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Neural Mechanisms of Delirium: Current Hypotheses and Evolving Concepts

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The purpose of this article is to review current knowledge regarding potential neural mechanisms of delirium. A MEDLINE search for relevant English language articles was undertaken using various combinations of delirium (including cognitive disorders, encephalopathy, and confusion) with pathogenesis and pathophysiology. These articles were scanned for content related to hypotheses concerning the neurobiology of delirium. Additional references were obtained from a manual search of the bibliography of these articles. A secondary MEDLINE search of delirium with the mechanism in question (i.e., serotonin, acetylcholine, etc.) was then undertaken. Literature review was last updated as of April 1998. Despite being a common problem among elderly patients, the mechanisms of delirium are poorly understood. Delirium is a syndrome that may occur as the result of multiple complex interacting neurotransmitter systems and pathologic processes. The neurotransmitters acetylcholine and serotonin may play particularly important roles in common medical and surgical delirium. Other neurotransmitters such as dopamine and gamma-aminobutyric acid each may be involved in the development of delirium under special conditions. Other neurobiologic factors such as cytokines, cortisol abnormalities, and oxygen free radicals will require further study to define their role in delirium. Distinct neuropathologic processes leading to delirium are beginning to be defined. Such mechanisms may differ in various clinical settings. There is probably no final common pathway to delirium, but rather, delirium is the final common symptom of multiple neurotransmitter abnormalities. Further situation-specific studies of delirium pathophysiology should lead to more effective prevention and treatment strategies.

DELIRIUM is a common and difficult problem in ill older persons, characterized by a fluctuating disturbance of consciousness and change in cognition that develops over a short period of time (1). Ten to 30% of elderly patients may be delirious on arrival to the hospital (2), and up to 55% may become delirious following admission (3,4). Delirium has significant human burdens such as increased morbidity and subsequent functional decline (4–8). The financial consequences are also significant, including increased length of hospitalization (5) and additional care requirements (4). Despite the importance of this problem, the pathophysiology of delirium remains obscure.

Unfortunately, a major limitation to treatment is that the strongest epidemiologic risk factors for delirium are conditions for which treatment is difficult or impossible, namely: preexisting cognitive impairment (2,4,9–17), age (2,4,9–11,13,14,16), and severity of illness (2,4,11–13,15). The weak association between delirium and more treatable factors such as azotemia (12,15) and electrolyte abnormalities (10,12) suggests that such factors may trigger delirium in predisposed individuals. Medications are also believed to be major contributors to delirium (7,18), but the mechanisms by which they do this may vary greatly between medication classes and individual patients.

Simply listing risk factors does not fully explain why elderly persons are at much greater risk for delirium when compared with younger individuals. It has been compellingly demonstrated that the risk for delirium with illness is a combination of predisposing and illness-related factors (17). Applying the concept of "homeostenosis" (the age-associated decline in physiologic reserve in body systems) to the problem of delirium suggests that age-related changes in the brain predispose older persons to delirium during physiologic disturbances that are tolerated in younger individuals. Changes in the brain with normal aging include a 28% decline in brain blood flow (19) and neuron loss in many areas including the neocortex and hippocampus. The locus ceruleus and substantia nigra are especially hard hit with loss of up to 35% of neurons (20). Furthermore, norepinephrine, acetylcholine, dopamine, and gamma-aminobutyric acid concentrations all decline with advanced age. Although great variability in the decline of organ systems is the rule among the older population, these structural and functional losses may be reflected in age-related declines in speed of learning, set formation (especially set formation and set shifting), reaction time, verbal fluency, visuoconstructive skills, and logical analysis (21). Thus, the result of the brain's failure to compensate for the neurologic stress of a drug or illness may then result in the phenomenology called delirium.

Epidemiologic research has contributed greatly to the understanding of delirium; however, the development of better preventive strategies and therapies requires a deeper understanding of its basic mechanisms. This article will review current understanding regarding potential neural mechanisms of delirium, particularly as that evidence relates to delirium commonly encountered in general medical and/or surgical conditions.

