the initial stages being characterized by: (1) Asymptomatic downregulation of glucocorticoid receptor sensitivity and increased amygdalar reactivity; (2) Undifferentiated symptoms of mild anxiety and distress, inflammatory cytokine activation, and decreased response inhibition in the frontal cognitive systems; and (3) Subsyndromal distress with some behavioral and functional decline, increased physiological reactivity to trauma-related stimuli and startle response, and prolonged autonomic arousal on provocation[40]. A staging model implies that although an array of putative biomarkers associated with PTSD risk and symptom progression have been identified across distinct biological domains, specific biomarkers might be relevant at one time point, *e.g.,* heart rate immediately following trauma exposure, and not at another[24]. The severity of exposure to traumatic stress may be crucial in determining the risk of systemic comorbidity. In a long-term prospective study of combat soldiers and prisoners of war (POWs)[41], ex-POWs were almost 3 times more likely to develop metabolic syndrome than combat-exposed controls; blood levels of CRP were abnormally high in a large percentage of ex-POWs and were related to the level of physical and psychological stressors experienced during captivity. Chronic and delayed PTSD trajectories were associated with elevated CRP levels and metabolic syndrome[41].

Combat stress reaction: In a long-term prospective study of combat veterans with or without a combat stress reaction (CSR) diagnosis following participation in frontline battles with no indication of serious physical injury and other psychiatric disorders, CSR increased the risk of chronic but not delayed PTSD. Delayed PTSD, defined as onset at 2, 3, and/or 20 years after nonendorsement at year 1, was endorsed by 23.8% (*n* = 20) of the no-CSR group and 16.1% (*n* = 21) of the CSR group[42].

Dissociation: Peritraumatic dissociation, *i.e.,* experiences of depersonalization or derealization during exposure to a traumatic event, has been suggested to predict the course of PTSD[17]. Dissociative amnesia, *i.e.,* awareness of 'time loss', may occur following exposure to trauma and may exist in delayed PTSD prior to the onset of symptoms[38]. In a large cross-sectional survey of dissociative symptoms in people with PTSD[43], depersonalization and derealization were associated with high incidence of re-experiencing symptoms. Dissociation among people with PTSD has been associated with childhood onset, exposure to a high number of prior traumatic events, and childhood adversities and is not related to trauma type[43].

Depression: Depressive disorders represent stress-responsive syndromes that often cooccur with PTSD, and PTSD and depressive disorders share several overlapping symptoms. A sensitization process to depressive states has been described, which predicts that with recurrent episodes of depression, there will be a progressive diminution of the role of environmental stressors[23]. The concepts of sensitization and kindling have been extensively studied in PTSD and a range of other psychiatric disorders and highlight the commonality of etiological mechanisms, particularly with depressive disorders[23].

Alzheimer's disease: A case report[44] described a WW2 veteran who, following several asymptomatic decades of successful adaptation to traumatic memories,

developed Alzheimer's disease and the associated cognitive autonomy loss, which subsequently led to the emergence of late-onset posttraumatic stress disorder. Animal research has provided evidence that stress biology interacts with biological mechanisms underlying neurodegenerative disease to produce comorbidities such as late-life PTSD. In a mouse model of Alzheimer's disease[45], exposure to PTSD-like inducing trauma elevated cerebrospinal fluid beta-amyloid levels in both the short (1–2 mo) and long term (6–12 mo), and Alzheimer's disease model mice displayed a stronger PTSD-like phenotype after trauma exposure than wild-type mice. An increase in beta-amyloid production was shown to directly activate corticotropin-releasing factor neurons to exacerbate HPA axis responses. Increased beta-amyloid levels might not only accelerate AD pathogenesis, leading to exacerbated amyloid plaque deposition, but also exacerbate chronic changes in behavior and corticosteroid regulation, resulting in a higher incidence of PTSD[45].

Other behavioral and polygenic risk factors: Polygenic risk scores based on multiple genetic variants known to contribute to psychopathology were calculated for individuals with European ancestry in a large, long-term prospective follow-up study of first responders working at the World Trade Center site (New York) following the 9/11/2001 terrorist attacks[46]. Re-experiencing, generalized anxiety, and schizo-phrenia polygenic risk scores were predictive of a severe PTSD symptom trajectory characterized by increasing incidence of chronic symptoms over the course of 17 years, and a depression polygenic risk score predicted a diagnosis of PTSD[46]. In a very large sample of community-dwelling women participating in the Nurses' Health Study[47], time spent viewing TV was analyzed in relation to the onset of PTSD symptoms following exposure to trauma. Among women who developed PTSD during follow-up, a significantly steeper increase in time spent viewing TV occurred prior to the onset of PTSD symptoms compared to women who did not go on to develop PTSD symptoms following trauma exposure. Women with high PTSD symptoms reported more TV viewing than trauma-unexposed women. TV viewing following trauma exposure may therefore be a marker of vulnerability for developing PTSD and a consequence of having PTSD[47].

DISCUSSION

The neurobiological mechanisms underlying PTSD symptoms, onset, and course are heterogeneous, as they involve several interconnected systems. Studies of each of these underlying systems support their involvement in delayed reactions and/or the capacity for time-dependent increases in system reactivity. Neural mechanisms involve the neurocircuitry subserving fear conditioning, including but not limited to the hippocampus, amygdala, and prefrontal cortex. Studies in both humans and animal models consistently show time-dependent increases in activity within the neurocircuitry of fear. Neural network models emphasize the effects of iterative learning, pruning, and top-down coordination on generalization of the fear response and progressive symptom development in PTSD. Neuroendocrine mechanisms consist of autonomic nervous system responses and HPA axis responses, both of which contribute to hyperresponsiveness and sensitization to stress. Neuroinflammatory mechanisms involve immune activation due to massive psychological stress and/or the effects of traumatic brain injury, with crosstalk between the immune and endocrine systems and neurotoxic effects of excess immune system activity contributing to long-standing and delayed neuroinflammatory reactions. Finally, neurobehavioral/contextual mechanisms involve the effects of intervening stressors, multiple traumatic exposures, and mental and physical disorder comorbidities on delayed manifestations of remote traumatic exposure.

Crucial concepts emerging from the study of neurobiological mechanisms of delayed PTSD include sensitization, kindling, and generalization. Exposure to traumatic stressors may increase an individual's reactivity to subsequent stressors, a process that has been termed stress sensitization. The progressive development of symptoms of PTSD after exposure to traumatic events may be based on either neural, neuroendocrine, or neuroinflammatory sensitization to stress or combinations of these mechanisms. Heterogeneity in sensitization mechanisms may underlie differences with regard to the duration of the prodromal phase and/or the presence of prodromal symptoms.

Sensitization in conjunction with kindling may be linked to PTSD. Sensitization refers to externally induced reactions, *e.g.*, flashbacks of traumatic events induced by subsequent exposure to a similar stressor, whereas kindling refers to spontaneous activity occurring in the absence of an apparent cue. Kindling may follow sensitization, when reactions are triggered by progressively less severe stressors over time and eventually occur spontaneously. Finally, generalization that may result from the pruning of dendrites within neural fear networks leads to increased responsiveness to increasingly less specific contextual cues and cross sensitization to heterotypic stressors.

Long delayed effects of traumatic exposures are likely to also involve neurobehavioral and contextual mechanisms. Exposure to specific stressful life events resembling remote traumatic events may trigger specific memories that initiate a cascade of neurobiological dysregulation characteristic of PTSD. Indeed, the impact of repeated stressor exposures and contextual reminders has been demonstrated across several human and animal studies. The effects of stressors or trauma reminders may operate in concert with comorbid mental or physical disease and the associated sense of vulnerability that could increase the salience of the triggering event(s).

These findings have implications for diagnostic assessment in both treatment and forensic settings. Delayed expression of trauma- and stressor-related disorders requires careful individual assessment of the trauma history, intervening stressors, and development of symptoms of mental and physical disorders. In addition to PTSD, other specific trauma- and stressor-related disorders and mental and physical disorder comorbidities need to be evaluated with regard to the potential causal link between traumatic exposure and delayed symptoms, while taking into account the frequently substantial etiological overlap.

Subthreshold PTSD symptoms may indicate clinically significant distress and functional impairment. Findings from a Korean cross-sectional study among 45,698 active firefighters indicated that the presence of subthreshold PTSD symptoms was associated with suicidal behavior, depression, alcohol use problems, and functional impairment[48]. Assessment of a history of TBI is mandatory in help-seeking, trauma-exposed individuals, specifically in soldiers and veterans, who are at increased risk of PTSD with delayed expression[2-4]. Foreseeable stressors and resource losses, including unemployment and physical impairments, may be an effective target for secondary prevention of psychological distress. Pharmacological prevention of PTSD following exposure to potentially traumatic events is not generally recommended, and there is insufficient evidence to recommend selective, indicated pharmacological prevention[49], with the possible exception of hydrocortisone[50], a corticosteroid drug with immunosuppressive effects. Our data provide support for exploring the preventive potential of normalizing immune reactivity by pharmacological means.

Limitations of the current review need to be considered. These include the methodological limitations of some of the included studies, such as small sample sizes that may prevent studies from obtaining sufficient statistical power to detect associations relevant to delayed PTSD, the use of self-report measures possibly leading to response biases, memory bias in studies that rely on retrospective reporting, and limited durations of follow-up that prevented the detection of long-delayed cases. Indeed, there is a paucity of long-term prospective follow-up studies investigating the impact of intervening stressors on delayed PTSD onset. Limitations of the current review include the selection of studies addressing delayed expression of PTSD and neurobiology. Since these studies represent a subset of studies addressing the neurobiology of PTSD, this selection precludes exhaustive descriptions of the state of knowledge regarding all involved mechanisms.

CONCLUSION

In conclusion, the capacity of PTSD to occur with delayed onset may result from the interaction of an array of underlying neurobiological mechanisms that may influence the likelihood of manifesting prodromal symptoms preceding the onset of full-blown PTSD. Highly specific contextual reminders, stressful life events or vulnerability associated with comorbid physical or mental disease may trigger the exacerbation of previously contained distress associated with traumatic memories.

ARTICLE HIGHLIGHTS

Research background

Posttraumatic stress disorder (PTSD) with delayed expression occurs in people who develop PTSD at least six mo following exposure to a potentially traumatic event. During the prodromal phase or delay interval between the traumatic event and the onset of the disorder, subthreshold symptoms are often present, although long delay intervals without prodromal symptoms have rarely been reported. This study reviews neurobiological mechanisms underpinning the occurrence of a prodromal phase with or without prodromal symptoms.

Research motivation

Delayed expression of PTSD may present diagnostic challenges in clinical settings as well as in litigation contexts. Insight in neurobiological mechanisms is crucial to optimize diagnostic assessment and management.

Research objectives

To identify and characterize neurobiological mechanisms and pathways underlying delayed expression of PTSD and to obtain an overview of types of supporting evidence.

Research methods

We performed a scoping review of neurobiological studies in humans and animals and reviews of such studies. Records were eligible if they reported about studies on trauma and PTSD, delayed onset, neurobiology, and causal mechanisms or risk factors.

Research results

Following the search and selection, 38 studies were included in the review. Neural, neuroendocrine, and neuroinflammatory mechanisms have been implicated in progressive PTSD symptom expression over time. Neurobehavioral and contextual pathways complement these mechanisms.

Research conclusions

A variety of interconnected systems underlies the heterogeneity in PTSD symptom expression over time, contributing to sensitization, kindling, and generalization.

Research perspectives

Delayed expression of trauma- and stressor-related disorders requires careful individual assessment of the trauma history, intervening stressors, and development of symptoms. Assessment of a history of TBI is mandatory in help-seeking, trauma-exposed individuals, specifically in soldiers and veterans, as this may be associated with symptom progression over time. Efforts to avert foreseeable stressors and resource losses may contribute to secondary prevention of psychological distress. Future research should explore the preventive potential of normalizing immune reactivity by pharmacological means.

REFERENCES

1   **American Psychiatric Association**. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Washington, DC, American Psychiatric Association, 2013 [DOI: 10.1007/springerreference_179660]

2   **Andrews B**, Brewin CR, Philpott R, Stewart L. Delayed-onset posttraumatic stress disorder: a systematic review of the evidence. *Am J Psychiatry* 2007; **164**: 1319-1326 [PMID: 17728415 DOI: 10.1176/appi.ajp.2007.06091491]

3   **Smid GE**, Mooren TT, van der Mast RC, Gersons BP, Kleber RJ. Delayed posttraumatic stress disorder: systematic review, meta-analysis, and meta-regression analysis of prospective studies. *J Clin Psychiatry* 2009; **70**: 1572-1582 [PMID: 19607763 DOI: 10.4088/jcp.08r04484]

4   **Utzon-Frank N**, Breinegaard N, Bertelsen M, Borritz M, Eller NH, Nordentoft M, Olesen K, Rod NH, Rugulies R, Bonde JP. Occurrence of delayed-onset post-traumatic stress disorder: a systematic review and meta-analysis of prospective studies. *Scand J Work Environ Health* 2014; **40**: 215-229 [PMID: 24599261 DOI: 10.5271/sjweh.3420]

5   **American Psychiatric Association**. Diagnostic and Statistical Manual of Mental Disorders, Third Edition. Washington, DC, American Psychiatric Association, 1980

6   **Munn Z**, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? *BMC Med Res Methodol* 2018; **18**: 143 [PMID: 30453902 DOI: 10.1186/s12874-018-0611-x]

7   **Tricco AC**, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, Moher D, Peters MDJ, Horsley T, wk L, Hempel S, Akl EA, Chang C, McGowan J, Stewart L, Hartling L, Aldcroft A, Wilson MG, Garritty C, Lewin S, Godfrey CM, Macdonald MT, Langlois EV, Soares-Weiser K, Moriarty J, Clifford T, Tunçalp Ö, Straus SE. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med* 2018; **169**: 467-473 [PMID: 30178033 DOI: 10.7326/M18-0850]

8   **Bramer WM**, Giustini D, de Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. *J Med Libr Assoc* 2016; **104**: 240-243 [PMID: 27366130 DOI: 10.3163/1536-5050.104.3.014]

9   **Ouzzani M**, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016; **5**: 210 [PMID: 27919275 DOI: 10.1186/s13643-016-0384-4]

10   **Wilker S**, Kolassa IT. The formation of a neural fear network in posttraumatic stress disorder: Insights from molecular genetics. *Clinical Psychological Science* 2013; **1**: 452-469 [DOI: 10.1177/2167702613479583]

11   **Admon R**, Milad MR, Hendler T. A causal model of post-traumatic stress disorder: disentangling predisposed from acquired neural abnormalities. *Trends Cogn Sci* 2013; **17**: 337-347 [PMID: 23768722 DOI: 10.1016/j.tics.2013.05.005]

12   **Zovkic IB**, Meadows JP, Kaas GA, Sweatt JD. Interindividual Variability in Stress Susceptibility: A Role for Epigenetic Mechanisms in PTSD. *Front Psychiatry* 2013; **4**: 60 [PMID: 23805109 DOI: 10.3389/fpsyt.2013.00060]

13   **Cacciaglia R**, Nees F, Grimm O, Ridder S, Pohlack ST, Diener SJ, Liebscher C, Flor H. Trauma exposure relates to heightened stress, altered amygdala morphology and deficient extinction learning: Implications for psychopathology. *Psychoneuroendocrinology* 2017; **76**: 19-28 [PMID: 27871027 DOI: 10.1016/j.psyneuen.2016.11.012]

14   **Admon R**, Leykin D, Lubin G, Engert V, Andrews J, Pruessner J, Hendler T. Stress-induced reduction in hippocampal volume and connectivity with the ventromedial prefrontal cortex are related to maladaptive responses to stressful military service. *Hum Brain Mapp* 2013; **34**: 2808-2816 [PMID: 22807242 DOI: 10.1002/hbm.22100]

15   **Ardi Z**, Ritov G, Lucas M, Richter-Levin G. The effects of a reminder of underwater trauma on behaviour and memory-related mechanisms in the rat dentate gyrus. *Int J Neuropsychopharmacol* 2014; **17**: 571-580 [PMID: 24565178 DOI: 10.1017/S1461145713001272]

16   **McFarlane AC**, Yehuda R, Clark CR. Biologic models of traumatic memories and post-traumatic stress disorder. The role of neural networks. *Psychiatr Clin North Am* 2002; **25**: 253-270, v [PMID: 12136500 DOI: 10.1016/s0193-953x(01)00008-9]

17   **McFarlane AC**. Posttraumatic stress disorder: a model of the longitudinal course and the role of risk factors. *J Clin Psychiatry* 2000; **61** Suppl 5: 15-20; discussion 21 [PMID: 10761675]

18   **Kim YK**, Amidfar M, Won E. A review on inflammatory cytokine-induced alterations of the brain as potential neural biomarkers in post-traumatic stress disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2019; **91**: 103-112 [PMID: 29932946 DOI: 10.1016/j.pnpbp.2018.06.008]

19   **Gandubert C**, Scali J, Ancelin ML, Carrière I, Dupuy AM, Bagnolini G, Ritchie K, Sebanne M, Martrille L, Baccino E, Hermès A, Attal J, Chaudieu I. Biological and psychological predictors of posttraumatic stress disorder onset and chronicity. A one-year prospective study. *Neurobiol Stress* 2016; **3**: 61-67 [PMID: 27981178 DOI: 10.1016/j.ynstr.2016.02.002]

20   **Vaiva G**, Boss V, Molenda S, Rosenstrauch C, Ducrocq F, Fontaine M. Taux plasmatiques de GABA: au decours d'un psychotrauma et survenue de troubles psychotraumatiques. *Revue Francophone du Stress et du Trauma;* **5**: 131-139

21   **Busso DS**, McLaughlin KA, Sheridan MA. Media exposure and sympathetic nervous system reactivity predict PTSD symptoms after the Boston marathon bombings. *Depress Anxiety* 2014; **31**: 551-558 [PMID: 24995832 DOI: 10.1002/da.22282]

22   **Belda X**, Fuentes S, Daviu N, Nadal R, Armario A. Stress-induced sensitization: the hypothalamic-pituitary-adrenal axis and beyond. *Stress* 2015; **18**: 269-279 [PMID: 26300109 DOI: 10.3109/10253890.2015.1067678]

23   **McFarlane A**. The delayed and cumulative consequences of traumatic stress: Challenges and issues in compensation settings. *Psychological Injury and Law* 2010; **3**: 100-110 [DOI: 10.1007/s12207-010-9074-z]

24   **Michopoulos V**, Norrholm SD, Jovanovic T. Diagnostic Biomarkers for Posttraumatic Stress Disorder: Promising Horizons from Translational Neuroscience Research. *Biol Psychiatry* 2015; **78**: 344-353 [PMID: 25727177 DOI: 10.1016/j.biopsych.2015.01.005]

25   **Serova LI**, Nwokafor C, Van Bockstaele EJ, Reyes BAS, Lin X, Sabban EL. Single prolonged stress PTSD model triggers progressive severity of anxiety, altered gene expression in locus coeruleus and hypothalamus and effected sensitivity to NPY. *Eur Neuropsychopharmacol* 2019; **29**: 482-492 [PMID: 30878321 DOI: 10.1016/j.euroneuro.2019.02.010]

26   **Smid GE**, van Zuiden M, Geuze E, Kavelaars A, Heijnen CJ, Vermetten E. Cytokine production as a putative biological mechanism underlying stress sensitization in high combat exposed soldiers. *Psychoneuroendocrinology* 2015; **51**: 534-546 [PMID: 25106657 DOI: 10.1016/j.psyneuen.2014.07.010]

27 **Glenn DE**, Acheson DT, Geyer MA, Nievergelt CM, Baker DG, Risbrough VB; MRS-II Team. Fear learning alterations after traumatic brain injury and their role in development of posttraumatic stress symptoms. *Depress Anxiety* 2017; **34**: 723-733 [PMID: 28489272 DOI: 10.1002/da.22642]

28 **Bryant RA**, O'Donnell ML, Creamer M, McFarlane AC, Silove D. A multisite analysis of the fluctuating course of posttraumatic stress disorder. *JAMA Psychiatry* 2013; **70**: 839-846 [PMID: 23784521 DOI: 10.1001/jamapsychiatry.2013.1137]

29 **Bryant RA**, Creamer M, O'Donnell M, Silove D, Clark CR, McFarlane AC. Post-traumatic amnesia and the nature of post-traumatic stress disorder after mild traumatic brain injury. *J Int Neuropsychol Soc* 2009; **15**: 862-867 [PMID: 19703323 DOI: 10.1017/S1355617709990671]

30 **Alway Y**, Gould KR, McKay A, Johnston L, Ponsford J. The Evolution of Post-Traumatic Stress Disorder following Moderate-to-Severe Traumatic Brain Injury. *J Neurotrauma* 2016; **33**: 825-831 [PMID: 26176500 DOI: 10.1089/neu.2015.3992]

31 **do Prado CH**, Grassi-Oliveira R, Daruy-Filho L, Wieck A, Bauer ME. Evidence for Immune Activation and Resistance to Glucocorticoids Following Childhood Maltreatment in Adolescents Without Psychopathology. *Neuropsychopharmacology* 2017; **42**: 2272-2282 [PMID: 28664925 DOI: 10.1038/npp.2017.137]

32 **Uddin M**, Aiello AE, Wildman DE, Koenen KC, Pawelec G, de Los Santos R, Goldmann E, Galea S. Epigenetic and immune function profiles associated with posttraumatic stress disorder. *Proc Natl Acad Sci U S A* 2010; **107**: 9470-9475 [PMID: 20439746 DOI: 10.1073/pnas.0910794107]