The Cholinergic System

Acetylcholine plays an important role in consciousness, perhaps by modulating the signal-noise ratio of sensory and cognitive input and focusing awareness (22). The major pathogenic mechanism in delirium is thus often presumed to be central cholinergic deficiency (23). This belief stems from a well-described association between delirium and anticholinergic toxins such as *Datuea sauveolens* (Angel's Trumpet—a plant found throughout the Gulf Coast) (24) and medications such as atropine (25). The administration of anticholinergic substances to both experimental animals (26) and humans (27) results in the

characteristic manifestations of delirium including typical electroencephalogram (EEG) changes. Age-related reductions in acetylcholine release and muscarinic receptor function (28) may further predispose elderly persons to harmful effects of cholinergic inhibition. Physostigmine (a cholinergic agonist) is known to be helpful in the treatment of delirium caused by anticholinergic toxicity (25) but its use has been limited by peripheral cholinergic (parasympathetic) toxicity such as excessive respiratory tract secretion, emesis, diarrhea, and cardiac dysrhythmia.

Other evidence linking cholinergic deficiency with delirium has been gathered using a functional competitive binding assay for serum anticholinergic activity developed by Tune and Coyle (29). This assay measures the ability of the patient's serum to block central muscarinic receptors. Elevated serum anticholinergic activity has been positively correlated with delirium in small numbers of patients in a surgical intensive care unit (30), in postcardiotomy patients (31), and in patients following electroconvulsive therapy (32). An association between elevated serum anticholinergic activity and delirium has been demonstrated in two studies of older medical patients (33,34). Interestingly, there may be a dose-response relationship between anticholinergic activity and major symptoms of delirium (34).

The origins of serum anticholinergic activity remain to be elucidated. Serum anticholinergic activity has generally been thought to arise from medications or their metabolites. This theory has important implications. If true, withdrawing all potential anticholinergic medications should result in an absence of anticholinergic activity and an improvement in delirium. Some drugs not typically thought of as anticholinergic, such as furosemide, cimetidine, and digoxin, may bind to muscarinic receptor in vitro (35) and should be considered for reduction or withdrawal as well. The potential for unrecognized anticholinergic effects of drug metabolites also exists (36). Some other medications to be considered are beta-adrenergic and dopaminergic agonists, opiates, and barbiturates that may interfere with cholinergic neurotransmission through presynaptic inhibition of acetylcholine release (37). The belief that medications or their metabolites are the sole source of serum anticholinergic activity has lead some to propose that pharmacologic management of delirious patients include monitoring of serum anticholinergic activity (38).

Some evidence suggests that endogenous anticholinergic substances may exist and be of clinical importance. One study that included six hospitalized older persons with delirium showed a decline in serum anticholinergic activity with resolution of delirium that was seemingly unrelated to medication changes (33). Another study of long-term care residents with fever found that serum anticholinergic activity declined significantly by 1 month following the febrile illness, and was independent of medication changes (39). Some endogenous molecules inhibit muscarinic receptors in experimental animals such as dynorphin A, myelin basic protein (40), and protamine (41). Interestingly, most epidemiologic studies indicate that anticholinergic medications are not statistically associated with delirium in either medical (2,7) or elderly postoperative surgical patients (42). Thus, medications and other substances that interfere with cholinergic neurotransmission may predispose elderly patients to delirium, but other factors may modify the individual patient's response.

In addition to the potential role of circulating anticholinergic substances, another mechanism of central cholinergic deficiency could be impaired acetylcholine production. Acetylcholine production, through its precursor acetyl coenzyme A (CoA), is closely tied to the oxygen and glucose citric acid cycle. Hypoglycemia, in experimental animals, depresses acetylcholine synthesis in the cortex and striatum (43). Methyl donors such as serine and methionine are important to the production of acetylcholine, and it has been proposed that some neuropsychiatric manifestations of schizophrenia are due to decreased transmethylation of methyl donors (44). One study of delirium following elective cardiac surgery found an association between delirium and reduced plasma levels of methionine and serine postoperatively (45).

Enhanced cholinergic transmission may also contribute to delirium under special circumstances. Delirium related to the use of tacrine has been reported in Alzheimer's patients (46). Evidence in experimental animals also suggests that increased hippocampal acetylcholine release may play a role in cognitive changes associated with alcohol withdrawal (47).

That central cholinergic inhibition is an important mechanism of delirium in common clinical settings seems strongly supported by the available evidence. This hypothesis suggests that attempting to augment central cholinergic transmission with medications such as central cholinesterase inhibitors is worthy of further study. Whether central cholinergic inhibition is the "final common pathway" of all commonly encountered medical and surgical delirium, however, is open to question. Serum anticholinergic activity levels in delirious and nondelirious patients have a great deal of overlap (30–34,39), suggesting the importance of other contributing factors. Thus, other potential mechanisms warrant investigation.