33 **Wang XW**, Karki A, Du DY, Zhao XJ, Xiang XY, Lu ZQ. Plasma levels of high mobility group box 1 increase in patients with posttraumatic stress disorder after severe blunt chest trauma: a prospective cohort study. *J Surg Res* 2015; **193**: 308-315 [PMID: 25016440 DOI: 10.1016/j.jss.2014.06.020]

34 **Wilson CB**, McLaughlin LD, Nair A, Ebenezer PJ, Dange R, Francis J. Inflammation and oxidative stress are elevated in the brain, blood, and adrenal glands during the progression of post-traumatic stress disorder in a predator exposure animal model. *PLoS One* 2013; **8**: e76146 [PMID: 24130763 DOI: 10.1371/journal.pone.0076146]

35 **Gil S**, Caspi Y, Ben-Ari IZ, Koren D, Klein E. Does memory of a traumatic event increase the risk for posttraumatic stress disorder in patients with traumatic brain injury? *Am J Psychiatry* 2005; **162**: 963-969 [PMID: 15863799 DOI: 10.1176/appi.ajp.162.5.963]

36 **Roy MJ**, Costanzo M, Gill J, Leaman S, Law W, Ndiongue R, Taylor P, Kim HS, Bieler GS, Garge N, Rapp PE, Keyser D, Nathan D, Xydakis M, Pham D, Wassermann E. Predictors of Neurocognitive Syndromes in Combat Veterans. *Cureus* 2015; **7**: e293 [PMID: 26251769 DOI: 10.7759/cureus.293]

37 **Soreq H**. Gulf War syndrome, psychological and chemical stressors. In: G Fink, editor. Encyclopedia of Stress (Second Edition). New York: Academic Press; 2007 [DOI: 10.1016/b978-012373947-6.00184-7]

38 **Smid GE**, Van Der Mast RC, Gersons BPR. De uitgestelde posttraumatische stressstoornis. *Tijdschrift voor Psychiatrie* 2003; **45**: 265-276

39 **Chase RP**, McMahon SA, Winch PJ. Injury careers after blast exposure among combat veterans deployed to Iraq or Afghanistan. *Soc Sci Med* 2015; **147**: 309-316 [PMID: 26618495 DOI: 10.1016/j.socscimed.2015.11.015]

40 **McFarlane AC**, Lawrence-Wood E, Van Hooff M, Malhi GS, Yehuda R. The Need to Take a Staging Approach to the Biological Mechanisms of PTSD and its Treatment. *Curr Psychiatry Rep* 2017; **19**: 10 [PMID: 28168596 DOI: 10.1007/s11920-017-0761-2]

41 **Solomon Z**, Levin Y, Assayag EB, Furman O, Shenhar-Tsarfaty S, Berliner S, Ohry A. The Implication of Combat Stress and PTSD Trajectories in Metabolic Syndrome and Elevated C-Reactive Protein Levels: A Longitudinal Study. *J Clin Psychiatry* 2017; **78**: e1180-e1186 [PMID: 28994516 DOI: 10.4088/JCP.16m11344]

42 **Solomon Z**, Mikulincer M. Trajectories of PTSD: a 20-year longitudinal study. *Am J Psychiatry* 2006; **163**: 659-666 [PMID: 16585441 DOI: 10.1176/appi.ajp.163.4.659]

43 **Stein DJ**, Koenen KC, Friedman MJ, Hill E, McLaughlin KA, Petukhova M, Ruscio AM, Shahly V, Spiegel D, Borges G, Bunting B, Caldas-de-Almeida JM, de Girolamo G, Demyttenaere K, Florescu S, Haro JM, Karam EG, Kovess-Masfety V, Lee S, Matschinger H, Mladenova M, Posada-Villa J, Tachimori H, Viana MC, Kessler RC. Dissociation in posttraumatic stress disorder: evidence from the world mental health surveys. *Biol Psychiatry* 2013; **73**: 302-312 [PMID: 23059051 DOI: 10.1016/j.biopsych.2012.08.022]

44 **Monfort E**, Trehel G. État de stress post-traumatique consécutif à une maladie d'Alzheimer: é mergence d'une pathologie sous-jacente dans le très grand âge [Post-traumatic stress disorder secondary to Alzheimer's disease: Emergence of an underlying pathology in the oldest old]. *Annales Medico-Psychologiques* 2017; **175**: 776-780 [DOI: 10.1016/j.amp.2017.03.020]

45 **Justice NJ**, Huang L, Tian JB, Cole A, Pruski M, Hunt AJ Jr, Flores R, Zhu MX, Arenkiel BR, Zheng H. Posttraumatic stress disorder-like induction elevates β-amyloid levels, which directly activates corticotropin-releasing factor neurons to exacerbate stress responses. *J Neurosci* 2015; **35**: 2612-2623 [PMID: 25673853 DOI: 10.1523/jneurosci.3333-14.2015]

46 **Waszczuk MA**, Docherty AR, Shabalin AA, Miao J, Yang X, Kuan PF, Bromet E, Kotov R, Luft BJ. Polygenic prediction of PTSD trajectories in 9/11 responders. *Psychol Med* 2020; 1-9 [PMID: 33092657 DOI: 10.1017/S0033291720003839]

47 **Jung SJ**, Winning A, Roberts AL, Nishimi K, Chen Q, Gilsanz P, Sumner JA, Fernandez CA, Rimm EB, Kubzansky LD, Koenen KC. Posttraumatic stress disorder symptoms and television viewing patterns in the Nurses' Health Study II: A longitudinal analysis. *PLoS One* 2019; **14**: e0213441

[PMID: 30897111 DOI: 10.1371/journal.pone.0213441]

48   **Kim JI**, Oh S, Park H, Min B, Kim JH. The prevalence and clinical impairment of subthreshold PTSD using DSM-5 criteria in a national sample of Korean firefighters. *Depress Anxiety* 2020; **37**: 375-385 [PMID: 32017289 DOI: 10.1002/da.22998]

49   **Department of Veterans Affairs/Department of Defense**.   VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder. Washington, DC, Department of Veterans Affairs / Department of Defense, 2017. [cited 20 February 2021]. Available from: https://www.healthquality.va.gov/guidelines/MH/ptsd/VADoDPTSDCPGFinal012418.pdf

50   **International Society for Traumatic Stress Studies**.   ISTSS Posttraumatic Stress Disorder Prevention and Treatment Guidelines: Methodology and Recommendations. Chicago, Il, ISTSS, 2018. [cited 20 February 2021]. Available from: https://istss.org/getattachment/Treating-Trauma/New-ISTSS-Prevention-and-Treatment-Guidelines/ISTSS_PreventionTreatmentGuidelines_FNL-March-19-2019.pdf.aspx

Impacts of acupressure treatment on depression: A systematic review and meta-analysis

Jingxia Lin, Tianhao Chen, Jiali He, Raymond CK Chung, Haixia Ma, HWH Tsang

ORCID number: Jingxia Lin 0000-0002-8189-8216; Tianhao Chen 0000-0002-0226-5112; Jiali He 0000-0003-1824-1710; Raymond CK Chung 0000-0003-4051-9133; Haixia Ma 0000-0003-2906-9936; HWH Tsang 0000-0003-3003-8598.

Author contributions: Lin J acquisition of data, analysis and interpretation of data, drafting the article, final approval; Chen T acquisition of data, analysis of data, drafting the results, final approval; He J acquisition of data, quality and risk of bias assessment, drafting the introduction, final approval; Chung RC analysis and interpretation of data, final approval; Ma H results interpretation and critical revision; Tsang H conception and design of the study, critical revision, final approval.

Conflict-of-interest statement: All the authors have no conflict-of-interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: China

Specialty type: Integrative and complementary medicine

Jingxia Lin, Tianhao Chen, Jiali He, Raymond CK Chung, Haixia Ma, HWH Tsang, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong 00852, China

Jingxia Lin, HWH Tsang, Mental Health Research Centre, The Hong Kong Polytechnic University, Hong Kong 00852, China

Corresponding author: HWH Tsang, PhD, Chair Professor, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong 00852, China. hector.tsang@polyu.edu.hk

Abstract

BACKGROUND
Depression is recognized as a major public health problem with a substantial impact on individuals and society. Complementary therapies such as acupressure may be considered a safe and cost-effective treatment for people with depression. An increasing body of research has been undertaken to assess the effectiveness of acupressure in various populations with depression, but the evidence thus far is inconclusive.

AIM
To examine the efficacy of acupressure on depression.

METHODS
A systematic literature search was performed on PubMed, PsycINFO, Scopus, Embase, MEDLINE, and China National Knowledge (CNKI). Randomized clinical trials (RCTs) or single-group trials in which acupressure was compared with control methods or baseline in people with depression were included. Data were synthesized using a random-effects or a fixed-effects model to analyze the impacts of acupressure treatment on depression and anxiety in people with depression. The primary outcome measures were set for depression symptoms. Subgroups were created, and meta-regression analyses were performed to explore which factors are relevant to the greater or lesser effects of treating symptoms.

RESULTS
A total of 14 RCTs (1439 participants) were identified. Analysis of the between-group showed that acupressure was effective in reducing depression [Standardized mean differences (SMDs) = -0.58, 95%CI: -0.85 to -0.32, $P < 0.0001$] and anxiety (SMD = -0.67, 95%CI: -0.99 to -0.36, $P < 0.0001$) in participants with mild-to-moderate primary and secondary depression. Subgroup analyses suggested

that acupressure significantly reduced depressive symptoms compared with different controlled conditions and in participants with different ages, clinical conditions, and duration of intervention. Adverse events, including hypotension, dizziness, palpitation, and headache, were reported in one study.

CONCLUSION
The evidence of acupressure for mild-to-moderate depressive symptoms was significant. Importantly, the findings should be interpreted with caution due to study limitations. Future research with a well-designed mixed method is required to consolidate the conclusion and provide an in-depth understanding of potential mechanisms underlying the effects.

Key Words: Acupressure; Depression; Mild-to-moderate depressive symptoms; Systematic review; Meta-analysis

Core Tip: Acupressure is effective on mild-to-moderate depressive symptoms. However, no confirmed evidence is available about the impacts of acupressure on patients with severe depressive disorders. This is the first study investigating the impacts of acupressure on depression among clinical and general populations.

INTRODUCTION

Depression is a prevalent and debilitating mental disorder that is estimated to affect more than 264 million people worldwide[1]. Individuals with depression commonly experience dysfunctional symptoms, including undesirable mood, impaired concentration, poor quality of sleep, and a high risk of suicide. Up to 15% of clinically depressed patients eventually commit suicide[2]. Besides, depression is the commonest comorbidity of chronic physical illnesses, such as cardiovascular and respiratory diseases, diabetes, arthritis and osteoporosis, and cancer[3]. Moreover, evidence shows that depression is also a risk factor for physical illnesses[4]. It will become the second major contributor to the general medical service burden by 2030[5]. Thus, depression needs to be considered when providing integrated treatments for common chronic diseases.

In primary care, subthreshold and mild depression are most often managed with psychological interventions, such as cognitive-behavioral therapies, interpersonal therapy, and psychological counseling. Antidepressant medication is usually prescribed for moderate-to-severe depression[6]. However, medications are associated with drug dependence and side effects, which negatively impact adherence. Psychological therapies require considerable time and resources, resulting in high drop-out rates and unsustainable effects. Surveys have shown that self-help and complementary therapies for depression were extensively reported[7,8].

Acupressure is a non-invasive complementary and alternative technique that shares common characteristics with acupuncture[9]. It is defined as the stimulation on acupuncture points located along meridians (also known as "acupoints") using fingers, hands, knuckles, or dull instruments to exert pressure, leading to a sensation of soreness, numbness, and distention[10]. According to the core concept of traditional Chinese medicine (TCM) theory, acupressure stimulates the meridian. It restores health by balancing the "qi" flow, which could be described as bioenergy[11]. Results from studies of acupuncture have suggested that effects on neurotransmitter levels of serotonin and noradrenaline may be one of the potential mechanisms underlying the therapeutic effects. On the other hand, the pressure exerted on the acupoints regulates the sympathetic and parasympathetic nervous systems to create feelings of calm and

relaxation[12].

Acupressure has received increased attention for the alleviation of pain or discomfort associated with physical illnesses, injuries, and surgical operations in different populations, ranging from children[13] to the elderly[14]. Furthermore, the benefits of acupressure in psychological well-being have also been observed. While emerging evidence shows that acupressure has encouraging and promising effects on depression[15,16], there has been no systematic review and meta-analysis of its effectiveness for this condition. The present study aimed to synthesize findings of randomized clinical trials (RCTs) and quantify the effectiveness of acupressure for the treatment of depression in adults. Moreover, selection of acupoints and manipulation techniques, adverse events, drop-out rates, and quality of the included RCTs are described for treatment decision-making.

MATERIALS AND METHODS

This systematic review and meta-analysis were performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement guideline.

Literature search

The following electronic databases were systematically searched until December 2020: PubMed, PsycINFO, Scopus, Embase, MEDLINE, and China National Knowledge (CNKI). The main keywords used were "acupressure" OR "finger massage" OR "acupoint massage" OR "shiatsu" AND "depress*" OR "mental health" OR "mental disorder*" OR "psychiatric disorder*" OR "mood disorder*" OR "bipolar disorder.*" Reference lists of retrieved studies and review articles were screened for additional references.

We screened the studies in two phases. First, two review authors (He J and Chen T) independently screened the titles and the abstracts. Second, the full text of potentially eligible studies was retrieved and assessed independently by the same two authors. Any disagreement between the review authors was resolved by a third review author (Lin J).

Study selection

Inclusion criteria were defined using the PICO (Population, Intervention, Comparison, and Outcomes)[17]: (1) Were clinical trials, including RCTs and non RCTs that included acupressure as one of the study groups; (2) Used acupressure as the sole intervention compared with the control condition of either sham control or standard control (*e.g.*, standard care); (3) Used a sample of participants aged 18 years old or above; and (4) Were published in either English or Chinese.

Studies were excluded: (1) If they did not target depression as one of the outcome measures before and after acupressure intervention; or (2) If they used acupressure as part of a multi-component intervention.

Data extraction

All data were extracted from studies by two review authors (He J and Chen T) according to predefined criteria, including: (1) The first author, year, and country of publication; (2) The number and characteristics of the participants; (3) The regimen of the experimental and control interventions; (4) The manipulation techniques of acupressure; (5) Drop-out rate; (6) Baseline depressive symptoms, and (7) Outcome measures. For the purpose of this review, our primary outcome was the change of depressive symptoms before and after an intervention. That was evaluated using any standardized clinical measures, including Beck Depression Inventory (BDI), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), Depression Anxiety Stress Scales (DASS), Major Depression Inventory (MDI), and Edinburgh Postnatal Depression Scale (EPDS). The anxiety level, manipulation, and frequency of acupressure, drop-out rate, and adverse events were reported as the secondary outcomes. Discrepancies between the two reviewers were resolved by consensus decision.

Quality and risk of bias evaluation

The quality of reporting for the acupressure trials was evaluated independently by two authors (He J and Chen T) using revised STRICTA (Standards for Reporting

Interventions in Clinical Trials of Acupuncture). A total of 10 items were applicable to the acupressure studies, which covered acupressure rationale, pressure details (instead of needling details), treatment regimen, other components of treatment, practitioner background, and control intervention[18]. The acupressure procedure was considered well-reported if at least six out of the ten STRICTA items were reported.

The methodological quality of identified studies was assessed according to the six domains in the Cochrane risk of bias tool. These are random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, and selective outcome reporting. Each domain was rated as "high" (seriously weakens confidence in the results), "unclear," or "low" (unlikely to significantly alter the results). Given the nature of the intervention, it was difficult to blind the personnel who applied the acupressure, so only the participants and outcome assessors were blinded. To follow the guidelines recommended by the Cochrane Back Review Group, a compliance threshold of < 50% of the criteria was associated with bias[19]. Studies that met at least four domains with no serious flaws were considered as having a low risk of bias. If necessary, attempts were made to contact authors to obtain additional information.

Funnel plots were constructed to assess the risk of publication bias across series for all outcome measures. The Egger regression was used to test the asymmetry of the Funnel plots, with $P > 0.1$ indicating no publication bias.

Data synthesis and statistical analysis

According to Jackson & Turner[20], meta-analysis was performed when at least five studies with similarities in clinical characteristics and with no domain rated as having a high risk of bias were included. Meta-analyses were conducted using the changes of the scores between pre- and post-intervention measured by different scales. Heterogeneity among studies was evaluated by calculating the I^2 statistic and χ^2 test (assessing the P value) using Review Manager 5 software (V5.4, The Nordic Cochrane Centre, Copenhagen). If the P value was < 0.05 and $I^2 > 50\%$, we considered the heterogeneity to be substantial. A random-effect model was used to combine the data if significant heterogeneity existed. Standardized mean differences (SMDs) with 95%CI were used for continuous outcomes. The magnitude of the overall effect size was calculated based on the pooled SMD. Following Cohen's categories, the effect sizes of 0.20, 0.50, and 0.80 were considered small, medium, and large, respectively[21].

Sensitivity analyses and subgroup analyses were performed to investigate the effects of acupressure with different study designs, ages of participants, control conditions, and treatment duration. Meta-regression was also performed to identify the potential predictors of the effects of acupressure on depression.

RESULTS

Study selection

A PRISMA flow diagram is shown in Figure 1. The search initially found 552 articles. After screening the title and abstract, 46 of which were examined full text. Of these, 16 were excluded based on the inclusion/exclusion criteria, and 16 Chinese articles were excluded due to their low quality, resulting in a total of 14 eligible articles for systematic review. There was no publication bias based on the Funnel plots and Egger-regression test results (Figure 2). Fourteen RCTs involving 1439 participants were included for meta-analyses.

Study characteristics

The main characteristics of the included studies are described in Table 1. The sample size of the 14 studies varied from 12 to 288. Four studies focused on old participants (aged 65 or above)[22-25], while the remaining studies recruited participants from 20-64 years. Ten studies recruited participants with chronic diseases, including chronic obstructive pulmonary disease[22], lung cancer[26], acute myocardial infarction[27], breast cancer[28], low back pain[29], multiple sclerosis[30], hemodialysis[31-33], and unilateral knee osteoarthritis[34]. Three studies recruited patients with depression[24, 25,35]. One study was for patients with Alzheimer's disease comorbided with depression[23]. None of them included patients with major depressive disorders (MDD), and the overall severity of depressive symptoms in the participants was mild to moderate. The drop-out rate ranged from 0 to 28.8%, with a mean of 10.2%.