Serotonin and Large Neutral Amino Acids

Serotonin, the most abundant monoaminergic neurotransmitter in the brainstem (48), may also play an important role in the development of delirium. Serotonergic neurons project widely throughout the brain. Serotonin is involved in many behaviors affected by delirium, including mood, wakefulness, and cognition, at least in experimental animals (49). Considerable evidence has been accumulated that suggests increased serotonergic activity can lead to delirium.

Excessive activation of the serotonin system produces a "serotonin syndrome," characterized by confusion, restlessness, tremor, and diaphoresis. The serotonin syndrome may result from the combined administration of many medications with serotonergic effects. These include various combinations of L-tryptophan, monamine oxidase inhibitors, and fluoxetine (a selective serotonin reuptake inhibitor) (50–52). The syndrome is believed to result from enhancement of brainstem and/or general serotonin neurotransmission (53). Pretreatment with inhibitors of serotonin synthesis such as *p*-chlorophenylalanine, or serotonin receptor antagonists such as methylsergide prevents the serotonin syndrome in experimental animals (54).

Although elevated levels of cerebrospinal fluid 5-hydroxyindole acetic acid (a metabolite of serotonin) in ill, delirious, nondemented patients and ill, delirious patients with cerebrovascular disease have been reported (55), the control subjects were healthy, so it cannot be determined if these changes are specific to delirium or a general consequence of illness. In another study, cerebrospinal fluid 5-hydroxyindole acetic acid levels were found to be elevated in patients with delirium tremens and clozapine-induced delirium when compared to healthy controls, asymptomatic alcoholics, and clozapine-treated patients

who were not delirious (56). In this latter study, the elevated cerebrospinal fluid 5-hydroxyindole acetic acid levels returned to normal following recovery from delirium. Therefore, excessive serotonin activation, particularly in the setting of medication intoxication, seems to be associated with delirium; but whether this mechanism has a role in more common medical and surgical types of delirium remains to be demonstrated.

A relative deficiency of serotonin, through reduced tryptophan availability associated with illness, has also been proposed as a mechanism of delirium (57). The large neutral amino acids (isoleucine, leucine, methionine, phenylalanine, tyrosine, tryptophan, and valine) compete for a single receptor that allows entry into the central nervous system. Thus, as the concentration of one large neutral amino acid increases, central nervous system entry of other large neutral amino acids decrease (58). The ratio of tryptophan to the other large neutral amino acids therefore controls both tryptophan entry into the brain and the amount of serotonin in the brain (59). Clinical conditions associated with delirium may affect tryptophan and other serum large neutral amino acid levels. Catabolic states, for example, cause muscle breakdown that releases less tryptophan relative to the other large neutral amino acids. Stress, as induced in animal models through use of restraints, reduces the tryptophan to large neutral amino acid ratio (60).

Direct measurements of tryptophan levels and tryptophan to large neutral amino acid ratios in humans do suggest that a relative tryptophan deficiency may be associated with delirium. Plasma tryptophan levels and tryptophan to large neutral amino acid ratios were significantly lower in one group of seven delirious postcardiotomy patients when compared with nondelirious patients (57). Furthermore, a follow-up study of 296 patients before and after cardiac surgery demonstrated an association between delirium and lower postoperative tryptophan to large neutral amino acid ratio (45). Furthermore, dietary tryptophan depletion in healthy young adults may lead to changes in mood, but not acute confusion (61). One retrospective, but not randomized or blinded, study of 32 patients with early symptoms of delirium tremens did find that treatment with daily L-tryptophan infusion improved Mini-Mental Status Exam (MMSE) score, sleep/wake cycle, and reduced tranquilizer use (62). Aside from the methodologic problems with this study, tryptophan infusion may act simply to reduce the brain entry of phenylalanine, another amino acid that may play an important role in delirium when present at increased concentration.