Table 1 Characteristics of included studies

Ref.	Type of study	Participants (sample size, mean age ± SD)	Drop-out rate, *n* (%)	Treatment (frequency and duration)	Manupilation techniques (acupoints composition, and techniques used)	Control	Depressive symptoms at baseline M (SD)	Outcome measures
Bergmann *et al*[27], 2014	RCT	Acute myocardial infarction with PPS acore ≥ 60 (213, 61.0 ± 8.1)	32 (15.0)	Acupressure (45 min twice a day for 12 wk)	Figure pressure on two points at the sternum	Treat as usual (TAU)	MDI: 8.9 (7.4), PPS: 81 (13)	MDI, QOL, WHO-5's well-being index, PPS
Dehghanmehr *et al*[31], 2020	RCT	Hemodialysis with no severe depression and anxiety (60, 39.2 ± 11.32)	0	Acupressure (8 min, 3 d weekly for 4 wk)	Figure pressure on acupoint Saiyinjiao	Sham, TAU	BDI: 31.44 (20.95), STAI: 47.60 (7.04)	STAI, BDI
Hmwe *et al*[32],2015	RCT	Hemodialysis with depressive symptom (108, 58.06 ± 11.4)	0	Acupressure (12 min per session, 3 sessions weekly for 4 wk)	Figure pressure on acupoints Yintang, Shenmen, and Taixi	TAU	DASS depression: 10.93 (8.38), GHQ total: 25.33 (12.56)	DASS, GHQ-28
Honda *et al*[35], 2012	RCT	College students with depressive symptoms (25, 33.2 ± 10.0)	Not mentioned	Acupressure (30 seconds per session, 3 sessions daily for 4 wk)	Figure pressure on six points on the neck (three points on the left and right side each)	TAU	BDI: 55 (10)	BDI
Kalani *et al*[33], 2019	RCT	Hemodialysis with BDI score ≥ 10 (96, 53.4 ± 13.9)	0	Acupressure (18 min per session, 3 sessions weekly for 4 wk)	Figure pressure on acupoints Sanyinjiao, Zusanli, Yanglingquan, Yongquan, Shenshu, and Shenmen	Sham, TAU	BDI: 27.5 (9.1)	BDI
Lanza *et al*[23], 2018	RCT	Alzheimer with CDR score ≤ 2 (12, 80.0 ± 9.0)	0	Acupressure (40 min weekly for 40 wk)	Figure pressure on relevant trigger points of the meridians	TAU	GDS: 13 (2)	GDS, MMSE, ADL, IADL
Molassiotis *et al*[24], 2020	RCT	Depression with GDS score ≥ 8 (118, 79.5 ± 14.5)	34 (28.8)	Acupressure (5 min per session, twice weekly for 12 wk)	Figure pressure on acupoints Zusanli, Zhongfu, Shenmen, Taichong, Baihui	Sham, TAU	GDS: 10.6 (2.1), GHQ: 18.8 (5.9)	GDS, PSQI
Rahimi *et al*[30], 2020	RCT	Multiple sclerosis with EDSS score = 0-5.5 (106, 20-45 years old)	20 (18.9)	Acupressure (15 min every day for 4 wk)	Figure pressure on acupoints Shenmen and Yintang	Sham	DASS depression: 11.48 (3.1)	DASS, FSS
Rani *et al*[34], 2020	RCT	Knee osteoarthritis with Kellgrene Lawrance scale grade 2 or 3 (212, 58.07 ± 11.22)	11 (5.2)	Acupressure (15 min per session, 2 sessions per day, 5 d weekly for 32 wk)	Figure pressure on acupoints Liangqiu, Dubi, Zusanli, Yinglingquan, Xuehai, Yanglingquan	TAU	DASS depression: 14.56 (8.63)	DASS, VAS, GHQ-12, BMSWBI, WHOQOL-BREF
Tang *et al*[26], 2014	RCT	Lung cancer undergoing chemotherapy (40, 64.4 ± 9.2)	10 (25)	Acupressure (3 min once every morning for 20 wk)	Figure pressure on acupoints Hegu, Zusanli, and Sanyinjiao	Sham	HADS: 7.29 (4.39), ECOG-PSR: 11 (45.8)	HADS, TFRS, ECOG-PSR, PSQI
Tseng *et al*[25], 2020	RCT	Depression with GDS score > 5 (47, 82.78 ± 6.88)	8 (17.0)	Acupressure with a magnetic bead (7 d weekly for 2 wk)	Magnetic bead on ear Shenmen point	Sham	GDS: 8.71 (2.31) BAI: 13.63 (7.36)	GDS, BAI
Wu *et al*[22], 2007	RCT	Chronic obstructive pulmonary disease with depressive symptom (44, 73.0	0	Acupressure (16 min per session, 5 sessions weekly for 4 wk)	Figure pressure on acupoints Dazhui, Tiantu, Shousaili, Feishu, Shenshu	Sham	GDS score at basline not available	GDS, DVAS

		± 9.7)					
Yu *et al*[29], 2020	RCT	Postpartum wome with low back pain score ≥ 1 (70, 34.4 ± 4.8)	0	Acupressure (10 min per session, 5 sessions weekly for 4 wk)	Figure pressure on acupoints Shenhu, Dachangshu, Guanyuanshu, Weiyang, and Sanyinjiao	Sham	EPDS: 9.4 (4.5)	EPDS, RMDQ, ODI, VAS
Zick *et al*[28], 2018	RCT	Breast cancer with depressive symptom (288, 60.5 ± 10.0)	Not mentioned	Acupressure (30 min every day for 10 wk)	Figure pressure on acupoints Hegu, Zusanli, Sanyinjiao, Taixi, Baihui, and Qihai	Sham, TAU	HADS: 6.2 (3.2)	VAS, BPI

ADL: Activity of daily living; BAI: Beck anxiety inventory; BDI: Beck depression inventory; BMSWBI: Body-mind-spirit well-being inventory; BPI: Brief pain inventory; CDR: Clinical dementia rating; COPD: Chronic obstructive pulmonary disease; DASS: Depression anxiety stress scales; DVAS: Dyspnea visual analogue scale; ECOG-PSR: Eastern cooperative oncology group performance status rating; EDSS: Expanded disability status scale; EPDS: Edinburgh postnatal depression scale; FSS: Fatigue severity scale; GDS: Geriatric depression scale; GHQ: General health questionnaire; HADS: Hospital anxiety and depression scale; IADL: Instrumental ADL; MDI: Major depression inventory; MMSE: Mini mental state examination; ODI: Oswestry disability index; PFS: Piper fatigue scale; PPS: Pressure pain sensitivity; PSQI: Pittsburgh sleep quality index; QOL: SF-36 quality of life; RMDQ: Roland-morris disability questionnaire; STAI: Spielberger state-trait anxiety inventory; TAU: treat as usual; TFRS: Tang fatigue rating scale; VAS: Visual analog scale.

Quality and risk of bias assessment

Table 2 describes the standards of reporting for the included trials. The standards reflect the revised STRICTA criteria (2010). All studies reported the frequency of treatment, the setting and context of intervention, and the control condition. Only one study did not mention the rationale of acupressure[27]. Three studies did not report the acupoints used in the intervention[23,27,35]. All studies provided a detailed description of the method/materials used for acupressure. All studies except two[23,25] specified the duration of pressure retention. Two studies reported other components, such as the details of other interventions[23,26].

Risk of bias was assessed and summarized in Figure 3. Fourteen studies were described as "randomized," of which eight studies reported detailed randomization methods[25,26,28,30-34]. All studies reported allocation concealment in detail. Blinding of outcome assessments was sufficiently carried out in 13 studies, with only one study providing no detailed description[26]. Five of them expressly stated a completion rate of their participants and were at low risk of attrition bias[22,24,26,27,34], while the others gave no details of missing data. All studies presented the outcomes clearly and were rated as having a low risk of selection bias. Overall, all studies were rated low in at least four domains, and therefore, were considered as having low risk of bias.

Rationale of acupoint selection

Among the included studies, five of them applied three acupoints or fewer[25,26,30-32], and six studies applied more than three acupressure points[22,24,28,29,33,34]. However, three studies did not report the specific acupoints used for the intervention[23,27,35]. The most used acupoints were Zusanli, Sanyinjiao, and Shenmen.

Table 2 Quality assessment using standards for reporting interventions in clinical trials of acupuncture for the included studies

Ref.	Acupressure details						Other components of treatment			
	Acupressure rationale	Acupoints used	Materials used for acupressure	Frequency of acupressure	Acupressure retention	Description of method/materials used for acupressure	Other components	Setting and context	Practitioner background	Control intervention
Bergmann (2014)	NR	NR	Y	Y	Y	Y	NR	Y	Y	Y
Dehghanmehr (2020)	Y	Y	Y	Y	Y	Y	NR	Y	NR	Y
Hmwe (2015)	Y	Y	NR	Y	Y	Y	NR	Y	NR	Y
Honda (2012)	Y	NR	NR	Y	Y	Y	NR	Y	Y	Y
Kalani (2019)	Y	Y	Y	Y	Y	Y	NR	Y	NR	Y
Lanza (2018)	Y	NR	NR	Y	NR	Y	Y	Y	NR	Y
Molassiotis (2020)	Y	Y	Y	Y	Y	Y	NR	Y	NR	Y
Rahimi (2020)	Y	Y	Y	Y	Y	Y	NR	Y	Y	Y
Rani (2020)	Y	Y	NR	Y	Y	Y	NR	Y	Y	Y
Tang (2014)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Tseng (2020)	Y	Y	NR	Y	NR	Y	NR	Y	NR	Y
Wu (2007)	Y	Y	Y	Y	Y	Y	NR	Y	Y	Y
Yu (2020)	Y	Y	NR	Y	Y	Y	NR	Y	NR	Y
Zick (2018)	Y	Y	Y	Y	Y	Y	NR	Y	Y	Y

NR: Not reported; Y: Reported.

All studies mentioned that selection of acupoints was based on the TCM principles and aimed to improve the body's natural self-healing capacity by regulating and balancing Qi. Three studies[22,24,29] selected the acupoints based on a thorough literature review of the effects of acupressure on depression. Hmwe *et al*[32] reported that two TCM specialists from local universities had reviewed the selection of acupoints.

Manipulation technique

The duration of acupressure interventions varied across studies. They ranged from 5 s to 4 min on each acupressure point and from 30 s to 45 min per session, with an
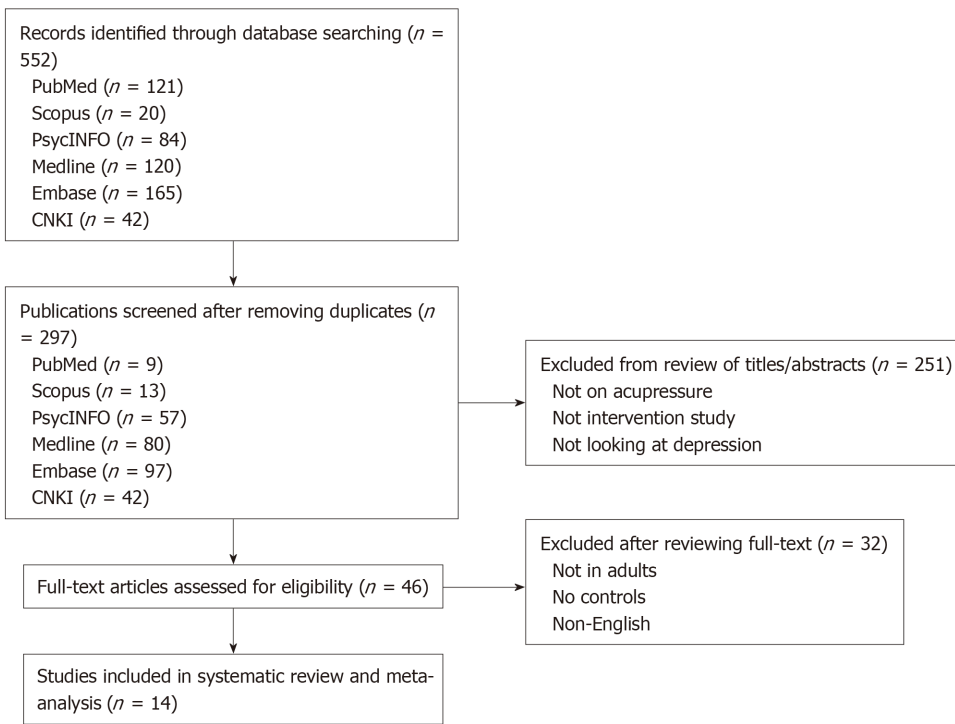
Figure 1 Flow diagram for data collection and analysis.
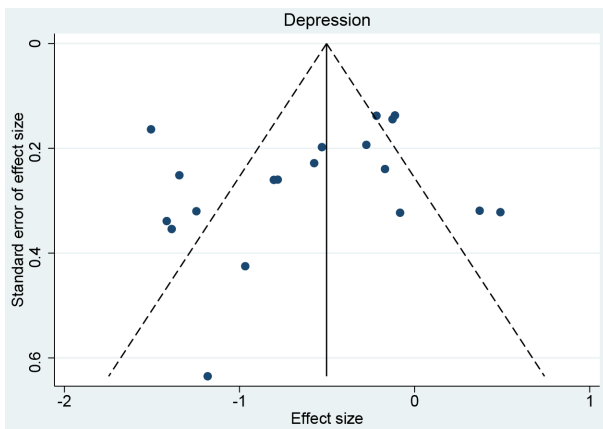
Figure 2 Funnel plots of studies with depression outcomes.

average of 15-20 min per session in most studies. The study duration ranged from 2 wk[25] to 40 wk[23]. All studies applied acupressure with finger pressure, except one study which applied the magnetic bead at relevant points[25].

The background of the therapists delivering acupressure differed in the included studies: Two trials involved research personnel[22,26], two trials employed allied health professionals[27,35], and three trials involved an acupuncturist[28,33,34]. Either "sham" or "treat as usual" (TAU) were used as controls. Nine studies employed sham stimulation that located around the true acupoints and were irrelevant to the treatment of depression[22,24-26,28-31,33]. Four studies had both a sham and a TAU control group[24,26,28,33]. The other studies used TAU as the control group.

Overall effectiveness of acupressure on depression

Three trials adopted BDI[31,33,35]; four trials adopted GDS[22-25]; two trial used HADS[26,28]; three trials used DASS[30,32,34]; one trial used MDI[27], and the other trial used EPDS for depression[29]. Similar findings were reported in all studies that the acupressure group had a greater reduction in depression after treatment than the sham or the TAU control groups.
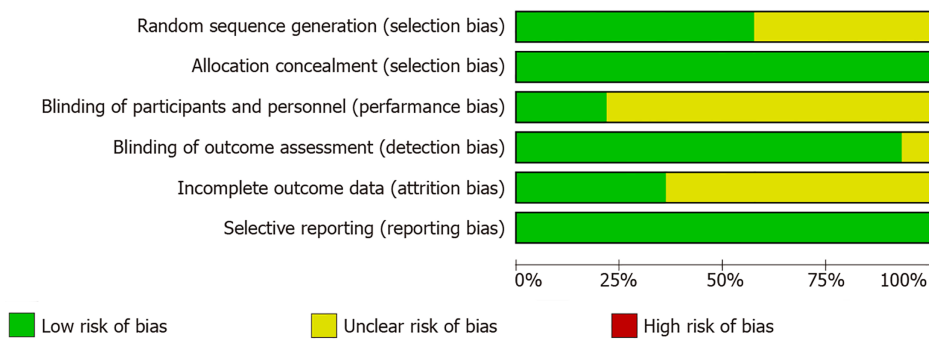
Figure 3 Risk of bias evaluation for the included studies.

Meta-analysis of these 14 RCTs suggested a lager overall improvement in the depression level in the acupressure group than sham or TAU control groups (SMD = -0.58; 95%CI = -0.85 to -0.32; $P < 0.0001$; $I^2 = 84\%$; $\chi^2 = 110.96$; $P < 0.0001$) (Figure 4). The combined effect size was 4.39, which equals to a small effect size according to Cohen's categories.

Effectiveness of acupressure on depression with different control conditions

Subgroup analyses were performed in studies using different control groups (Figure 4). The combined results of 10 studies using TAU control groups showed a greater reduction in depression level in the acupressure group with a small effect size (SMD = -0.34; 95%CI = -0.63 to -0.05; $P = 0.02$; $I^2 = 76\%$; $\chi^2 = 37.78$; $P < 0.00001$; $Z = 2.33$). Similar results were shown in the nine studies using sham controls with a moderate effect size (SMD = -0.83; 95%CI = -1.2 to -0.46; $P < 0.00001$; $I^2 = 80\%$; $\chi^2 =39.77$; $P < 0.00001$; $Z = 4.42$).

Effectiveness of acupressure on depression with different treatment durations

Subgroup analyses were also performed in studies with different durations. The combined results of eight studies with a duration of 2-4 wk showed acupressure significantly reduced depression levels compared to sham or TAU controls with a moderate effect size (SMD = -0.67; 95%CI = -0.99 to -0.35; $P < 0.0001$; $I^2 = 71\%$; $\chi^2 = 30.82$; $P = 0.0003$; $Z = 4.16$) (Figure 5). Significant reductions in the depression levels were found in six studies with a duration of more than 4 wk in the acupressure group compared to the sham or TAU controls with a small effect size (SMD = -0.48; 95%CI = -0.9 to -0.07; $P = 0.02$; $I^2 = 90\%$; $\chi^2 = 78.05$; $P < 0.00001$; $Z = 2.28$) (Figure 6).

Effectiveness of acupressure on depression in different participants

Subgroup analyses were also performed in studies with different participants. The combined results of eleven studies in participants with depressive symptoms comorbidded with chronic diseases showed acupressure significantly reduced depression level compared to sham or TAU controls with a small effect size (SMD = -0.48; 95%CI = -0.77 to -0.19; $P = 0.001$; $I^2 = 85\%$; $\chi^2 = 91.96$; $P < 0.00001$; $Z = 3.23$) (Figure 7). Significant reductions of depressive symptoms were also found in three studies in participants with depression with a moderate effect size (SMD = -1; 95%CI = -1.40 to -0.60; $P < 0.00001$; $I^2 = 48\%$; $\chi^2 = 5.79$; $P = 0.12$; $Z = 4.91$) (Figure 8).

Effectiveness of acupressure on depression in participants of different ages

Subgroup analyses were also performed in studies with different ages. The combined results of ten studies with individuals aged 20-64 showed acupressure significantly reduced depression levels compared to the sham or TAU controls with a small effect size (SMD = -0.42; 95%CI = -0.71 to -0.14; $P = 0.004$; $I^2 = 85\%$; $\chi^2 = 84.08$; $P < 0.00001$; $Z = 2.89$) (Figure 9). Significant reductions in depression levels after acupressure interventions with a large effect size were also found in four studies in participants over 65 years old (SMD = -1.09; 95%CI = -1.45 to -0.72; $P < 0.00001$; heterogeneity: $I^2 = 43\%$; $\chi^2 = 7.01$; $P = 0.14$; $Z = 5.82$) (Figure 10).

Effects of acupressure on depression using different acupoints

Subgroup analyses were performed in studies using different numbers of acupoints. The combined results of RCTs with no more than 3 acupoints (3 included) (SMD = -0.36; 95%CI = -0.56 to -0.17; $P < 0.0001$; $I^2 = 79\%$; $\chi^2 = 28.86$; $P = 0.0003$; $Z = 3.63$)
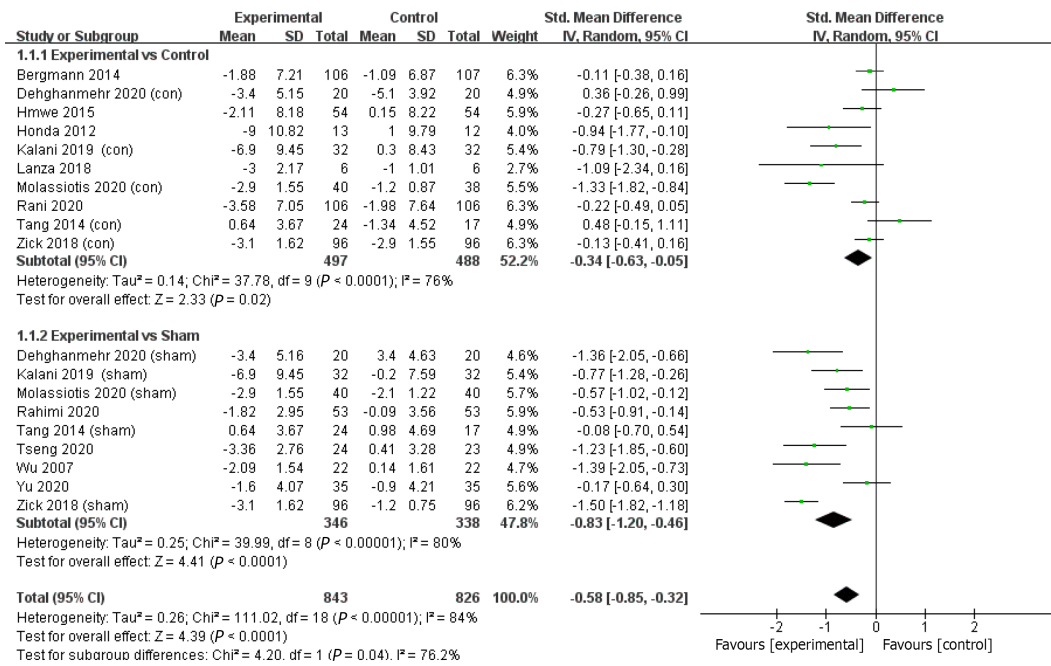
Figure 4 Effects of acupressure on depression. 1.1.1. Subgroup meta-analyses of studies using treat-as-usual (TAU) as controls; 1.1.2. Subgroup meta-analyses of studies using Sham controls.
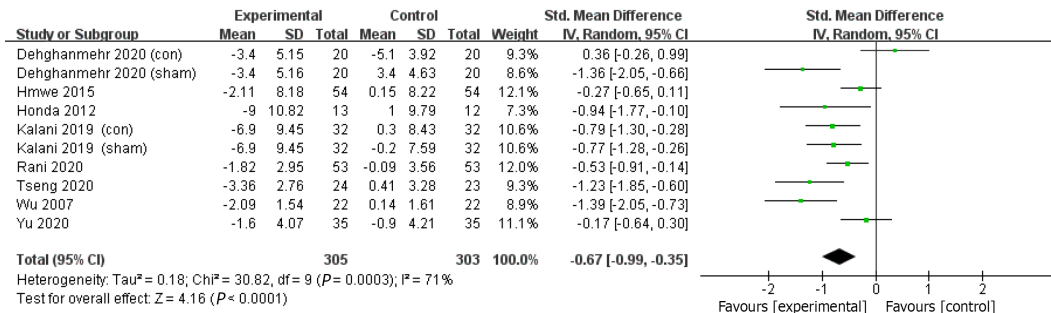
Figure 5 Effects of acupressure on depression with treatment duration of 2 to 4 wk.
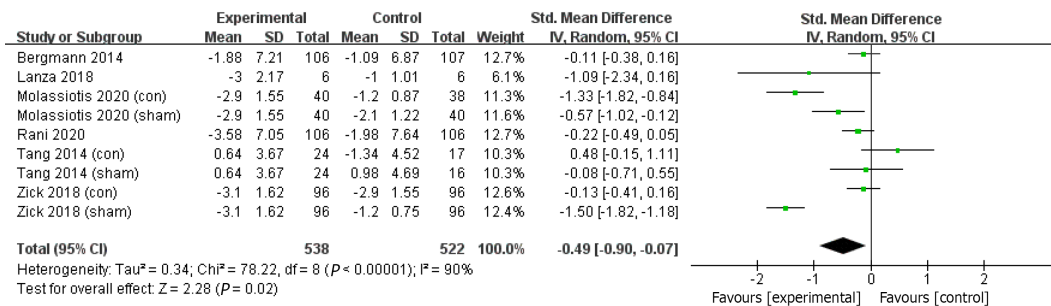
Figure 6 Effects of acupressure on depression with treatment duration of more than 4 wk.

(Figure 11), and more than 3 acupoints showed significant effects on depression in acupressure compared to controls with moderate effects (SMD = -0.74; 95%CI = -1.13 to -0.36; P = 0.0002; I^2 = 88%; χ^2 = 66.63; P < 0.00001; Z = 3.75) (Figure 12).

Subgroup analyses were also performed in studies using the three most used acupoints. The combined results of the studies showed significant beneficial effects on depression in the acupressure treatment group compared to controls, with a large effect size for Sanyinjiao (SMD = -0.54; 95%CI= -0.69 to -0.39; P < 0.00001; heterogeneity: I^2 = 89%; χ^2 = 72.17; P < 0.00001; Z = 7.03), a moderate effects size for Shenmen
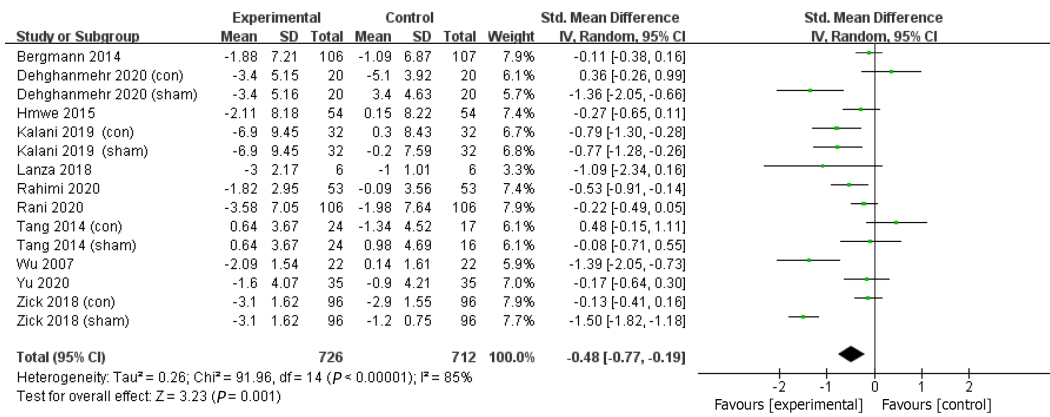
Figure 7 Effects of acupressure on depressive symptoms in participants with chronic diseases.
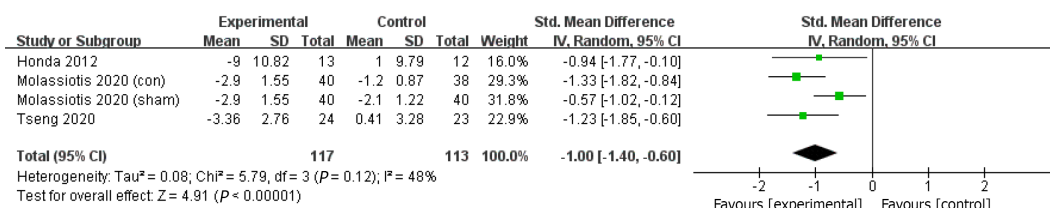
Figure 8 Effects of acupressure on depressive symptoms in participants with primary depression.
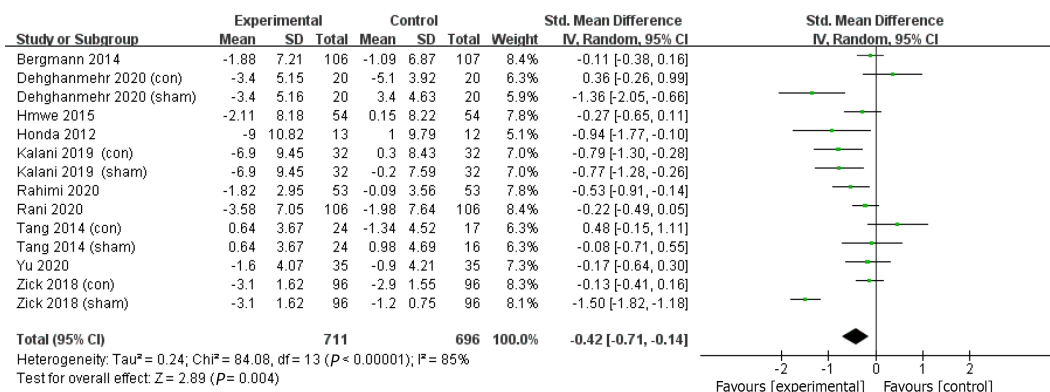
Figure 9 Effects of acupressure on depression in participants aged 18-64 years old.
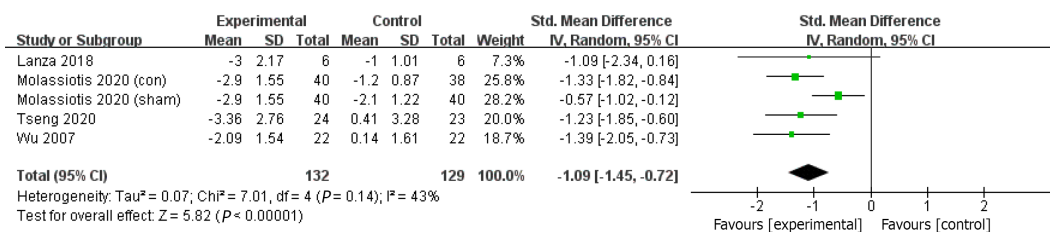
Figure 10 Effects of acupressure on depression in participants aged 65 years old or above.

(SMD = -0.75; 95%CI = -1.03 to -0.47; P < 0.00001; I^2 = 60%; χ^2 = 15.14; P = 0.02; Z = 5.20) and a small effect size for Zusanli (SMD = -0.56; 95%CI = -0.97 to -0.15; P = 0.008; I^2 = 89%; χ^2 = 71.65; P < 0.00001; Z = 2.67).

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Dehghanmehr 2020 (con)	-3.4	5.15	20	-5.1	3.92	20	9.9%	0.36 [-0.26, 0.99]
Dehghanmehr 2020 (sham)	-3.4	5.16	20	3.4	4.63	20	8.0%	-1.36 [-2.05, -0.66]
Hmwe 2015	-2.11	8.18	54	0.15	8.22	54	27.0%	-0.27 [-0.65, 0.11]
Rahimi 2020	-1.82	2.95	53	-0.09	3.56	53	25.8%	-0.53 [-0.91, -0.14]
Tang 2014 (con)	0.64	3.67	24	-1.34	4.52	17	9.7%	0.48 [-0.15, 1.11]
Tang 2014 (sham)	0.64	3.67	24	0.98	4.69	16	9.7%	-0.08 [-0.71, 0.55]
Tseng 2020	-3.36	2.76	24	0.41	3.28	23	9.8%	-1.23 [-1.85, -0.60]
Total (95% CI)			**219**			**203**	**100.0%**	**-0.36 [-0.56, -0.17]**

Heterogeneity: Chi² = 28.86, df = 6 (P < 0.0001); I² = 79%
Test for overall effect: Z = 3.63 (P = 0.0003)

Figure 11 Effects of acupressure using no more than 3 (3 included) acupoints on depression.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Kalani 2019 (con)	-6.9	9.45	32	0.3	8.43	32	10.6%	-0.79 [-1.30, -0.28]
Kalani 2019 (sham)	-6.9	9.45	32	-0.2	7.59	32	10.7%	-0.77 [-1.28, -0.26]
Molassiotis 2020 (con)	-2.9	1.55	40	-1.2	0.87	38	10.8%	-1.33 [-1.82, -0.84]
Molassiotis 2020 (sham)	-2.9	1.55	40	-2.1	1.22	40	11.1%	-0.57 [-1.02, -0.12]
Rani 2020	-3.58	7.05	106	-1.98	7.64	106	12.3%	-0.22 [-0.49, 0.05]
Wu 2007	-2.09	1.54	22	0.14	1.61	22	9.4%	-1.39 [-2.05, -0.73]
Yu 2020	-1.6	4.07	35	-0.9	4.21	35	11.0%	-0.17 [-0.64, 0.30]
Zick 2018 (con)	-3.1	1.62	96	-2.9	1.55	96	12.2%	-0.13 [-0.41, 0.16]
Zick 2018 (sham)	-3.1	1.62	96	-1.2	0.75	96	12.0%	-1.50 [-1.82, -1.18]
Total (95% CI)			**499**			**497**	**100.0%**	**-0.74 [-1.13, -0.36]**

Heterogeneity: Tau² = 0.30; Chi² = 66.63, df = 8 (P < 0.00001); I² = 88%
Test for overall effect: Z = 3.75 (P = 0.0002)

Figure 12 Effects of acupressure using more than 3 acupoints on depression.

Effect of acupressure on anxiety

Three trials adopted HADS[26,28,31], one trial used Beck Anxiety Inventory (BAI)[25], and two trials used DASS[32,34] to measure anxiety level. Consistent findings were found in six studies that the acupressure group reported a greater reduction in anxiety after acupressure application than the sham or TAU controls. Meta-analyses of the six trials indicated an overall improvement in anxiety levels in the acupressure group compared with sham or TAU control groups with a small effect size (SMD = -0.67; 95%CI = -0.99 to -0.36; P < 0.0001; I^2 = 79%; χ^2 = 37.82; P < 0.00001; Z = 4.16) (Figure 13).

Adverse events

Only one study[32] reported the adverse events of acupressure during four-week acupressure in patients with end-stage renal disease, including intradialytic hypotension (n = 11), dizziness (n = 6), palpitation (n = 2), and headache (n = 1). Intradialytic hypotension was reported to occur within 30 min after acupressure, and two participants discontinued the study in the final week due to the increased frequency of hypotension. The episodes of dizziness, palpitation, and headache occurred while acupressure was being applied. These side-effects disappeared within a few min and the acupressure treatment did not cease.

Sensitivity analyses

Sensitivity analyses were performed after excluding one study[26], as it contained no description of blinding details. The results were similar to all the other studies involved (Figure 14).

Meta-regression analyses

Meta-regression analyses were performed to investigate if there were any factors associated with the effects on depression. Age, the number of acupoints used, the total time of intervention, and the physical illnesses were included to investigate if there were any associated factors with the effects on depression. However, no significant results were found.

DISCUSSION

We included in the systematic review and meta-analysis 14 RCTs with 1439 participants with depressive symptoms. Overall, the data showed that acupressure

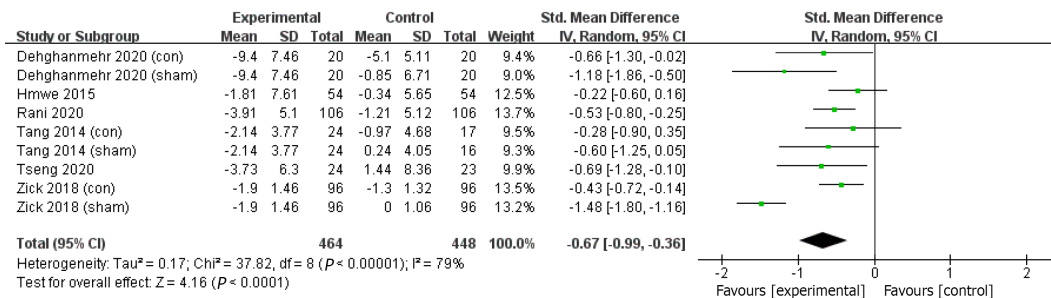| Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Dehghanmehr 2020 (con)	-9.4	7.46	20	-5.1	5.11	20	9.4%	-0.66 [-1.30, -0.02]
Dehghanmehr 2020 (sham)	-9.4	7.46	20	-0.85	6.71	20	9.0%	-1.18 [-1.86, -0.50]
Hmwe 2015	-1.81	7.61	54	-0.34	5.65	54	12.5%	-0.22 [-0.60, 0.16]
Rani 2020	-3.91	5.1	106	-1.21	5.12	106	13.7%	-0.53 [-0.80, -0.25]
Tang 2014 (con)	-2.14	3.77	24	-0.97	4.68	17	9.5%	-0.28 [-0.90, 0.35]
Tang 2014 (sham)	-2.14	3.77	24	0.24	4.05	16	9.3%	-0.60 [-1.25, 0.05]
Tseng 2020	-3.73	6.3	24	1.44	8.36	23	9.9%	-0.69 [-1.28, -0.10]
Zick 2018 (con)	-1.9	1.46	96	-1.3	1.32	96	13.5%	-0.43 [-0.72, -0.14]
Zick 2018 (sham)	-1.9	1.46	96	0	1.06	96	13.2%	-1.48 [-1.80, -1.16]
Total (95% CI)			464			448	100.0%	-0.67 [-0.99, -0.36]

Heterogeneity: Tau² = 0.17; Chi² = 37.82, df = 8 (*P* < 0.00001); I² = 79%
Test for overall effect: Z = 4.16 (*P* < 0.0001)

Figure 13 Effects of acupressure on anxiety.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.13.1 Experimental vs Control								
Bergmann 2014	-1.88	7.21	106	-1.09	6.87	107	7.1%	-0.11 [-0.38, 0.16]
Dehghanmehr 2020 (con)	-3.4	5.15	20	-5.1	3.92	20	5.4%	0.36 [-0.26, 0.99]
Hmwe 2015	-2.11	8.18	54	0.15	8.22	54	6.6%	-0.27 [-0.65, 0.11]
Honda 2012	-9	10.82	13	1	9.79	12	4.4%	-0.94 [-1.77, -0.10]
Kalani 2019 (con)	-6.9	9.45	32	0.3	8.43	32	6.0%	-0.79 [-1.30, -0.28]
Lanza 2018	-3	2.17	6	-1	1.01	6	2.9%	-1.09 [-2.34, 0.16]
Molassiotis 2020 (con)	-2.9	1.55	40	-1.2	0.87	38	6.1%	-1.33 [-1.82, -0.84]
Rani 2020	-3.58	7.05	106	-1.98	7.64	106	7.1%	-0.22 [-0.49, 0.05]
Zick 2018 (con)	-3.1	1.62	96	-2.9	1.55	96	7.0%	-0.13 [-0.41, 0.16]
Subtotal (95% CI)			473			471	52.5%	-0.42 [-0.71, -0.13]

Heterogeneity: Tau² = 0.13; Chi² = 32.19, df = 8 (*P* < 0.0001); I² = 75%
Test for overall effect: Z = 2.83 (*P* = 0.005)

1.13.2 Experimental vs Sham								
Dehghanmehr 2020 (sham)	-3.4	5.16	20	3.4	4.63	20	5.1%	-1.36 [-2.05, -0.66]
Kalani 2019 (sham)	-6.9	9.45	32	-0.2	7.59	32	6.0%	-0.77 [-1.28, -0.26]
Molassiotis 2020 (sham)	-2.9	1.55	40	-2.1	1.22	40	6.3%	-0.57 [-1.02, -0.12]
Rahimi 2020	-1.82	2.95	53	-0.09	3.56	53	6.6%	-0.53 [-0.91, -0.14]
Tseng 2020	-3.36	2.76	24	0.41	3.28	23	5.4%	-1.23 [-1.85, -0.60]
Wu 2007	-2.09	1.54	22	0.14	1.61	22	5.2%	-1.39 [-2.05, -0.73]
Yu 2020	-1.6	4.07	35	-0.9	4.21	35	6.2%	-0.17 [-0.64, 0.30]
Zick 2018 (sham)	-3.1	1.62	96	-1.2	0.75	96	6.9%	-1.50 [-1.82, -1.18]
Subtotal (95% CI)			322			321	47.5%	-0.92 [-1.29, -0.54]

Heterogeneity: Tau² = 0.22; Chi² = 33.45, df = 7 (*P* < 0.0001); I² = 79%
Test for overall effect: Z = 4.79 (*P* < 0.00001)

Total (95% CI)			795			792	100.0%	-0.67 [-0.94, -0.40]

Heterogeneity: Tau² = 0.25; Chi² = 99.58, df = 16 (*P* < 0.00001); I² = 84%
Test for overall effect: Z = 4.86 (*P* < 0.00001)
Test for subgroup differences: Chi² = 4.30, df = 1 (*P* = 0.04), I² = 76.7%
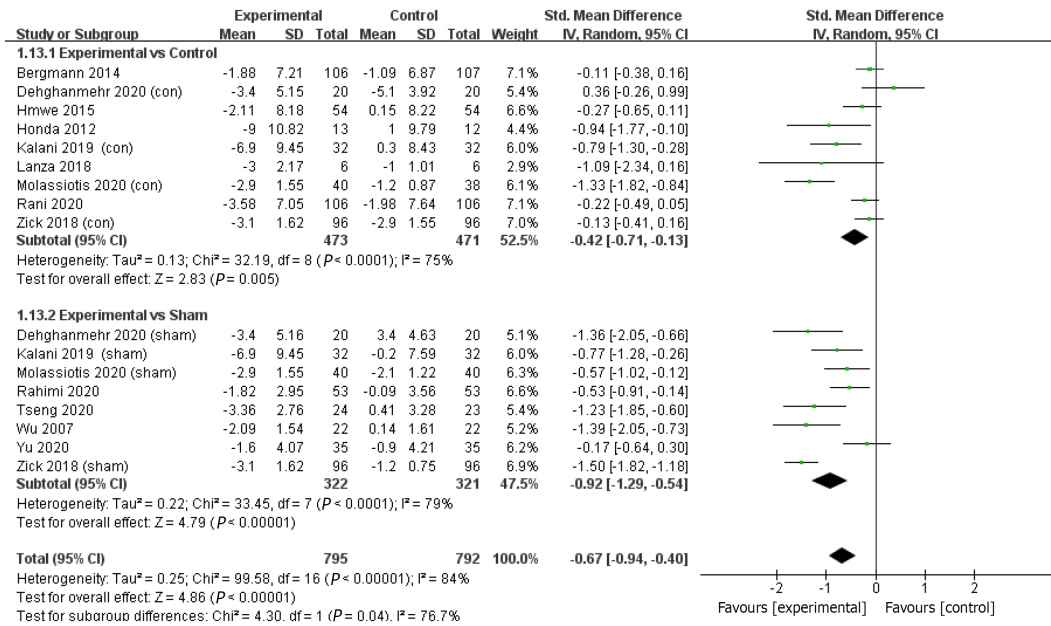
Figure 14 Sensitivity analyses of acupressure on depression.

had great potential to improve mild-to-moderate depressive symptoms in both primary and secondary depression. No systematic review and meta-analysis have been performed to assess the effectiveness of acupressure on depression in various clinical population. A recent integrative review showed that acupressure reduced depression in older people in the community, whether or not they had chronic illnesses[32]. Subgroup analyses in our meta-analysis consistently showed significant reductions in depression levels after acupressure treatment for adults with a large effect size in participants aged 65 years or above. Moreover, subgroup analyses also suggested that acupressure significantly reduced depression regardless of the clinical conditions. A recent scope review of six studies indicated that acupressure improved depression and psychological health in dementia[36], which is consistent with our findings in participants with Alzheimer's disease. However, these significant findings should be interpreted with caution due to the heterogeneity of the clinical conditions of the participants, manipulation techniques of acupressure, the selected acupoints, and the outcome measures.

Most studies in our review investigated the effects of acupressure on mild-to-moderate secondary depression in patients with chronic diseases. Three studies examined in patients with mild-to-moderate primary depression and all reported significant improvement in symptoms. However, it is not clear if acupressure is effective for patients with moderate-to-severe primary depressive disorders. Furthermore, none of the studies included in our meta-analysis mentioned specifically which symptom domains of depression were improved by acupressure treatment. Future research may focus on the effects of acupressure for moderate-to-severe depressive disorders and specific symptom domains.

Data showed a wide range of durations in acupressure interventions, ranging from 2 wk to 40 wk. More than half the studies (57.1%) involved acupressure treatment for 2-4 wk. The subgroup analyses suggested significant reductions in depression after either less than or more than 4 wk, indicating that acupressure benefits psychological well-being even after short-term treatment.

The acupressure manipulation applied in the included studies differed widely, and no confirmative conclusion could be drawn on the most effective acupressure technique. In general, 15 to 20-min sessions and 4-wk durations were commonly adopted. The majority of studies applied more than three acupoints, and the commonest acupoints used for depression are Yintang, Sanyinjiao, and Zusanli. Future research may compare the effects on depression among different acupoints to ascertain the effect of acupressure using specific acupoints. The most fundamental technique of acupressure is firm pressure on the acupoints. No included studies mentioned the amount of pressure on the acupoint, which is related to the thickness of skin, muscle, and fatty tissue at the point. The intensity of the pressure may be associated with the effect of acupressure due to the potential mechanism of stimulating the nerve systems; this needs to be clarified. Furthermore, adjusting the intensity of pressure based on the individual's tolerance is important in clinical practice.

All studies mentioned that the selection of acupoints was based on the TCM principles of balancing the "qi" flow in the body to promote inner self-recovery abilities. However, none of the included studies measured "qi" which may be a confounding factor for the outcomes, and none of them specified the particular neuro-mechanisms underlying the selection of acupoints. According to TCM, the "qi" circulates through 12 principal meridians between different organs of the body. There are 361 acupoints distributed along the meridians, and each is associated with a specific part of the body. Selecting acupoints along the meridian is the vital principle for acupressure treatment in depression. The application of specific acupoints related to refreshing the brain and soothing the liver function is the primary procedure across all the studies.

Acupressure also reduced anxiety in participants with psychiatric disorders, sclerosis, uremia, and osteoarthritis in both clinical and community settings. The findings were consistent with a previous systematic review and meta-analysis of acupressure on anxiety by Au *et al*[16]. However, Hmwe *et al*[32] suggested inconsistent findings on the effects of acupressure on anxiety and agitation in older people. Anxiety is a common comorbidity of depression, and the generalization of the effects of acupressure on anxiety needs to be further explored.

Ten of the 14 studies reported drop-out rates ranging from 0 to 28.8%, with a mean drop-out rate of 10.2%. Only one study reported the number that dropped out from each group and the reasons for withdrawal[24]. The completion rate was similar to previous studies of acupressure in older people in both clinical and community settings[32]. It was relatively lower than psychological treatment in depression[37]. It should be noted that none of the included studies had long-term follow-up. Furthermore, only one study reported adverse events, including hypotension, dizziness, palpitation, and headache, but without details. Addressing the effects during medium and long-term follow-up periods and the detailed adverse events of acupressure are the priorities suggested for future studies.