If reduced serotonin function is related to delirium through amino acids concentration changes, then phenylalanine may be the primary culprit producing delirium. Phenylalanine enters the central nervous system as does tryptophan, via competition for the large neutral amino acid transport system. Phenylalanine also competes with tryptophan for hydroxylation, and phenylalanine metabolites compete with tryptophan metabolites for decarboxylation on the pathway to neurotransmitter synthesis (63). Elevated phenylalanine levels in older treated patients with phenylketonuria has been reported to reduce plasma dihydroxyphenylalanine (L-DOPA) concentrations, and urinary serotonin excretion (64,65), suggesting that impairment of biogenic amine production from elevated phenylalanine levels can occur in humans. Additionally, in phenylketonuria, phenylalanine undergoes alternate metabolism, and these metabolites of phenylalanine or phenylalanine itself may be neurotoxic (66). Because tyrosine hydroxylase is rate limiting for dopamine synthesis, overproduction of dopamine caused by elevated brain phenylalanine concentrations is unlikely to occur.

Elevated levels of phenylalanine have been shown to prolong performance time, impair higher integrative function (64), and reduce EEG mean power frequency (65) in treated adult patients with phenylketonuria. Sepsis, an event commonly associated with delirium, results in elevated serum levels of phenylalanine (67). In one small series of patients with septic encephalopathy, markedly elevated cerebrospinal fluid phenylalanine levels were found (68). Elevated cerebrospinal fluid levels of phenylalanine were also found in 17 patients with hepatic encephalopathy when compared to cirrhotic patients without encephalopathy (69). A preoperative elevation of phenylalanine to large neutral amino acid ratio was reported to be an independent predictor of post–cardiac surgery delirium, and a higher postoperative phenylalanine to large neutral amino acid ratio was also associated with delirium (45). Branched-chain amino acid infusions should theoretically decrease the entry of tyrosine and phenylalanine into the central nervous system. Such infusions have been used with some success to reverse encephalopathy secondary to sepsis and hepatic failure (68).

Thus, evidence suggests that phenylalanine, either through its negative effect on tryptophan entry into the brain and biogenic amine production, and/or by metabolism to neurotoxic substances, may lead to delirium. There are important clinical ramifications of this theory, if true. First, administration of glucose-containing fluids, through an effect on insulin, may serve to increase serum phenylalanine levels and predispose to delirium. Second, if this hypothesis is borne out, dietary manipulation, or infusion of competing large neutral amino acids could become important adjuncts to the care of delirious patients.

Other Neurotransmitters

Abnormalities in the activation of the dopaminergic system may participate in the neuropathogenesis of acute confusion. L-Dopa itself may lead to delirium (70), as may other dopaminergic agents such as deprenyl and pergolide (71). Dopamine activation is the putative mechanism of buproprion-associated delirium (72). Potent dopaminergic blockers such as haldol are commonly used to treat symptoms of delirium. However, the response to a dopamine blocker is not proof in itself that abnormalities of dopamine are the basic abnormality responsible for that patient's symptomatology. There is some experimental animal evidence that focal brain lesions, particularly in the frontal and parietal brain areas, may result in increased dopamine turnover and receptor number in subcortical areas (73). Strokes and trauma of the frontal and parietal brain regions may produce similar changes leading to psychosis in humans (74). Psychosis may or may not be part of delirium, and there is no evidence to suggest that hyperdopaminergic states are a fundamental mechanism of delirium related to general medical or surgical conditions.

Gamma-aminobutyric acid (GABA) is the major inhibitory transmitter in the central nervous system. Aside from hepatic encephalopathy, limited evidence links GABA abnormalities with delirium. In hepatic encephalopathy, enhanced hypothalamic GABAergic function, through the action of an endogenous benzodiazepine-like substance, seems to be of central importance (75,76). Quinilone antibiotics activate the $GABA_A$ receptor, particularly when coadministered with a nonsteroidal anti-inflammatory drug (77) and may lead to delirium (78). Sedative drug–with-

drawal delirium is associated with increased GABA activity, which is likely related to increased receptor sensitivity (79). A relevance of GABA function to general medical/surgical delirium aside from hepatic encephalopathy has not been demonstrated.

Glutamate is an excitatory amino acid neurotransmitter that could lead to decreased cortical arousal with increased glutamate activity in the thalamus (80). Increased glutamate activity is also believed to play a role in both hepatic encephalopathy (81) and delirium associated with alcohol withdrawal (82). Studies of glutamate in common medical and surgical patients with delirium have not been performed.