Only one study included in our review suggested the potential mechanisms through which the stimulation of particular acupoints on the skin can reduce depression and anxiety by altering the concentration of neurotransmitters, reducing the levels of adrenocorticotrophic hormones and hydroxytryptamine-5 in the brain, resulting in calmness[31]. Previous studies of acupuncture, which shared the same TCM theory with acupressure but used different manipulation technique (acupuncture uses needle), suggested that antidepressant effects of acupuncture are the result of the interaction inbetween multiple targets and levels in neural system. Acupuncture not only improves monoamine neurotransmitters, inhibits the hyperactive HPA axis, but also activates neurotrophic pathways, improves hippocampal neurogenesis, and inhibits inflammatory cytokines[38]. A study of electroacupuncture of acupoints "Baihui" and "Sanyingjiao" in chronically stressed rates significantly increased the activities of 5-HT by increasing the bingding site of 5-HT_{1A} receptors in the hippocampus of depressed rats[39]. A clinical study of acupuncture in women with menopausal depression showed significant increases in serum levels of Norepinephrine and Dopamine[40]. Furthermore, acupuncture at acupoints "Baihui" and "Yintang" combined with 5-HT reuptake inhibitors in older adults with depression significantly increased the serum Brain-derived Neurotrophic Factor (BDNF) level [41]. Song *et al*[42] found that electroacupuncture can significantly reduce the levels of serum interleukin IL-1β and tumor necrosis privacy (TNF-α) in patients with

depression, and the ratio of interferon to IL-4.

Limitations of the review

The first systematic review and meta-analysis of acupressure in depression showed a significantly greater overall effect than the controls. However, it is important to be aware of several limitations when interpreting the results.

We excluded 16 Chinese studies that reported poorly, and we were unable to find complete details of study design features relevant to the risk of bias assessment. Thus, trials meeting our inclusion criteria beyond those identified may exist.

Also, only three included trials focused on mild-to-moderate primary depression, and no evidence was found in patients with moderate or severe depression, making generalizability to this patient group difficult.

The included studies differ substantially with regard to participants, treatment frequency and duration, and acupoints selected. Meanwhile, the exact techniques of acupressure and therapeutic composition of acupoints were less undermined and inclusive, making comparisons between these included RCT studies difficult.

No study included in our meta-analysis measured "qi", which is the primary rationale for the selection of acupoints, and may be a confounding factor for the interpretation of the findings. Even though, we could still perform a meta-analysis and a quantitative synthesis of the included studies.

Implications for clinical practice and further research

As a non-invasive, safe and simple technique, acupressure has the potential to be promoted in clinical practice. The present study found that acupressure is feasible to improve depression and anxiety. Integration of this technique in the care of people vulnerable to mental illnesses, such as older people and postnatal women, would promote their emotional well-being and quality of life. That should further reduce the costs and side effects of conventional medication treatment in the standard care system. However, well-designed trials are recommended to provide more solid evidences on the effectiveness of acupressure for mental health promotion.

It is apparent that research in acupressure for mental health is still in its infancy, and further studies of high quality, with large sample sizes and medium- to long-term follow-ups, are warranted to examine the impacts on depression with different severity. Furthermore, effects of different acupoints and pressure retention on depression should be further examined for better understanding of the underlying mechanisms of acupressure in depression. Preliminary findings from our review suggested the potential mechanisms of acupressure may be associated with sympathetic and parasympathetic activities and the concentration of neurotransmitters and hormones in the neural networks. Future studies investigating the neurophysiological changes using imaging techniques (*e.g.*, fNIRS and MRI) are suggested.

CONCLUSION

This review found emerging evidence to support certain positive effects of acupressure for adults suffering from mild-to-moderate depression. Future well-designed research is needed to provide robust evidence for clinical practice and recommendation for its application, and an in-depth understanding of acupressure treatment in the context of integrative care as well.

ARTICLE HIGHLIGHTS

Research background

Originated from traditional Chinese medicine (TCM), acupressure is a safe and cost-effective complementary treatment for depression.

Research motivation

An increase body of research has been undertaken to assess effectiveness of acupressure in depression, but the evidence thus far is inconclusive.

Research objectives

Via the systematic review and meta-analysis, we compared clinical data using

acupressure and controls with usual care or sham treatment.

Research methods

The databases PubMed, PsycINFO, Scopus, Embase, MEDLINE, and China National Knowledge (CNKI) were searched. Randomized clinical trials (RCTs) or single-group trials in which acupressure was compared with control methods or baseline in people with depressive symptoms were included. The primary outcomes were the change between pre- and post-treatment in depression measures. Data were synthesized using a random-effects or a fixed-effects model to analyze the impacts of acupressure treatment on depression and anxiety in people with depression.

Research results

A total of 14 RCTs (1439 participants) were identified. Analysis of the between-group showed that acupressure was effective in reducing depression (SMD = -0.58, 95%CI: -0.85 to -0.32, *P* < 0.0001) and anxiety (SMD = -0.67, 95%CI: -0.99 to -0.36, *P* < 0.0001) in clinical patients with depressive symptoms. The evidence of acupressure for mild-to-moderate depressive symptoms in patients with chronic diseases was significant. The evidence of certainty in moderate-to-severe primary depression was low. No severe adverse events were reported.

Research conclusions

This present review indicated acupressure to be safe and exert certain positive effects in people with mild-to-moderate depressive symptoms. Importantly, the findings should be interpreted with caution due to study limitaitons, including heterogeneity of participants, treatment frequency and duration, the selected acupoints, and sample size.

Research perspectives

Future research with a well-designed mixed method is required to provide stronger evidence for clinical decisions and recommendations for its application, as well as an in-depth understanding of acupressure mechanisms and symptoms domains in depression.

REFERENCES

1   **GBD 2017 Disease and Injury Incidence and Prevalence Collaborators**. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392**: 1789-1858 [PMID: 30496104 DOI: 10.1016/S0140-6736(18)32279-7]

2   **Alsalman R**, Alansari B. Relationship of suicide ideation with depression and hopelessness. *European Psychiatry* 2020; **33**: S597-S597 [DOI: 10.1016/j.eurpsy.2016.01.2228]

3   **Clarke DM**, Currie KC. Depression, anxiety and their relationship with chronic diseases: a review of the epidemiology, risk and treatment evidence. *Med J Aust* 2009; **190**: S54-S60 [PMID: 19351294 DOI: 10.5694/j.1326-5377.2009.tb02471.x]

4   **Wulsin LR**, Vaillant GE, Wells VE. A systematic review of the mortality of depression. *Psychosom Med* 1999; **61**: 6-17 [PMID: 10024062 DOI: 10.1097/00006842-199901000-00003]

5   **Mathers CD**, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006; **3**: e442 [PMID: 17132052 DOI: 10.1371/journal.pmed.0030442]

6   **Goldman LS**, Nielsen NH, Champion HC. Awareness, diagnosis, and treatment of depression. *J Gen Intern Med* 1999; **14**: 569-580 [PMID: 10491249 DOI: 10.1046/j.1525-1497.1999.03478.x]

7   **Jorm AF**, Medway J, Christensen H, Korten AE, Jacomb PA, Rodgers B. Public beliefs about the helpfulness of interventions for depression: effects on actions taken when experiencing anxiety and depression symptoms. *Aust Nz J Psychiat* 2000; **34**: 619-626 [DOI: 10.1046/j.1440-1614.2000.00761.x]

8   **Kessler RC**, Soukup J, Davis RB, Foster DF, Wilkey SA, Van Rompay MI, Eisenberg DM. The use of complementary and alternative therapies to treat anxiety and depression in the United States. *Am J Psychiatry* 2001; **158**: 289-294 [PMID: 11156813 DOI: 10.1176/appi.ajp.158.2.289]

9   **Maxwell J**. The gentle power of acupressure. *RN* 1997; **60**: 53-56 [PMID: 9110874]

10   **Beal MW**. Acupuncture and oriental body work: traditional and modern biomedical concepts in holistic care--conceptual frameworks and biomedical developments. *Holist Nurs Pract* 2000; **15**: 78-87 [PMID: 12119622 DOI: 10.1097/00004650-200010000-00010]

11   **Robinson N**, Lorenc A, Liao X. The evidence for Shiatsu a systematic review of Shiatsu and acupressure. *BMC Complement Altern Med* 2011; **11**: 88 [PMID: 21982157 DOI: 10.1186/1472-6882-11-88]

12   **Lane JR**. The neurochemistry of counterconditioning Acupressure desensitization in psychotherapy.

Energy Psychology Theory, Research, Treatment 2009; **1**: 31-44 [DOI: 10.9769/EPJ.2009.1.1.JRL]

13   **Borimnejad LAN**, Seydfatemi N. The effects of acupressure on preoperative anxiety reduction in school aged children. *Healthmed* 2012; **6**: 2359-2361

14   **Yang MH**, Lin L-C. Acupressure in the care of the elderly. *Hu Li Za Zhi J Nurs* 2007; **54**: 10-11

15   **Lee EJ**, Frazier SK. The efficacy of acupressure for symptom management: a systematic review. *J Pain Symptom Manage* 2011; **42**: 589-603 [PMID: 21531533 DOI: 10.1016/j.jpainsymman.2011.01.007]

16   **Au DW**, Tsang HW, Ling PP, Leung CH, Ip PK, Cheung WM. Effects of acupressure on anxiety: a systematic review and meta-analysis. *Acupunct Med* 2015; **33**: 353-359 [PMID: 26002571 DOI: 10.1136/acupmed-2014-010720]

17   **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010; **8**: 336-341 [PMID: 20171303 DOI: 10.1016/j.ijsu.2010.02.007]

18   **Prady SL**, Richmond SJ, Morton VM, Macpherson H. A systematic evaluation of the impact of STRICTA and CONSORT recommendations on quality of reporting for acupuncture trials. *PLoS One* 2008; **3**: e1577 [PMID: 18270568 DOI: 10.1371/journal.pone.0001577]

19   **Furlan AD**, Pennick V, Bombardier C, van Tulder M; Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine (Phila Pa 1976)* 2009; **34**: 1929-1941 [PMID: 19680101 DOI: 10.1097/BRS.0b013e3181b1c99f]

20   **Jackson D**, Turner R. Power analysis for random-effects meta-analysis. *Res Synth Methods* 2017; **8**: 290-302 [PMID: 28378395 DOI: 10.1002/jrsm.1240]

21   **Cohen J**.   Statistical Power Analysis for the Behavioral Sciences. 1988 [DOI: 10.4324/9780203771587]

22   **Wu HS**, Lin LC, Wu SC, Lin JG. The psychologic consequences of chronic dyspnea in chronic pulmonary obstruction disease: the effects of acupressure on depression. *J Altern Complement Med* 2007; **13**: 253-261 [PMID: 17388769 DOI: 10.1089/acm.2006.5342]

23   **Lanza G**, Centonze SS, Destro G, Vella V, Bellomo M, Pennisi M, Bella R, Ciavardelli D. Shiatsu as an adjuvant therapy for depression in patients with Alzheimer's disease: A pilot study. *Complement Ther Med* 2018; **38**: 74-78 [PMID: 29857884 DOI: 10.1016/j.ctim.2018.04.013]

24   **Molassiotis A**, Suen L, Lai C, Chan B, Wat KHY, Tang J, To KL, Leung CO, Lee S, Lee P, Chien WT. The effectiveness of acupressure in the management of depressive symptoms and in improving quality of life in older people living in the community: a randomised sham-controlled trial. *Aging Ment Health* 2020; **24**: 1001-1009 [PMID: 30869991 DOI: 10.1080/13607863.2019.1584789]

25   **Tseng YT**, Chen IH, Lee PH, Lin PC. Effects of auricular acupressure on depression and anxiety in older adult residents of long-term care institutions: A randomized clinical trial. *Geriatr Nurs* 2021; **42**: 205-212 [PMID: 32921508 DOI: 10.1016/j.gerinurse.2020.08.003]

26   **Tang WR**, Chen WJ, Yu CT, Chang YC, Chen CM, Wang CH, Yang SH. Effects of acupressure on fatigue of lung cancer patients undergoing chemotherapy: an experimental pilot study. *Complement Ther Med* 2014; **22**: 581-591 [PMID: 25146059 DOI: 10.1016/j.ctim.2014.05.006]

27   **Bergmann N**, Ballegaard S, Bech P, Hjalmarson A, Krogh J, Gyntelberg F, Faber J. The effect of daily self-measurement of pressure pain sensitivity followed by acupressure on depression and quality of life *vs* treatment as usual in ischemic heart disease: a randomized clinical trial. *PLoS One* 2014; **9**: e97553 [PMID: 24849077 DOI: 10.1371/journal.pone.0097553]

28   **Zick SM**, Sen A, Hassett AL, Schrepf A, Wyatt GK, Murphy SL, Arnedt JT, Harris RE. Impact of Self-Acupressure on Co-Occurring Symptoms in Cancer Survivors. *JNCI Cancer Spectr* 2018; **2**: pky064 [PMID: 30687806 DOI: 10.1093/jncics/pky064]

29   **Yu HC**, Carol S; Wu B; Cheng YF. Effect of acupressure on postpartum low back pain, salivary cortisol, physical limitations, and depression: a randomized controlled pilot study. *J Tradit Chin Med* 2020; **40**: 128-136

30   **Rahimi H**, Mehrpooya N, Vagharseyyedin S, BahramiTaghanaki H. Self-acupressure for multiple sclerosis-related depression and fatigue A feasibility randomized controlled trial. *J Adv Med Biomed Res* 2020; **28**: 276-283 [DOI: 10.30699/jambs.28.130.276]

31   **Dehghanmehr S**, Sargazi GH, Biabani A, Nooraein S, Allahyari J. Comparing the Effect of Acupressure and Foot Reflexology on Anxiety and Depression in Hemodialysis Patients: A Clinical Trial. *Med Sur Nur J* 2020; **8** [DOI: 10.5812/msnj.100386]

32   **Hmwe NT**, Subramanian P, Tan LP, Chong WK. The effects of acupressure on depression, anxiety and stress in patients with hemodialysis: a randomized controlled trial. *Int J Nurs Stud* 2015; **52**: 509-518 [PMID: 25468282 DOI: 10.1016/j.ijnurstu.2014.11.002]

33   **Kalani L**, Aghababaeian, H, Majidipour, N. , Alasvand M, Bahrami H. The effects of acupressure on severity of depression in hemodialysis patients a randomized controlled Trial. *J Advanced Pharmacy Education Research* 2019; **9**: 67-72

34   **Rani M**, Sharma L, Advani U, Kumar S. Acupressure as an Adjunct to Pharmacological Treatment for Depression, Anxiety, and Stress in Patients with Knee Osteoarthritis. *J Acupunct Meridian Stud* 2020; **13**: 129-135 [PMID: 32738365 DOI: 10.1016/j.jams.2020.07.001]

35   **Honda Y**, Tsuda A, Horiuchi S. Four-Week Self-Administered Acupressure Improves Depressive Mood. *Psychology* 2012; **3**: 802-804 [DOI: 10.4236/psych.2012.329121]

36   **Harris ML**, Titler MG, Struble LM. Acupuncture and Acupressure for Dementia Behavioral and Psychological Symptoms: A Scoping Review. *West J Nurs Res* 2020; **42**: 867-880 [PMID: 31802723

DOI: 10.1177/0193945919890552]

37   **Smith CA**, Armour M, Lee MS, Wang LQ, Hay PJ. Acupuncture for depression. *Cochrane Database Syst Rev* 2018; **3**: CD004046 [PMID: 29502347 DOI: 10.1002/14651858.CD004046.pub4]

38   **Hu L**, Liang J, Jin SY, Han YJ, Lu J, Tu Y. [Progress of researches on mechanisms of acupuncture underlying improvement of depression in the past five years]. *Zhen Ci Yan Jiu* 2013; **38**: 253-258 [PMID: 24006675]

39   **Kang HT**, Wang. CW. Effect of electroacupuncture on 5-HT1A receptor of hippocampus of the rat model with chronic stress depression. *Henan Zhongyi Zazhi* **30**: 38-40

40   **Zhou SH**, Wu FD. [Therapeutic effect of acupuncture on female's climacteric depression and its effects on DA, NE and 5-HIAA contents]. *Zhongguo Zhen Jiu* 2007; **27**: 317-321 [PMID: 17645249]

41   **Huang XB**, Mu N, Mei F.   Therapeutic effect of acupuncture combined with medicine for the aged depression and its effect on the level of serum brain derived neurotrophic factor. J Pract Med 2011; 27: 127-129

42   **Song C**, Halbreich U, Han C, Leonard BE, Luo H. Imbalance between pro- and anti-inflammatory cytokines, and between Th1 and Th2 cytokines in depressed patients: the effect of electroacupuncture or fluoxetine treatment. *Pharmacopsychiatry* 2009; **42**: 182-188 [PMID: 19724980 DOI: 10.1055/s-0029-1202263]

SYSTEMATIC REVIEWS

Risk factors for suicidal behaviour in late-life depression: A systematic review

Veronica Fernandez-Rodrigues, Yolanda Sanchez-Carro, Luisa Natalia Lagunas, Laura Alejandra Rico-Uribe, Andres Pemau, Patricia Diaz-Carracedo, Marina Diaz-Marsa, Gonzalo Hervas, Alejandro de la Torre-Luque

ORCID number: Veronica Fernandez-Rodrigues 0000-0003-0397-513X; Yolanda Sanchez-Carro 0000-0002-8644-9436; Luisa Natalia Lagunas 0000-0003-4847-9578; Laura Alejandra Rico-Uribe 0000-0003-1530-6638; Andres Pemau 0000-0002-5835-507X; Patricia Diaz-Carracedo 0000-0001-6595-2377; Marina Diaz-Marsa 0000-0003-1364-3163; Gonzalo Hervas 0000-0003-2760-8035; Alejandro de la Torre-Luque 0000-0003-0595-6127.

Veronica Fernandez-Rodrigues, Andres Pemau, Patricia Diaz-Carracedo, Gonzalo Hervas, Department of Psychology, Universidad Complutense de Madrid, Madrid 28223, Spain

Yolanda Sanchez-Carro, Department of Psychiatry, Universidad Autonoma de Madrid, Madrid 28046, Spain

Yolanda Sanchez-Carro, Laura Alejandra Rico-Uribe, Marina Diaz-Marsa, Alejandro de la Torre-Luque, Centre for Biomedical Research in Mental Health (CIBERSAM), Madrid 28029, Spain

Luisa Natalia Lagunas, Marina Diaz-Marsa, Alejandro de la Torre-Luque, Department of Legal Medicine, Psychiatry and Pathology, Universidad Complutense de Madrid, Madrid 28046, Spain

Laura Alejandra Rico-Uribe, Department of Psychology, La Rioja International University, Logrono 26006, Spain

Marina Diaz-Marsa, Institute of Psychiatry and Mental Health, San Carlos Clinical Hospital, Madrid 28040, Spain

Corresponding author: Luisa Natalia Lagunas, PhD, Academic Fellow, Assistant Professor, Department of Legal Medicine, Psychiatry and Pathology, Universidad Complutense de Madrid, 2 Seneca Avenue, Madrid 28046, Spain. llagunas@ucm.es

Abstract

BACKGROUND
Suicide is a leading cause of preventable death worldwide, with its peak of maximum incidence in later life. Depression often puts an individual at higher risk for suicidal behaviour. In turn, depression deserves particular interest in old age due to its high prevalence and dramatic impact on health and wellbeing.

AIM
To gather integrated evidence on the potential risk factors for suicide behaviour development in depressive older adults, and to examine the effects of depression treatment to tackle suicide behaviour in this population.

METHODS
A systematic review of empirical studies, published from 2000 onwards, was conducted. Suicidal behaviour was addressed considering its varying forms (*i.e.*,

wish to die, ideation, attempt, and completed suicide).

RESULTS
Thirty-five papers were selected for review, comprising both clinical and epidemiological studies. Most of studies focused on suicidal ideation (60%). The studies consistently pointed out that the risk was related to depressive episode severity, psychiatric comorbidity (anxiety or substance use disorders), poorer health status, and loss of functionality. Reduced social support and loneliness were also associated with suicide behaviour in depressive older adults. Finally, the intervention studies showed that suicidal behaviour was a robust predictor of depression treatment response. Reductions in suicidal ideation were moderated by reductions in risk factors for suicide symptoms.

CONCLUSION
To sum up, common and age-specific risk factors seem to be involved in suicide development in depressive older adults. A major effort should be made to tackle this serious public health concern so as to promote older people to age healthily and well.

Key Words: Late-life depression; Suicide behaviour; Disability; Chronic disease; Loneliness

Core Tip: Suicide constitutes a global health concern. In this regard, suicide is one of the leading ten causes of death in five of the 21 Global Burden of Disease defined regions. Suicide mortality is more prevalent in older adults in comparison to younger adults, due to the cumulated influence of multiple risk factors over time. The role of depression in late-life suicide deserves particular interest due to its elevated prevalence and relationship with functional disability and chronic disease development. Results from this study may contribute to planning intensive assessment protocols in older adults with depression to target suicide, as well as to monitoring suicide behaviour as a key indicator of depression treatment success.

INTRODUCTION

Over 700000 deaths are attributed to suicide every year, making it the second leading cause of preventable death across the world and a serious public health concern[1]. An increasing trend of suicide death has also been reported between 2000 and 2017, with the highest rate of completed suicide observed in men older than 85 years[2-5].

Suicide should be considered a multifactorial phenomenon, involving dreadful consequences at varying levels, such as medical, legal, psychological, and economic levels among others[6]. Furthermore, it should be noted that psychiatric patients are more likely to die by suicide than the general population individuals[7-9].