Central catecholaminergic function is intimately involved in the maintenance of arousal, selective attention (83), and may play a role in the cognitive impairments associated with sleep deprivation (84). Many stressful situations such as hypoxia, acidosis, and transient ischemia are accompanied by evidence of increased noradrenergic activity in animal models (85). It has long been known that elevated levels of epinephrine and norepinephrine may be found in the urine of those with delirium tremens, and these levels roughly parallel symptom intensity (86). Cerebrospinal fluid levels of 3-methoxy-4-hydroxyphenylglycol, a metabolite of norepinephrine, have also been reported to be elevated during delirium tremens (87). Whether these changes are the result of agitation caused by the delirium or a cause of delirium is open to question. The role of catecholamines in delirium unrelated to alcohol use has not been well investigated in humans.

Histamine blockers are well known for their ability to produce delirium (88). The mechanism of this delirium is not known, but may be related to the anticholinergic effects of these medications, rather than an effect on the histamine receptor itself. Some cases of probable H_2-blocker delirium reversed by physostigmine have been reported (89,90). The histamine system has not otherwise been implicated in delirium. Data regarding neuropeptides and delirium are quite limited. A reduced cerebrospinal fluid somatostatin-like immunoreactivity was found in one study of delirious patients (91), but these reductions were still present 4 years after the delirium and following resolution of all delirium symptoms (92). Based on available data, no significant support for a causal role of neuropeptides in delirium exists.

Endogenous Opiods

The endogenous opiate system is activated in conditions associated with the stress response, such as surgery. The opiates meperidine and morphine are clearly associated with delirium in the postoperative setting (42), although this may be more a reflection of the anticholinergic effects of these drugs than the opiate effects. A disruption in the circadian rhythms of beta-endorphin and cortisol, with sustained elevations of these substances, was reported to be associated with delirium in three postoperative patients (93). It is difficult to assess the significance of this study, as minimal clinical information about the patients or controls was published. Delirium has also reportedly been precipitated by intrathecal beta-endorphin administration (94). One study that found reduced central nervous system beta-endorphin immunoreactivity during delirium among 69 nonsurgical patients (95) may have been confounded by prior dementia.

Endogenous Cortisol

Hypercortisolism has adverse effects on mood, sleep, energy, and cognition, especially in elderly persons (96), but the mechanism of this effect is not clear. Glucocorticoids influence cerebral blood flow, oxygen consumption, and cerebral excitability (97), but the hippocampus seems to be the main site of action for neurosteroids including hippocampal neurotoxicity (98). Prednisone at usual therapeutic concentrations inhibits binding to central muscarinic cholinergic receptors in vitro (35). Glucocorticoids have wide-ranging effects on other neurotransmitter systems, including modulation of serotonin turnover, hypothalamic dopamine balance, and suppression of beta-endorphin levels in the brain (97).

Clinical evidence supports a relationship between glucocorticoids and delirium. Delirium is an occasional manifestation of Cushing's syndrome. The acute psychosis of Cushing's syndrome reportedly may be reversed by the cortisol-receptor antagonist mifepristone (RU-486) (99). Initial reports using dexamethasone-suppression testing to assess the hypothalamic-pituitary-adrenal axis were conflicting, with one study reporting a 27% prevalence of nonsuppression in 25 patients with delirium (100) and another reporting a 100% nonsuppression in 6 patients with delirium (101). One more recent study performed dexamethasone-suppression tests on 16 consecutive admissions to an acute-care geriatric unit, and found that 7 of 9 nonsuppressors, compared with only 1 of 7 suppressors, developed delirium (102). Complicating this issue is that the dexamethasone-suppression test may not be an accurate reflection of hypercortisolism at least in elderly persons with dementia (103).

When cortisol levels are studied directly, one study of 83 patients with an acute stroke found that delirium in this setting was associated with persistent hypercortisolism (104). Studies of cortisol levels in postoperative patients have come to different conclusions, with one study of general postoperative patients finding prolonged elevation of plasma cortisol level and a delay in the return of normal circadian variation in delirious individuals (93), and a study of postcardiac surgery patients finding no independent association between delirium and pre- or postoperative cortisol levels (45). Pathologic elevations in cortisol may be associated with delirium, but the relationship of physiologic cortisol levels to common delirium in medical and surgical patients is not compelling.