Major depression deserves particular attention in old age as over 16% of community-dwelling older adults may experience an episode of clinically-relevant depressive symptoms susceptible for a clinical diagnosis, although not all report suicidal symptoms[10,11]. Some authors claim for considering the distinctive features of depression in old age. In this sense, a greater burden of somatic symptoms (*e.g.*, agitation, insomnia, and weight loss) may be evident in late-life depression[12]. Moreover, a higher risk of depressive episode onset may be observed among people with a history of depression in comparison to those who do not show any previous

episode. Since first episodes tend to appear from adolescence to middle age, late-life depression relapses may adopt more enduring statuses with a poorer prognosis in comparison to other life periods[13,14].

Besides, neurodegenerative and other ageing-related processes have to be taken into account in later life[15,16]. From this perspective, ageing-related frailty (*i.e.*, decreased physiological reserves, leading to adverse effects on health) and related disability have been extensively associated with poorer health status, including a higher rate of falls, increased health care service utilization, and mortality. Some studies have also linked limitations in activities of daily living with some somatic symptoms also seen in depression (*e.g.*, fatigue and agitation) as well as with risk factors for depressive symptom aggravation, such as reduced social participation and feelings of loneliness. On the other hand, the increased risk of showing metabolic diseases (*e.g.*, diabetes, hypercholesterolemia, and hypertension) and their daily management may decisively lead to emotional distress and depression development in late life[17,18]. Finally, the aging-related cognitive decline and its pathological evolution to dementia may be expected to increase the risk of late-life depression development[19].

Evidence is mixed regarding the contribution of aging-related factors (*e.g.*, increased metabolic and cognitive decline risk and loss of functionality) on the emergence of suicidal behavior symptoms in late-life depression[20-22]. Note that suicide behaviour should be understood more widely, comprising its varying forms (*i.e.*, wish to die, suicidal ideation, planning, attempt, and completed suicide) falling over the suicidality continuum. In this regard, it is relevant to mention that the strongest risk factors for death by suicide are the engagement in suicidal attempt and suicidal ideation[10].

Each suicidality form may have a distinctive way of expression[23]. Likewise, each form may be influenced by specific risk factors. For instance, suicidal ideation in old age was proven to be associated with sociodemographic factors (*e.g.*, lower educational attainment, living alone, and economic hassles) as well as some clinical factors, such as history of childhood abuse, poor self-perceived health, psychiatric comorbidity, and poorer social support (leading to loneliness and isolation) among others[2,24]. On the other hand, persistent suicidal ideation may be a major risk factor for suicide attempt, as well as other sociodemographic and clinical features, such as being White Caucasian, higher impulsivity levels, and suffering from chronic pain syndromes[21,25,26]. Unfortunately, inconsistencies have been described between the studies focused on suicide behaviour development and its related risk factors in depressive older adults.

This systematic review aimed to gather evidence on the risk of engaging in suicide behaviour among older adults with late-life depression. Moreover, it intended to investigate form-specific nuances of suicidality among older adults with depression, by studying the influence of sociodemographic, clinical, and psychological risk factors on suicidality form risk. Finally, we were interested in exploring the effect of interventions to reduce suicide behaviour on depressive symptoms.

MATERIALS AND METHODS

This study was conducted following the guidelines proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015) initiative[27,28]. Moreover, this systematic review was registered in PROSPERO platform (ID: CRD42021223897).

Article selection criteria

Studies were selected according to PICOS strategy in line with PRISMA-P 2015 guidelines. In this sense, the population criteria guided to select the following studies: Studies focused on human samples of older individuals (aged 65 years or higher) with a diagnosis of major depression disorder (MDD), according to a diagnostic manual of (mental) diseases. To satisfy intervention criteria, studies should assess suicide behaviour (by means of interviews, self-reports, or hospital/local or national records). Control criteria guided to select studies that comprised a control group of individuals who had been diagnosed with a MDD (and no suicide behaviour). In longitudinal studies, a baseline assessment of MDD patients would serve as a control condition. Regarding the outcome criteria, study should have a measure of suicide in its varying forms: Ideation, plan, attempt, and completed suicide. In addition, the passive wish to die was also considered as an outcome, as it can be understood as a passive form of suicidal ideation[29-31]. Composite scores derived from integrating multiple suicidality forms (*e.g.*, suicidality risk) were also considered. Finally, criteria on study

item were: Empirical studies published in scientific literature in Spanish or English, from 2000 onwards.

Search strategy

Papers were located following a two-way approach: An ascendant approach which involves scientific databases being consulted. The consulted databases were: Web of Science, PubMed, PsycInfo, and SCOPUS. The database search was conducted between November and December 2020. Queries were created combining three main key terms and their respective thesaurus (see the search queries in the Supplementary Table 1): Suicide (related MeSH terms: "Suicide, Attempted" and "Suicide, Completed"), depression (related MeSH terms: "Depressive Disorder", OR "Depressive Disorder, Treatment-Resistant" and "Depressive Disorder, Major"), and old age (exact MeSH term: 'Aged').

Articles were screened by a reviewer on an initial review of title, abstract, and keywords. Pre-selected papers were fully read by an independent reviewer to ratify the selection. A third peer reviewer approved the adequate selection of every paper to be included in this study. Discrepancies on paper selection were resolved by discussion.

Data extraction and bias assessment

Relevant data were extracted from each article using a coding manual by an independent coder (different from the reviewers who selected the article). Data from these variables were extracted: Age, sex, sample size, depression status, presence of a psychiatric comorbidity, chronic diseases, and disability; loneliness feelings, self-esteem, mental health treatment, follow-up length (longitudinal studies), and results of the study.

The Newcastle–Ottawa Quality Assessment Scale (NOQAS) was used to measure methodological quality of studies as a way to control for publication bias[32].

RESULTS

Database searches resulted in a total of 16431 hits retrieved. Over 64% (n = 10495) of them were duplicated records (Figure 1). A total of 5936 articles were excluded in the screening phase (*i.e.*, title, abstract, and keyword reading). A final sample size of 35 articles were reviewed after the full-text review phase.

The selected articles and their main features are displayed in Table 1. Over 54% of articles were published in 2010 onwards. On the other hand, 42.86% of articles were led by United States research groups, far followed by studies conducted in the United Kingdom and Taiwan (8.57% of studies in both cases). Study sample size ranged from 24[33] to 654232[34], with a mean of 22211.77 (SD: 109023.38). Male/female ratio was also quite diverse across studies, with a percentage of female participants ranging from 0[2,35,36] to 74%[37]. Mean age fluctuated between studies from 69.51[38] to 84.37 years[39], with an overall mean age of 72.5 (SD: 0.5) years. Finally, the methodological quality of studies ranged from 2 to 9 (Table 1).

Most studies (60%) selected examined suicidal ideation outcome[3,10,20-22,25,36,38-52]. On the other hand, suicide attempt was assessed in 40% of studies[2,3,21,35,37,41,44,52-57]. Finally, nine studies (25.71%) addressed death by suicide[2,33,34,37,54,56], three (8.57%) assessed wish to die[22,39,58], two (5.71% of studies) focused on suicidality risk[59,60], and only one evaluated suicide planning[45]. The most commonly used scale to measure suicidal ideation was the Hamilton depression rating scale (HDRS)[61] in 23.81% of suicidal ideation studies; a clinical interview relied on the Diagnostic and Statistical Manual of Mental Disorders (DSM)[62], and the Beck scale for suicidal ideation (SSI)[63], both used in 14.29% of studies measuring suicidal ideation. In suicide attempt studies, most of studies collected data on attempts from either national or local registers (42.86% of these studies) due to hospital admission.

Regarding sociodemographic risk factors, Barnow *et al*[39] showed a relationship between increased levels of wish to die and age among German seniors. Moreover, some studies have highlighted a higher risk of suicidal behaviour in women[39,52] and White Caucasian[25]. In the same vein, Lohman *et al*[47] observed lower scores in the HDRS among older adults from ethnic minority groups. On the other hand, the study by Bartels *et al*[41] reported higher scores of suicidal ideation among older Americans from Asian ethnic groups (in comparison to those from the African ethnic group). These authors also found that suicidal ideation was associated with comorbid anxiety disorder, fewer social support, and more medical comorbidity. Moreover, the level of

Table 1 Summary of studies included in the review

Ref.	Sample size	Sex (% female)	Mean age (yr)	Methodological quality	Suicide outcome	Suicide assessment	Treatment study testing and result	Depression-related factors	Significant risk factors
Almeida *et al*[2], 2016	38170	0	72	5	Suicide attempt and completed suicide	National register			Chronic diseases (+)
Arslanoglou *et al*[20], 2019	63	73.02	80.52	4	Suicidal ideation	Scale: HDRS	Psychological: PATH. Better outcomes for the PATH intervention *vs* supportive care	Depressive episode onset (-)	Cognitive function, (+) disability, (-) and social factors (social support) (-)
Aslan *et al*[3], 2019	150	72.7	71.3	4	Suicidal ideation and suicide attempt	Clinical interview: DSM-IV			Education attainment, (-) anxiety symptoms (+)
Awata *et al*[40], 2005	1145	58.07	76.29	4	Suicidal ideation	Clinical interview: DSM-IV		Depressive symptoms (+)	Disability (+) and social factors (social support) (+)
Barak *et al*[53], 2006	202	58.41	76.55	5	Suicide attempt	Local/regional register		Antidepressant use (-)	
Barnow *et al*[39], 2004	516	48.1	84.37	4	Wish to die and suicidal ideation	Scale: HDRS, GMS-A			Age, (+) sex (female), (+) subjective health status (-)
Bartels *et al*[41], 2002	2240	23.9		5	Suicidal ideation and suicide attempt	Scale: PSS			Ethnic group (Asians), (+)[1] medical diseases, (+) social factors (social support), (-) comorbid anxiety disorder (+)
Bakkane Bendixen *et al*[59], 2018	218	67	75.6	4	Suicidality risk	Scale: MADRS			Anxiety symptoms (+)
Bickford *et al*[42], 2021	88	62.5	71.5	4	Suicidal ideation	Scale: GSIS		Depressive symptoms (+)	Frailty and disability (+)
Bickford *et al*[10], 2020	225	64.9	71.4	4	Suicidal ideation	Scale: GSIS			Perceived stress (+)
Bonnewyn *et al*[58], 2017	68	59.29	73.87	5	Wish to die	Scale: SSI			
Brådvik and Berglund[54], 2009	1206			5	Suicide attempt and completed suicide	National register			
Bruce *et al*[43], 2004	412			6	Suicidal ideation	Scale: SSI	Pharmacological: PROSPECT. Reductions in suicidal ideation due to treatment		
Cole *et al*[44], 2006	113	63.4	79.2	5	Suicidal ideation and suicide	Clinical interview: DSM-IV		Major depression (+)	

attempt

Ref	N	%	Age	Score	Outcome	Assessment	Treatment/intervention	Factors	Factors
Coupland *et al* [55], 2011	60746	66.7	75	6	Suicide attempt	Local/regional register	Pharmacological: Antidepressants. No effect of treatments on suicidal outcomes	Antidepressant use (+)	Self-harm (+)
Hwang *et al*[35], 2010	70	0	79.4	6	Suicide attempt	Clinical interview			Brain volume (*i.e.*, reductions in dorsal medial prefrontal cortex) (+)
Innamorati *et al* [56], 2014	331	24.4		4	Suicide attempt and completed suicide	Autopsy			Social factors: Widowhood, (+) loneliness, (+) social support. (-) Life stressors (+)
Jokinen and Nordström[37], 2008	99	73.73	73	5	Suicide attempt and completed suicide	National register			Dexamethasone suppression (-)
Kiosses *et al*[45], 2017	74	73.66	80.90	4	Suicidal ideation and plan	Scale: MADRS	Psychological: PATH. Better outcomes for the PATH intervention *vs* supportive care		Negative emotions, (+) cognitive function (-)
La Pia *et al*[46], 2001	36	55.55		4	Suicidal ideation	Scale: HDRS	Pharmacological: Fluoxetine. Suicidal ideation reductions as a robust predictor of response		
Lee *et al*[21], 2003	156	32.69	73.6	2	Suicidal ideation and suicide attempt	Scale: HDRS; Clinical interview: DSM-IV		Delusional symptoms, (+) depressive symptoms (+)	Cognitive function, (-) disability (+)
Liu *et al*[36], 2020	47	0	83.8	5	Suicidal ideation	Scale: SSI		Depressive symptoms (+)	Chemokines (MCP-2/CCL8) (+)
Lohman *et al*[47], 2016	112	69.6	76.5	6	Suicidal ideation	Scale: HDRS	Nurse-based: CAREPATH. Lower proportions (31.3%) of CAREPATH patients showing suicidal ideation at follow-up, *vs* TAU patients (63.6%)		Ethnic group (minorities), (-) disability, (+) burdensomeness (+)
Lutz *et al*[48], 2021	75	66	71.57	4	Suicidal ideation	Scale: GSIS	Psychological: 12-wk problem-solving therapy. Changes in functional disability predicted the changes in suicidal ideation		Disability (+)
Lynch *et al*[38], 2004	77	62.3	69.51	3	Suicidal ideation	Scale: ASIQ		Hopelesness (+)	Negative affect intensity and reactivity (+)
Mansour *et al*[25], 2020	5546	61.5	76.8	7	Suicidal ideation	Clinical Interview: ICD-10			Ethnic group (White) (+)
McIntyre *et al* [22], 2008	1763	28.59	73.68	4	Wish to die and suicidal ideation	Scale: GSIS			Subjective health status, (-) medical conditions, (+) disability, (+) health service utilization, (+) anxiety disorder (+)

Meeks *et al*[49], 2008	148	60	80.3	5	Suicidal ideation	Center admission record		Sleep difficulty (+)	Chronic pain, (+)
Morse and Lynch [50], 2004	65	69.2	70.3	4	Suicidal ideation	Scale: ASIQ			
Nishida *et al*[33], 2015	24	41.67	78.7	8	Completed suicide	Autopsy			Stroke severity (+)
Richard-Devantoy *et al*[57], 2012	40	62.5	76.5	9	Suicide attempt	Clinical interview: DSM-IV			Cognitive function (-)
Sacco *et al*[60], 2015	8480	52.97	75.91	5	Suicidality risk	Clinical Interview: ICD-10		Depressive symptoms (+)	Alcohol use disorder, (+) liver disease (+)
Szanto *et al*[51], 2003	395	72.91	71.4	4	Suicidal ideation	Scale: HDRS	Pharmacological and psychological: Paroxetine, nortriptyline with or without psychotherapy. Participants with a higher risk of suicidality needed a greater time for suicidal ideation reduction	Depressive episode onset, (-) number of episodes, (+) depressive symptoms, (+) recurrence of depressive episode (+)	Psychiatric inpatient (+)
Tan and Wong [52], 2008	80	69.1	72.7	5	Suicidal ideation and suicide attempt	Scale: BDI, SSI. Clinical interview (not specified)		History of suicide behavior (+)	Sex (female), (+) psychiatric inpatient treatment (-)
Zivin *et al*[34], 2007	654232			7	Completed suicide	National register			Substance use disorder, (+) PTSD (-)

[1]In comparison to black participants.

The methodological quality of the studies was assessed by means of the Newcastle-Ottawa Quality Assessment Scale. The relationships between the depression-related and risk factors with the suicide outcome were positive (+), indicating the higher the level of the factor (or the presence of this condition), the higher the risk of the suicide outcome. An inverse relationship between the depression-related and risk factors with the suicide outcome was indicated by (-), with higher levels of the factor (or the presence of this condition) associated with a lower suicide outcome risk. ASIQ: Adult suicidal ideation questionnaire; DSM: Diagnostic and statistical manual of mental disorders; BDI: Beck depression inventory; GMS-A: Geriatric mental state examination; GSIS: Geriatric suicide ideation scale; HDRS: Hamilton depression rating scale; ICD: International classification of diseases manual; MADRS: Montgomery-Asberg depression rating scale; SSI: Beck scale for suicidal ideation.

education was negatively associated with a higher risk of suicide behaviour engagement (*i.e.*, suicidal ideation and attempt), as Aslan *et al*[3] reported.

In terms of depression features, the studies showed a higher risk of suicide in depressive episodes with earlier onset[20,51]. On the other hand, the use of antidepressants was associated with a lower risk of suicide behaviour[53], but results did not seem to be conclusive due to divergences with other studies. In this vein, Coupland *et al*[55] observed a higher probability to show suicide behaviour in patients under antidepressant treatment. Finally, the severity of depressive symptoms was strongly associated with higher suicide behaviour across studies[36,40,42,51,60]. Meeks *et al*[49] highlighted the relationship between sleep difficulty and suicidal ideation. More concretely, the study aimed to assess whether chronic pain would be associated with comorbidity, length of hospitalisation, suicidal ideation, and sleep duration in depressive geriatric inpatients. As a result, the authors found an elevated prevalence
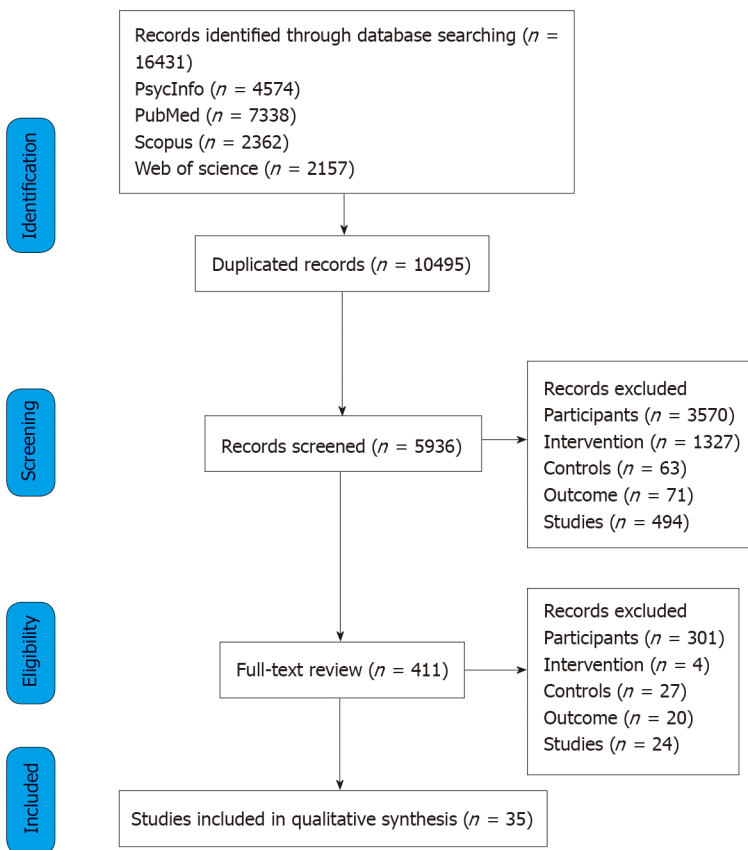
Figure 1 Flow diagram of study selection

of chronic pain among these patients (62% of patients). Moreover, patients with comorbid depression and chronic pain showed a higher risk of suicidal ideation than patients without chronic pain. Other factors associated with suicidal ideation in this study were the diagnosis of a personality disorder, more elevated medical burden, and total sleep time decrease.

The study by Lynch *et al*[38] provided some evidence in line with the well-known relationship between suicidal ideation and hopelessness. Finally, other studies point to a higher risk of suicidal behaviour in patient with both history of depressive episodes (*i.e.*, number of episodes and recurrence) and number of suicide episodes[51,52].

Regarding clinical factors, studies agree in highlighting the relationship between health status indicators and suicidality forms. First, some studies showed an increased risk of suicidality in psychiatric inpatients[34,52]. Moreover, mounting evidence has suggested a consistent relationship between anxiety (*i.e.*, comorbid anxiety disorder or elevated anxiety symptoms) and suicide, regardless of suicidality form[3,22,41,59]. Other studies focused on comorbidity with other psychiatric disorders. In this vein, Zivin *et al*[34] highlighted a reduced risk of death by suicide among veterans with comorbid depression and posttraumatic stress disorder. However, this result was moderated by age, as younger veterans did show a higher suicide rate than their older counterparts. Results were contradictory regarding personality traits. As aforementioned, Meeks *et al*[49] did find a positive relationship between suicidal ideation and a diagnosis of a personality disorder in depressive older adults with chronic pain. However, Morse and Lynch[50] failed to identify positive correlations between pathological personality traits (*i.e.*, paranoid, schizotypic, narcissistic, borderline, and avoidant) and suicidal ideation. On the other hand, the presence of co-occurring substance abuse disorder was associated with a higher suicide risk in this sample. Sacco *et al*[60] also found a significant relationship with alcohol use disorder. The association between cognitive decline and suicidal ideation seems to be evident as shown by Kiosses *et al*[45] and Richard-Devantoy *et al*[57], even though none of the studies addressing cognitive function included samples with either dementia or mild cognitive impairment.

Several studies showed an increased risk for suicidal behaviour with higher disability levels[20,22,40,42,47,48], poorer health status[22,39], and multimorbidity[41, 47]. Almeida *et al*[2] studied the relationship of multiple clinical factors with suicide

attempt and completed suicide among older men from Australia. The authors found that more than 57% of depressive men who completed suicide showed physical multimorbidity (*i.e.*, five or more health conditions). McIntyre *et al*[22] aimed at providing some evidence on the influence of comorbid anxiety on suicidal risk of depressive patients. The authors concluded that anxiety and depression co-occurrence may represent a gradient of clinical severity, leading to increasing levels of poorer self-reported health status, higher number of medical disorders, worse mental functioning, and greater use of emergency services. On the other hand, as aforementioned, chronic pain was associated with increased suicidal ideation[49]. Finally, the postmortem study by Nishida *et al*[33] revealed a clear relationship between stroke severity and completed suicide in older adults who had presented acute poststroke depression. More concretely, suicide victims were more likely to have shown progressive supranuclear palsy with argyrophilic grain disease.

In terms of psychosocial factors, the lack of social support has been systematically associated with suicidality across studies, particularly with suicidal ideation[20,40,41]. Innamorati *et al*[56] conducted a postmortem study comparing data from psychological interviews of patients who died by suicide and psychiatric outpatients who did not engage in suicide attempt. The study revealed higher levels of loneliness and lack of social support among suicide victims. Moreover, victims were more likely to be widowed and living alone before death. Finally, higher levels of stress were found among suicide victims. Bickford *et al*[42] also highlighted the relationship between perceived stress levels and suicidal ideation. Jokinen and Nordström[37] provided a piece of evidence connecting physiological stress response and suicide. The study analysed how the dexamethasone test (DST) may be useful to predict suicide attempt or death by suicide among depressed inpatients. A total of 24 patients (24.24% of sample participants) committed a suicide attempt and six patients died by suicide. The DST no-suppression was proven to be able to distinguish between suicide victims and survivors. On the other hand, Liu *et al*[36] explored how inflammatory factors and chemokines (the hypothalamus-pituitary-adrenal axis is involved in regulation of inflammatory factors) may distinguish between depressive men with and without suicidal ideation. As a result, participants with suicidal ideation showed higher levels of MCP-2/CCL8 chemokines than healthy controls and depressive men without suicidal ideation, as well as a higher number of depressive symptoms.

Finally, interventions to deal with depression and suicide behaviour deserve being mentioned. Eight studies analysed the effects of interventions to ameliorate depressive symptoms, targeting suicidal behaviour (*i.e.*, ideation and attempting). Three studies tested psychological interventions[20,45,48], and three were focused on pharmacological interventions[43,46,55]; the study by Lohman *et al*[47] analysed the effects of a nursing-based intervention (the CAREPATH). On the other hand, the study by Szanto *et al*[51] included data from two primary trials on antidepressant treatments (*i.e.*, paroxetine and nortriptyline) and another trial combining pharmacological and psychological treatment. The 12-wk problem adaptation therapy (PATH) programme was studied by Kiosses *et al*[45] and Arslanoglou *et al*[20]. The intervention was focused on providing emotion regulation skills. The PATH yielded reductions in suicidal ideation during the course of treatment, in comparison to supportive therapy. On the other hand, Lutz *et al*[48] evaluated factors related to suicide ideation due to a psychological treatment delivery (12-wk problem-solving therapy). As a result, they found that the changes in functional disability derived from the intervention predicted the reductions in suicidal ideation.

Regarding pharmacological interventions, results were mixed. First, Coupland *et al*[55] showed that the use of antidepressants (regardless of typologies: Tricyclic antidepressants or selective serotonin reuptake inhibitors) was associated with the presence of suicide attempts among the patients. However, Bruce *et al*[43] found beneficial effects of the use of antidepressants following the PROSPECT clinical algorithm (citalopram and psychiatric sessions, with training for clinicians to better manage late-life depression) on suicidal ideation. La Pia *et al*[46] studied the effect of fluoxetine on late-life depression. The authors found that suicidal ideation change was a robust predictor of treatment response. Szanto *et al*[51] pointed that symptom amelioration due to pharmacological intervention (with or without psychotherapy) was slower in depressive patients with a higher suicidality risk.

Lohman *et al*[47] analysed the effectiveness of the nurse-based depression management intervention (CAREPATH) in older adults with depression. The authors found a decreased risk of suicidal ideation in the CAREPATH group (only 31.3% of patients showing suicidal ideation in the 1-year follow-up), in comparison to controls (63.6% of them showing suicidal ideation). The decreased risk of suicidal ideation was associated with being an ethnic minority member, and lower limitations in instru-

mental activities of daily living and burdensomeness.

DISCUSSION

This systematic review aimed to gain insight into the risk factors for suicide behaviour development in older people with depression. From a lifelong perspective, suicide behaviour may reach its level of maximum incidence rate in late life[5,10]. Depression constitutes a main contributor to suicide behaviour development across the lifespan[8, 64,65]. A total of 35 manuscripts were selected from our robust methodological approach, covering both clinical studies[20,33,55] and epidemiological studies[34]. Despite the wide heterogeneity observed between the studies, our review revealed that most papers focused on suicidal ideation, mainly using self-reported measures, followed by suicide-attempt studies. Very few studies addressed risk factors for early forms of suicidality, such as passive suicidal ideation (*i.e.*, wish to die ideation)[22,39, 58], as well as completed suicide and its potential risk factors[2,33,56].

Our study focused on the role of four types of risk factors for suicide behaviour: Sociodemographic factors, factors related to depressive episodes (current episode and history of episodes), other clinical factors (both psychiatric and organic factors), and psychosocial factors. In addition, the effect of mental health interventions was studied. First, it highlighted the influence of some sociodemographic factors on suicidal ideation among depressive older adults: Being woman and White Caucasian[39,47, 52]. According to the integrated motivational-volitional model (IVM)[23], the genetic, biologically-based vulnerabilities may put individuals at higher risk of particular suicidality forms. In this vein, findings derived from the studies reviewed suggest that sex (being woman) and ethnic factors may show an age-invariant effect on suicidal ideation among depressive individuals, in line with other studies across the lifespan [64,65]. Unfortunately, data exploring the relationship between sociodemographic factors and other suicidality forms (*i.e.*, attempt and completed suicide) were not available for late-life depression patients. The exception that proves the rule only comprises two studies. First, Aslan *et al*[3] found a relationship between elevated suicidal ideation and attempt, and lower education level. Innamorati *et al*[56] showed that widowhood may be associated with a higher risk of engaging in suicide attempt and death by suicide. Widowhood may make social networks and participation become limited, with the subsequent emergence of feelings of loneliness and other mediators of suicide behavior[23]. Difficulties in emotion regulation and disease management may be related with a lower education level in old age[17,66]. In other words, lower education level may therefore be associated with poorer coping strategies. In line with the IVM[63], deficits in coping strategies may increase motivational moderators of suicidal ideation (*i.e.*, feeling of defeat, hopelessness, humiliation, or entrapment). The difficulties in emotion regulation may also be seen in depressive older individuals with cognitive decline[67].

Some episode-related factors may be involved in the emergence of suicide behaviour symptoms. These factors may boost the influence of motivational moderators on suicidal ideation and may increase the probability of ideation turning into attempt subsequently. The history of recurrent depression deserves being mentioned. First, depressive older adults are very likely to show a history of previous episodes[13]. Moreover, a depressive episode tends to be associated with a poorer prognosis and enduring symptoms in late life[68,69]. The studies included in this review were quite consistent in highlighting an increased risk of suicidal ideation among people with more severe episodes (*i.e.*, episode with an earlier onset, more severe symptoms, and treatment resistance) and those with a history of depressive episodes[20,36,42,46,51,60]. Conversion of suicidal ideation into suicide attempt may be boosted by the history of self-harm and suicide episodes, due to habituation processes and increased physical pain tolerance[55]. In this vein, people may erroneously learn that the suicide attempt constitutes an optimal strategy to cope with hassles and problematic situations[63].

Other clinical factors highlighted in our study were the presence of either a comorbid anxiety disorder or a co-occurring substance use disorder. Both types of disorders have been strongly associated with suicide behaviour symptoms[70,71]. Of particular interest is the relationship found between comorbid depressive and anxious symptoms and suicide among community-dwelling older adults, even from earlier subclinical stages[72,73]. On the other hand, alcohol-related disorders are strongly associated with suicide, both at the individual level (*e.g.*, up to six times more likelihood to engage in suicide behaviour in alcohol abusers) and population (*i.e.*,

increasing population drinking trends are associated with raising suicide rates) level [74,75]. Conversely, the debate is still open on the relationship between pathological personality traits and suicide among depressive older adults, due to the low number of studies and mixed evidence obtained[49,50]. Some mediating factors (*e.g.*, impulsivity or emotion dysregulation) are very likely to play a relevant role in the relationship between personality and suicide[23].

Multimorbidity and poorer health status have been systematically associated with suicide behaviour symptoms across studies[2,41,47]. In the similar vein, disease burden and difficulties in activities of daily living have proven to put depressive older adults at higher risk of suicide behaviour, regardless of suicidality form[20,42,48]. Disability and chronic diseases have shown a main, independent association with suicide, apart from depression[76,77]. However, these results should be considered more cautiously due to the influence of multiple ageing-related processes (*e.g.*, inflammatory imbalance and metabolic dysregulation) on both depression and chronic disease development[78,79]. Anyway, disability and chronic disease management may be particularly challenging and stressful for older adults due to progressive functional losses, increased economic costs, and frequent hospital admission[80,81]. Elevated stress has also been associated with a higher risk of suicidality across the reviewed studies[10,56]. In line with the IVM, recurrent exposure to stressors and daily hassles may increase the salience and cognitive accessibility of suicide triggering individuals engaging in suicide attempt[23].

Regarding the psychosocial factors, the reviewed studies identified the lack of social support and increased feelings of loneliness as main contributors to suicide behaviour in depressive older adults[20,41,56]. Social participation and social support may buffer the impact of stress in late life. In turn, social resources may work as protective factors that prevent depressive symptom aggravation and suicide behaviour emergence[82, 83]. On the other hand, social isolation and related emotional states (*i.e.*, loneliness) may lead to systematic deficient emotion regulation due to its impact on cognitive bias development (*e.g.*, selective retrieval of negative memories), as well as metabolic dysregulation due to loss of adherence to healthy lifestyle habits[84-86].

Finally, eight intervention papers were reviewed in our study. Some of the papers analysed the effect of targeted treatments on suicide behaviour[45,47], and others (pharmacological treatments, mainly) focused on wide depressive symptoms[46,51]. As a main conclusion of these studies, the reductions in suicidal behaviour (suicidal ideation) were moderated by changes in risk factors (*e.g.*, functional disability and burdensomeness) that may presumably involve deactivation of suicide-related cognitive mediators (*e.g.*, hopelessness and feelings of entrapment). Unfortunately, further studies should be done to support this speculation. On the other hand, it was found that a robust predictor of treatment response to antidepressants was the reduction of suicidal ideation. Some studies postulate the role of suicide ideation as a central symptom of depression whose amelioration may lead to improvement in other symptoms, due to contagion mechanisms[87,88]. Therefore, all these studies stress the key role of suicide behaviour in the maintenance of a depressive disorder in late life.

The present study comes from a robust framework to systematically review the risk factors of suicide behaviour emergence, maintenance, and remission in depressive older adults. Depression constitutes a highly prevalent mental disorder with a dreadful impact in late life[89,90]. Suicide behaviour has been consistently associated with depression, leading to worse outcome. Our study examined suicide in depressive older adults considering varying suicidality forms (*i.e.*, wish to die, suicidal ideation, attempt, and completed suicide). Moreover, a wide variety of risk factors were studied. On the other hand, the present study has some limitations that deserve mentioning. First, conclusions from this systematic review are essentially qualitative. Further studies should address the relationship between depression and suicide from a more analytical standpoint (*i.e.*, meta-analysis). Furthermore, our review was focused on recent literature covering the period from 2000 onwards. In this regard, the present study serves as an updated picture of the existing literature on depression and suicide in older adults. On the other hand, subthreshold depression was not addressed in this study. Some studies have demonstrated an evident relationship between subclinical depression statuses and suicide in old age[73,91,92]. In this regard, full-blown depressive disorders are related to a higher risk of negative outcomes and usually show a poorer prognosis in late life[89,93]. Finally, this study came from defining older adults as individuals who are 65 years or older. Our definition goes in line with that proposed by the World Health Organization[94]. Although we are aware that this definition might be narrowed, we decided to adopt a robust criterion for older age definition due to the huge variability of definitions across cultures[95].

CONCLUSION

Some clinical implications may be derived from our study. First, further research should be done to disentangle specific mechanisms involved in some forms of suicidality. In this vein, it is particularly relevant to gain insight into potential risk factors for dangerous suicidality forms (*e.g.*, suicide attempt and re-attempt) in a vulnerable population as older adults are. Second, policy makers may have a decisive role in tackling suicide in old age by promoting multicomponent prevention strategies, addressing both health-related and social factors (*e.g.*, strategies to promote social participation). Finally, suicide-targeted interventions should be developed and delivered on a wider basis to tackle the excess of mortality by suicide and to treat depression syndromes in older adults. In the same vein, suicide behaviour should be prioritised as a key therapeutic goal, even from its earliest forms (*i.e.*, wish to die).

ARTICLE HIGHLIGHTS

Research background

Suicide is one of the most relevant health hazards worldwide, particularly in old age with elevated rates of mortality by suicide. Depression constitutes the most prevalent mental health condition in old age, affecting almost one in five older adults at a community level. Depression is one of the most relevant risk factor for suicide behaviour in its multiple forms (*i.e.*, ideation, attempt, and completed suicide).

Research motivation

This study comes from the interest in reinforcing lines on research at community and clinical levels so as to improve the quality of life of older patients that may show severe mental health conditions: Older adults with depression and suicidal ideation and behaviour.

Research objectives

This study aimed to analyse the relationship between risk factors for suicide behaviour development and late-life depression, as well as to explore the effects of depression treatment on suicide behaviour.

Research methods

A systematic review was conducted covering the period from 2000 onwards, by selecting scientific papers on the relationship between late-life depression and suicide. The review was conducted following the guidelines proposed by the PRISMA-P 2015 statement.

Research results

Factors related to depressive episode severity, psychiatric comorbidity, poorer health status, and disability were highlighted to be related with the emergence of suicide behaviour among depressive older adults. Psychosocial factors were also involved in suicide behaviour emergence. Finally, suicidal behaviour was proven to be a key predictor of depression treatment response.

Research conclusions

Very few studies were focused on severe suicidal behaviour. For that reason, further research is needed to accurately disentangle the pathways involved in the transition between ideation and suicide attempt to prevent death by suicide. Changes in suicidal ideation seem to be decisive in terms of depressive disorder prognosis in late life.

Research perspectives

The results may help increase the awareness on the study of mechanisms involved in suicide from people at risk, as those with a depressive disorder, an actual lure in late life, taking into account its devastating impact in terms of mental health and wellbeing.

REFERENCES

1   **World Health Organization (WHO)**.   Suicide Worldwide in 2019: Global Health Estimates. 2021. [cited 10 April 2021]. Available from: https://www.who.int/

2   **Almeida OP**, McCaul K, Hankey GJ, Yeap BB, Golledge J, Flicker L. Suicide in older men: The health in men cohort study (HIMS). *Prev Med* 2016; **93**: 33-38 [PMID: 27663430 DOI: 10.1016/j.ypmed.2016.09.022]

3   **Aslan M**, Hocaoglu C, Bahceci B. Description of suicide ideation among older adults and a psychological profile: a cross-sectional study in Turkey. *Cien Saude Colet* 2019; **24**: 1865-1874 [PMID: 31166519 DOI: 10.1590/1413-81232018245.14232017]

4   **Koo YW**, Kõlves K, De Leo D. Suicide in older adults: differences between the young-old, middle-old, and oldest old. *Int Psychogeriatr* 2017; **29**: 1297-1306 [PMID: 28511737 DOI: 10.1017/S1041610217000618]

5   **Snowdon J**, Phillips J, Zhong B, Yamauchi T, Chiu HF, Conwell Y. Changes in age patterns of suicide in Australia, the United States, Japan and Hong Kong. *J Affect Disord* 2017; **211**: 12-19 [PMID: 28081432 DOI: 10.1016/j.jad.2017.01.007]

6   **Espinosa JJ**, Grynberg BB, Patricia M, Mendoza R. Riesgo y letalidad suicida en pacientes con trastorno límite de la personalidad (TLP), en un hospital de psiquiatría. *Sal Ment* 2009; **32**: 317-25 [DOI: 10.26439/ulima.tesis/1882]

7   **Dong M**, Wang SB, Li Y, Xu DD, Ungvari GS, Ng CH, Chow IHI, Xiang YT. Prevalence of suicidal behaviors in patients with major depressive disorder in China: A comprehensive meta-analysis. *J Affect Disord* 2018; **225**: 32-39 [PMID: 28779680 DOI: 10.1016/j.jad.2017.07.043]

8   **Gili M**, Castellví P, Vives M, de la Torre-Luque A, Almenara J, Blasco MJ, Cebrià AI, Gabilondo A, Pérez-Ara MA, A MM, Lagares C, Parés-Badell O, Piqueras JA, Rodríguez-Jiménez T, Rodríguez-Marín J, Soto-Sanz V, Alonso J, Roca M. Mental disorders as risk factors for suicidal behavior in young people: A meta-analysis and systematic review of longitudinal studies. *J Affect Disord* 2019; **245**: 152-162 [PMID: 30390504 DOI: 10.1016/j.jad.2018.10.115]

9   **Gregory R**, Sperry SD, Williamson D, Kuch-Cecconi R, Spink GL Jr. High Prevalence of Borderline Personality Disorder Among Psychiatric Inpatients Admitted for Suicidality. *J Pers Disord* 2021; **35**: 776-787 [PMID: 33661019 DOI: 10.1521/pedi_2021_35_508]

10   **Bickford D**, Morin RT, Nelson JC, Mackin RS. Determinants of Suicide-related Ideation in Late Life Depression: Associations with Perceived Stress. *Clin Gerontol* 2020; **43**: 37-45 [PMID: 31514586 DOI: 10.1080/07317115.2019.1666442]

11   **Ferrari AJ**, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJ, Vos T, Whiteford HA. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Med* 2013; **10**: e1001547 [PMID: 24223526 DOI: 10.1371/journal.pmed.1001547]

12   **Hegeman JM**, Kok RM, van der Mast RC, Giltay EJ. Phenomenology of depression in older compared with younger adults: meta-analysis. *Br J Psychiatry* 2012; **200**: 275-281 [PMID: 22474233 DOI: 10.1192/bjp.bp.111.095950]

13   **de la Torre-Luque A**, de la Fuente J, Sanchez-Niubo A, Caballero FF, Prina M, Muniz-Terrera G, Haro JM, Ayuso-Mateos JL. Stability of clinically relevant depression symptoms in old-age across 11 cohorts: a multi-state study. *Acta Psychiatr Scand* 2019; **140**: 541-551 [PMID: 31566713 DOI: 10.1111/acps.13107]

14   **Subramaniam H**, Mitchell AJ. The prognosis of depression in late life *vs* mid-life: implications for the treatment of older adults. *Int Psychogeriatr* 2005; **17**: 533-537 [PMID: 16246263 DOI: 10.1017/S1041610205002437]

15   **Edde M**, Leroux G, Altena E, Chanraud S. Functional brain connectivity changes across the human life span: From fetal development to old age. *J Neurosci Res* 2021; **99**: 236-262 [PMID: 32557768 DOI: 10.1002/jnr.24669]

16   **Franceschi C**, Capri M, Monti D, Giunta S, Olivieri F, Sevini F, Panourgia MP, Invidia L, Celani L, Scurti M, Cevenini E, Castellani GC, Salvioli S. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. *Mech Ageing Dev* 2007; **128**: 92-105 [PMID: 17116321 DOI: 10.1016/j.mad.2006.11.016]

17   **de la Torre-Luque A**, de la Fuente J, Prina M, Sanchez-Niubo A, Haro JM, Ayuso-Mateos JL. Long-term trajectories of depressive symptoms in old age: Relationships with sociodemographic and health-related factors. *J Affect Disord* 2019; **246**: 329-337 [PMID: 30594876 DOI: 10.1016/j.jad.2018.12.122]

18   **Repousi N**, Masana MF, Sanchez-Niubo A, Haro JM, Tyrovolas S. Depression and metabolic syndrome in the older population: A review of evidence. *J Affect Disord* 2018; **237**: 56-64 [PMID: 29772477 DOI: 10.1016/j.jad.2018.04.102]

19   **Byers AL**, Yaffe K. Depression and risk of developing dementia. *Nat Rev Neurol* 2011; **7**: 323-331 [PMID: 21537355 DOI: 10.1038/nrneurol.2011.60]

20   **Arslanoglou E**, Banerjee S, Pantelides J, Evans L, Kiosses DN. Negative Emotions and the Course of Depression During Psychotherapy in Suicidal Older Adults With Depression and Cognitive Impairment. *Am J Geriatr Psychiatry* 2019; **27**: 1287-1295 [PMID: 31582195 DOI: 10.1016/j.jagp.2019.08.018]

21   **Lee TW**, Tsai SJ, Yang CH, Hwang JP. Clinical and phenomenological comparisons of delusional and non-delusional major depression in the Chinese elderly. *Int J Geriatr Psychiatry* 2003; **18**: 486-

490 [PMID: 12789668 DOI: 10.1002/gps.870]

22   **McIntyre J**, Cheal K, Bartels S, Durai UN, Herr BM, Quijano L, Llorente M, Ware JH, Constantino G, Miller C, Kirchner J, Levkoff, SE. Anxiety and Depressive Disorders in Older Primary Care Patients: Defining a Clinical Severity Gradient Corresponding to Differences in Health Status, Functioning, and Health Service Use. *Ageing Int* 2008; **32**: 93-107 [DOI: 10.1007/s12126-008-9011-6]

23   **O'Connor RC**, Kirtley OJ. The integrated motivational-volitional model of suicidal behaviour. *Philos Trans R Soc Lond B Biol Sci* 2018; **373** [PMID: 30012735 DOI: 10.1098/rstb.2017.0268]

24   **Fraser C**, Luther J, Kasckow J. Risk Factors for Suicide in Older Inpatient Veterans with Schizophrenia. *Community Ment Health J* 2019; **55**: 267-270 [PMID: 29589219 DOI: 10.1007/s10597-018-0267-3]

25   **Mansour R**, Tsamakis K, Rizos E, Perera G, Das-Munshi J, Stewart R, Mueller C. Late-life depression in people from ethnic minority backgrounds: Differences in presentation and management. *J Affect Disord* 2020; **264**: 340-347 [PMID: 32056770 DOI: 10.1016/j.jad.2019.12.031]

26   **Schmutte T**, Olfson M, Xie M, Marcus SC. Self-Harm, Suicidal Ideation, and Attempted Suicide in Older Adults: A National Study of Emergency Department Visits and Follow-Up Care. *Am J Geriatr Psychiatry* 2020; **28**: 646-658 [PMID: 31917069 DOI: 10.1016/j.jagp.2019.12.003]

27   **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097 [PMID: 19621072 DOI: 10.1371/journal.pmed.1000097]

28   **Moher D**, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; **4**: 1 [PMID: 25554246 DOI: 10.1186/2046-4053-4-1]

29   **O'Connell H**, Chin AV, Cunningham C, Lawlor BA. Recent developments: suicide in older people. *BMJ* 2004; **329**: 895-899 [PMID: 15485967 DOI: 10.1136/bmj.329.7471.895]

30   **Rurup ML**, Deeg DJ, Poppelaars JL, Kerkhof AJ, Onwuteaka-Philipsen BD. Wishes to die in older people: a quantitative study of prevalence and associated factors. *Crisis* 2011; **32**: 194-203 [PMID: 21940260 DOI: 10.1027/0227-5910/a000079]

31   **Rurup ML**, Pasman HR, Goedhart J, Deeg DJ, Kerkhof AJ, Onwuteaka-Philipsen BD. Understanding why older people develop a wish to die: a qualitative interview study. *Crisis* 2011; **32**: 204-216 [PMID: 21940258 DOI: 10.1027/0227-5910/a000078]

32   **Wells GA**, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P.   The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses, 2012. [cited 10 April 2021]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

33   **Nishida N**, Hata Y, Yoshida K, Kinoshita K. Neuropathologic features of suicide victims who presented with acute poststroke depression: significance of association with neurodegenerative disorders. *J Neuropathol Exp Neurol* 2015; **74**: 401-410 [PMID: 25853693 DOI: 10.1097/NEN.0000000000000184]

34   **Zivin K**, Kim HM, McCarthy JF, Austin KL, Hoggatt KJ, Walters H, Valenstein M. Suicide mortality among individuals receiving treatment for depression in the Veterans Affairs health system: associations with patient and treatment setting characteristics. *Am J Public Health* 2007; **97**: 2193-2198 [PMID: 17971541 DOI: 10.2105/AJPH.2007.115477]

35   **Hwang JP**, Lee TW, Tsai SJ, Chen TJ, Yang CH, Lirng JF, Tsai CF. Cortical and subcortical abnormalities in late-onset depression with history of suicide attempts investigated with MRI and voxel-based morphometry. *J Geriatr Psychiatry Neurol* 2010; **23**: 171-184 [PMID: 20430976 DOI: 10.1177/0891988710363713]

36   **Liu MN**, Tsai SJ, Yeh HL, Wu CC, Lin CP. MCP-2/CCL8 Level Associated With Suicidal Ideation in Elderly Men With Major Depression. *Arch Suicide Res* 2020; **24**: 467-476 [PMID: 32000634 DOI: 10.1080/13811118.2019.1649772]

37   **Jokinen J**, Nordström P. HPA axis hyperactivity as suicide predictor in elderly mood disorder inpatients. *Psychoneuroendocrinology* 2008; **33**: 1387-1393 [PMID: 18805641 DOI: 10.1016/j.psyneuen.2008.07.012]

38   **Lynch TR**, Cheavens JS, Morse JQ, Rosenthal MZ. A model predicting suicidal ideation and hopelessness in depressed older adults: the impact of emotion inhibition and affect intensity. *Aging Ment Health* 2004; **8**: 486-497 [PMID: 15724830 DOI: 10.1080/13607860412331303775]

39   **Barnow S**, Linden M, Freyberger HJ. The relation between suicidal feelings and mental disorders in the elderly: results from the Berlin Aging Study (BASE). *Psychol Med* 2004; **34**: 741-746 [PMID: 15099427 DOI: 10.1017/S0033291703008912]

40   **Awata S**, Seki T, Koizumi Y, Sato S, Hozawa A, Omori K, Kuriyama S, Arai H, Nagatomi R, Matsuoka H, Tsuji I. Factors associated with suicidal ideation in an elderly urban Japanese population: a community-based, cross-sectional study. *Psychiatry Clin Neurosci* 2005; **59**: 327-336 [PMID: 15896227 DOI: 10.1111/j.1440-1819.2005.01378.x]

41   **Bartels SJ**, Coakley E, Oxman TE, Constantino G, Oslin D, Chen H, Zubritsky C, Cheal K, Durai UN, Gallo JJ, Llorente M, Sanchez H. Suicidal and death ideation in older primary care patients with depression, anxiety, and at-risk alcohol use. *Am J Geriatr Psychiatry* 2002; **10**: 417-427 [PMID: 12095901]

42   **Bickford D**, Morin RT, Woodworth C, Verduzco E, Khan M, Burns E, Nelson JC, Mackin RS. The relationship of frailty and disability with suicidal ideation in late life depression. *Aging Ment Health* 2021; **25**: 439-444 [PMID: 31809584 DOI: 10.1080/13607863.2019.1698514]

43   **Bruce ML**, Ten Have TR, Reynolds CF 3rd, Katz II, Schulberg HC, Mulsant BH, Brown GK, McAvay GJ, Pearson JL, Alexopoulos GS. Reducing suicidal ideation and depressive symptoms in depressed older primary care patients: a randomized controlled trial. *JAMA* 2004; **291**: 1081-1091 [PMID: 14996777 DOI: 10.1001/jama.291.9.1081]

44   **Cole MG**, McCusker J, Ciampi A, Windholz S, Latimer E, Belzile E. The prognosis of major and minor depression in older medical inpatients. *Am J Geriatr Psychiatry* 2006; **14**: 966-975 [PMID: 17068319 DOI: 10.1097/01.JGP.0000224327.16963.9f]

45   **Kiosses DN**, Gross JJ, Banerjee S, Duberstein PR, Putrino D, Alexopoulos GS. Negative Emotions and Suicidal Ideation during Psychosocial Treatments in Older Adults with Major Depression and Cognitive Impairment. *Am J Geriatr Psychiatry* 2017; **25**: 620-629 [PMID: 28223082 DOI: 10.1016/j.jagp.2017.01.011]

46   **La Pia S**, Fuschillo C, Giorgio D, Ciriello R, Pinto A, Rivellini M, De Simone L. Sertonin (5-HT)-related symptoms and fluoxetine in geriatric depression. *Arch Gerontol Geriatr Suppl* 2001; **7**: 213-225 [PMID: 11431067 DOI: 10.1016/s0167-4943(01)00142-x]

47   **Lohman MC**, Raue PJ, Greenberg RL, Bruce ML. Reducing suicidal ideation in home health care: results from the CAREPATH depression care management trial. *Int J Geriatr Psychiatry* 2016; **31**: 708-715 [PMID: 26552852 DOI: 10.1002/gps.4381]

48   **Lutz J**, Mackin RS, Otero MC, Morin R, Bickford D, Tosun D, Satre DD, Gould CE, Nelson JC, Beaudreau SA. Improvements in Functional Disability After Psychotherapy for Depression Are Associated With Reduced Suicide Ideation Among Older Adults. *Am J Geriatr Psychiatry* 2021; **29**: 557-561 [PMID: 33097388 DOI: 10.1016/j.jagp.2020.09.021]

49   **Meeks TW**, Dunn LB, Kim DS, Golshan S, Sewell DD, Atkinson JH, Lebowitz BD. Chronic pain and depression among geriatric psychiatry inpatients. *Int J Geriatr Psychiatry* 2008; **23**: 637-642 [PMID: 18041102 DOI: 10.1002/gps.1954]

50   **Morse JQ**, Lynch TR. A preliminary investigation of self-reported personality disorders in late life: prevalence, predictors of depressive severity, and clinical correlates. *Aging Ment Health* 2004; **8**: 307-315 [PMID: 15370047 DOI: 10.1080/13607860410001709674]

51   **Szanto K**, Mulsant BH, Houck P, Dew MA, Reynolds CF 3rd. Occurrence and course of suicidality during short-term treatment of late-life depression. *Arch Gen Psychiatry* 2003; **60**: 610-617 [PMID: 12796224 DOI: 10.1001/archpsyc.60.6.610]

52   **Tan LL**, Wong HB. Severity of depression and suicidal ideations among elderly people in Singapore. *Int Psychogeriatr* 2008; **20**: 338-346 [PMID: 17651526 DOI: 10.1017/S1041610207005789]

53   **Barak Y**, Olmer A, Aizenberg D. Antidepressants reduce the risk of suicide among elderly depressed patients. *Neuropsychopharmacology* 2006; **31**: 178-181 [PMID: 16123751 DOI: 10.1038/sj.npp.1300863]

54   **Brådvik L**, Berglund M. Repetition and severity of suicide attempts across the life cycle: a comparison by age group between suicide victims and controls with severe depression. *BMC Psychiatry* 2009; **9**: 62 [PMID: 19788725 DOI: 10.1186/1471-244X-9-62]

55   **Coupland C**, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *BMJ* 2011; **343**: d4551 [PMID: 21810886 DOI: 10.1136/bmj.d4551]

56   **Innamorati M**, Pompili M, Di Vittorio C, Baratta S, Masotti V, Badaracco A, Conwell Y, Girardi P, Amore M. Suicide in the old elderly: results from one Italian county. *Am J Geriatr Psychiatry* 2014; **22**: 1158-1167 [PMID: 23890752 DOI: 10.1016/j.jagp.2013.03.003]

57   **Richard-Devantoy S**, Jollant F, Kefi Z, Turecki G, Olié JP, Annweiler C, Beauchet O, Le Gall D. Deficit of cognitive inhibition in depressed elderly: a neurocognitive marker of suicidal risk. *J Affect Disord* 2012; **140**: 193-199 [PMID: 22464009 DOI: 10.1016/j.jad.2012.03.006]

58   **Bonnewyn A**, Shah A, Bruffaerts R, Demyttenaere K. Factors determining the balance between the wish to die and the wish to live in older adults. *Int J Geriatr Psychiatry* 2017; **32**: 685-691 [PMID: 27237707 DOI: 10.1002/gps.4511]

59   **Bakkane Bendixen A**, Engedal K, Selbæk G, Hartberg CB. Anxiety Symptoms in Older Adults with Depression Are Associated with Suicidality. *Dement Geriatr Cogn Disord* 2018; **45**: 180-189 [PMID: 29860257 DOI: 10.1159/000488480]

60   **Sacco P**, Unick GJ, Zanjani F, Camlin EA. Hospital outcomes in major depression among older adults: differences by alcohol comorbidity. *J Dual Diagn* 2015; **11**: 83-92 [PMID: 25671685 DOI: 10.1080/15504263.2014.993295]

61   **HAMILTON M**. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; **23**: 56-62 [PMID: 14399272 DOI: 10.1136/jnnp.23.1.56]

62   **American Psychiatric Association**.   Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Panamerican publishing house; 1994

63   **Beck AT**, Kovacs M, Weissman A. Assessment of suicidal intention: the Scale for Suicide Ideation. *J Consult Clin Psychol* 1979; **47**: 343-352 [PMID: 469082 DOI: 10.1037//0022-006x.47.2.343]

64   **Ivey-Stephenson AZ**, Demissie Z, Crosby AE, Stone DM, Gaylor E, Wilkins N, Lowry R, Brown M. Suicidal Ideation and Behaviors Among High School Students - Youth Risk Behavior Survey, United States, 2019. *MMWR Suppl* 2020; **69**: 47-55 [PMID: 32817610 DOI: 10.15585/mmwr.su6901a6]

65   **Steele IH**, Thrower N, Noroian P, Saleh FM. Understanding Suicide Across the Lifespan: A United States Perspective of Suicide Risk Factors, Assessment & Management. *J Forensic Sci* 2018; **63**: 162-171 [PMID: 28639299 DOI: 10.1111/1556-4029.13519]

66   **Marengoni A**, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, Meinow B, Fratiglioni L.

Aging with multimorbidity: a systematic review of the literature. *Ageing Res Rev* 2011; **10**: 430-439 [PMID: 21402176 DOI: 10.1016/j.arr.2011.03.003]

67   **Joormann J**, Gotlib IH. Emotion regulation in depression: relation to cognitive inhibition. *Cogn Emot* 2010; **24**: 281-298 [PMID: 20300538 DOI: 10.1080/02699930903407948]

68   **Jeuring HW**, Stek ML, Huisman M, Oude Voshaar RC, Naarding P, Collard RM, van der Mast RC, Kok RM, Beekman ATF, Comijs HC. A Six-Year Prospective Study of the Prognosis and Predictors in Patients With Late-Life Depression. *Am J Geriatr Psychiatry* 2018; **26**: 985-997 [PMID: 29910018 DOI: 10.1016/j.jagp.2018.05.005]

69   **van den Berg KS**, Wiersema C, Hegeman JM, van den Brink RHS, Rhebergen D, Marijnissen RM, Oude Voshaar RC. Clinical characteristics of late-life depression predicting mortality. *Aging Ment Health* 2021; **25**: 476-483 [PMID: 31830826 DOI: 10.1080/13607863.2019.1699900]

70   **Bentley KH**, Franklin JC, Ribeiro JD, Kleiman EM, Fox KR, Nock MK. Anxiety and its disorders as risk factors for suicidal thoughts and behaviors: A meta-analytic review. *Clin Psychol Rev* 2016; **43**: 30-46 [PMID: 26688478 DOI: 10.1016/j.cpr.2015.11.008]

71   **Yuodelis-Flores C**, Ries RK. Addiction and suicide: A review. *Am J Addict* 2015; **24**: 98-104 [PMID: 25644860 DOI: 10.1111/ajad.12185]

72   **Mykletun A**, Bjerkeset O, Dewey M, Prince M, Overland S, Stewart R. Anxiety, depression, and cause-specific mortality: the HUNT study. *Psychosom Med* 2007; **69**: 323-331 [PMID: 17470669 DOI: 10.1097/PSY.0b013e31803cb862]

73   **Zhang J**, Liu X, Fang L. Combined effects of depression and anxiety on suicide: A case-control psychological autopsy study in rural China. *Psychiatry Res* 2019; **271**: 370-373 [PMID: 30529321 DOI: 10.1016/j.psychres.2018.11.010]

74   **Borges G**, Bagge CL, Cherpitel CJ, Conner KR, Orozco R, Rossow I. A meta-analysis of acute use of alcohol and the risk of suicide attempt. *Psychol Med* 2017; **47**: 949-957 [PMID: 27928972 DOI: 10.1017/S0033291716002841]

75   **Norström T**, Rossow I. Alcohol Consumption as a Risk Factor for Suicidal Behavior: A Systematic Review of Associations at the Individual and at the Population Level. *Arch Suicide Res* 2016; **20**: 489-506 [PMID: 26953621 DOI: 10.1080/13811118.2016.1158678]

76   **Erlangsen A**, Stenager E, Conwell Y. Physical diseases as predictors of suicide in older adults: a nationwide, register-based cohort study. *Soc Psychiatry Psychiatr Epidemiol* 2015; **50**: 1427-1439 [PMID: 25835959 DOI: 10.1007/s00127-015-1051-0]

77   **Zhu J**, Xu L, Sun L, Li J, Qin W, Ding G, Wang Q, Zhang J, Xie S, Yu Z. Chronic Disease, Disability, Psychological Distress and Suicide Ideation among Rural Elderly: Results from a Population Survey in Shandong. *Int J Environ Res Public Health* 2018; **15** [PMID: 30060593 DOI: 10.3390/ijerph15081604]

78   **Pan A**, Keum N, Okereke OI, Sun Q, Kivimaki M, Rubin RR, Hu FB. Bidirectional association between depression and metabolic syndrome: a systematic review and meta-analysis of epidemiological studies. *Diabetes Care* 2012; **35**: 1171-1180 [PMID: 22517938 DOI: 10.2337/dc11-2055]

79   **Salameh TS**, Rhea EM, Banks WA, Hanson AJ. Insulin resistance, dyslipidemia, and apolipoprotein E interactions as mechanisms in cognitive impairment and Alzheimer's disease. *Exp Biol Med (Maywood)* 2016; **241**: 1676-1683 [PMID: 27470930 DOI: 10.1177/1535370216660770]

80   **Hardy SE**, Concato J, Gill TM. Stressful life events among community-living older persons. *J Gen Intern Med* 2002; **17**: 832-838 [PMID: 12406354 DOI: 10.1046/j.1525-1497.2002.20105.x]

81   **McRae I**, Yen L, Jeon YH, Herath PM, Essue B. Multimorbidity is associated with higher out-of-pocket spending: a study of older Australians with multiple chronic conditions. *Aust J Prim Health* 2013; **19**: 144-149 [PMID: 22950881 DOI: 10.1071/PY12035]

82   **Moreno-Agostino D**, de la Torre-Luque A, da Silva-Sauer L, Smith BW, Fernández-Calvo B. The age-invariant role of resilience resources in emotional symptomatology. *Aging Ment Health* 2021; 1-8 [PMID: 33896284 DOI: 10.1080/13607863.2021.1913472]

83   **Oon-arom A**, Wongpakaran T, Kuntawong P, Wongpakaran N. Attachment anxiety, depression, and perceived social support: a moderated mediation model of suicide ideation among the elderly. *Int Psychogeriatr* 2021; **33**: 169-178 [PMID: 32375910 DOI: 10.1017/S104161022000054X]

84   **de la Torre-Luque A**, Lara E, de la Fuente J, Rico-Uribe LA, Caballero FF, Lopez-Garcia P, Sanchez-Niubo A, Bobak M, Koskinen S, Haro JM, Ayuso-Mateos JL. Metabolic dysregulation in older adults with depression and loneliness: The ATHLOS study. *Psychoneuroendocrinology* 2021; **123**: 104918 [PMID: 33113390 DOI: 10.1016/j.psyneuen.2020.104918]

85   **Hawkley LC**, Cacioppo JT. Loneliness matters: a theoretical and empirical review of consequences and mechanisms. *Ann Behav Med* 2010; **40**: 218-227 [PMID: 20652462 DOI: 10.1007/s12160-010-9210-8]

86   **Lauder W**, Mummery K, Jones M, Caperchione C. A comparison of health behaviours in lonely and non-lonely populations. *Psychol Health Med* 2006; **11**: 233-245 [PMID: 17129911 DOI: 10.1080/13548500500266607]

87   **Komulainen K**, Airaksinen J, Savelieva K, Gluschkoff K, García Velázquez R, Elovainio M, Jokela M. Network dynamics of depressive symptoms in antidepressant medication treatment: secondary analysis of eight clinical trials. *Mol Psychiatry* 2021; **26**: 3328-3335 [PMID: 32939019 DOI: 10.1038/s41380-020-00884-3]

88   **Savelieva K**, Komulainen K, Elovainio M, Jokela M. Longitudinal associations between specific symptoms of depression: Network analysis in a prospective cohort study. *J Affect Disord* 2021; **278**:

99-106 [PMID: 32956966 DOI: 10.1016/j.jad.2020.09.024]

89   **Braam AW**, Copeland JR, Delespaul PA, Beekman AT, Como A, Dewey M, Fichter M, Holwerda TJ, Lawlor BA, Lobo A, Magnússon H, Prince MJ, Reischies F, Wilson KC, Skoog I. Depression, subthreshold depression and comorbid anxiety symptoms in older Europeans: results from the EURODEP concerted action. *J Affect Disord* 2014; **155**: 266-272 [PMID: 24355647 DOI: 10.1016/j.jad.2013.11.011]

90   **Ferrari AJ**, Somerville AJ, Baxter AJ, Norman R, Patten SB, Vos T, Whiteford HA. Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. *Psychol Med* 2013; **43**: 471-481 [PMID: 22831756 DOI: 10.1017/S0033291712001511]

91   **Briere J**, Kwon O, Semple RJ, Godbout N. Recent Suicidal Ideation and Behavior in the General Population: The Role of Depression, Posttraumatic Stress, and Reactive Avoidance. *J Nerv Ment Dis* 2019; **207**: 320-325 [PMID: 30958420 DOI: 10.1097/NMD.0000000000000976]

92   **Turvey CL**, Conwell Y, Jones MP, Phillips C, Simonsick E, Pearson JL, Wallace R. Risk factors for late-life suicide: a prospective, community-based study. *Am J Geriatr Psychiatry* 2002; **10**: 398-406 [PMID: 12095899]

93   **Vaccaro R**, Borrelli P, Abbondanza S, Davin A, Polito L, Colombo M, Francesca Vitali S, Villani S, Guaita A. Subthreshold Depression and Clinically Significant Depression in an Italian Population of 70-74-Year-Olds: Prevalence and Association with Perceptions of Self. *Biomed Res Int* 2017; **2017**: 3592359 [PMID: 28393076 DOI: 10.1155/2017/3592359]

94   **World Health Organization (WHO)**.   Men Ageing and Health: Achieving health across the life span, 2001. [cited 10 April 2021]. Available from: https://apps.who.int/iris/bitstream/handle/10665/66941/WHO_NMH_NPH_01.2.pdf;jsessioni

95   **Song M**, Kong EH. Older adults' definitions of health: A metasynthesis. *Int J Nurs Stud* 2015; **52**: 1097-1106 [PMID: 25747672 DOI: 10.1016/j.ijnurstu.2015.02.001]