Other Potential Contributors

Cytokines, when used at supraphysiologic doses, may lead to delirium. Interleukin-2 (IL-2), which has a central role in both cellular and humoral immunity, is the best studied of the cytokines in this regard. Thirty percent of patients receiving high-dose IL-2 therapy became delirious in one study (105). There was a 50% delirium rate in another study of IL-2/lymphocyte–activated killer cell therapy (106). Disorientation and major problems with concentration occur less frequently with low-dose IL-2 therapy, where 10% of the patients develop such complications (107). The mechanism of this delirium is not understood, but EEG changes include an increased P300 latency, believed to be indicative of diffuse cerebral dysfunction related to the cholinergic system (108,109), have been identified in some individuals with IL-2–associated delirium (110). IL-2 has been reported to cause an increase in brain water content, but the percent increase in brain water content following IL-2 therapy as estimated by magnetic resonance imaging (MRI) was not associated with the development of confusion among seven study patients treated for non–central nervous system tumors

(111). Interleukin-1 induces sleep in experimental animals through a prostaglandin-mediated effect on the rostral basal forebrain (112). Although prostaglandin D_2 plays an important role in sleep regulation through its action as a neurohomone (113), its potential role as a mediator of altered level of consciousness in delirium has not been studied. An important role for cytokines in the occurrence of delirium, especially delirium related to infection or surgery, has yet to be demonstrated. Furthermore, any role for cytokines would likely occur as a result of an influence on neurotransmitter systems.

Acute irreversible neurotoxicity resulting in DNA damage is unlikely to be an important contributor to delirium, as widespread neuronal death is unusual in this situation. However, potentially reversible problems may occur due to oxidative stress. Neural membranes, upon whose function neurotransmission depends, consist of highly oxidizable polyunsaturated fats (114). One study of five patients with septic encephalopathy demonstrated a fourfold elevation of cerebrospinal fluid thiobarbituric acid–reactive substances (a marker of lipid peroxidation), with only mild increases in serum thiobarbituric acid–reactive substances in nonseptic healthy controls (66). This finding suggests that a marked increase in central nervous system lipid peroxidation may occur during sepsis, but the clinical significance is unclear.

Some have postulated that a disruption in the blood-brain barrier could lead to acute confusion, particularly during septicemia (115). However, disruption of the blood-brain barrier is neither necessary nor sufficient on its own to produce acute confusion. This barrier may be osmotically disrupted during treatment of central nervous system lymphoma without any apparent effect on cognitive function, as measured by extensive neuropsychological evaluation (116). In addition, animal models of hepatic encephalopathy display no evidence of disruption in the blood-brain barrier (117).

Structural Considerations

The neuroanatomic location of the abnormalities in the brain that lead to delirium have been as much the subject of speculation than careful study. Engel and Romano, based on their EEG studies of delirium, put forth the hypothesis that delirium is the result of a global failure of cerebral oxidative metabolism (118). Later it was proposed that such a global metabolic failure would lead to cholinergic deficiency due to decreased cerebral production of acetylcholine (119). By extension, the production and function of other neurotransmitters would also be affected by a global failure of cerebral metabolism. Although the "global failure" theory of delirium is attractive when explaining confusional states associated with severe illness, such as prolonged hypotension or hypoxia, the occurance of delirium during less severe illness and common infections are more difficult to explain by this hypothesis.

The obvious alternative hypothesis would be a "limited failure" theory proposed by Geshwind (120). In this theory dysfunction limited to particular structural or neurochemical component of the attentional systems of the brain lead to delirium. That limited structural abnormalities can lead to delirium is supported by the fact that localized strokes, particularly nondominant parietal lobe strokes, lead to delirious states (121). Similarly, right hemisphere dysfunction may predispose to the development of delirium in patients with dementia (122). The finding of abnormal somatosensory-evoked potentials in a small group of delirious patients, compared to nondelirious patients, with liver disease is suggestive of a brainstem abnormality (123). Brain imaging studies of delirious patients are difficult to perform, and have generally been small in number with no consistent pattern of findings (124), suggesting that several different neuroanatomic areas may be involved in delirium under different circumstances. EEG studies have also yielded mixed results, suggesting involvement of localized thalamocortical projection deficits, white matter and cortical dysfunction, and more generalized metabolic failure (125).

Other evidence for the ability of anatomically limited processes to induce delirium comes from the study of dementia. Dementing processes preferentially affect different parts of the brain. Of all dementias, dementia with Lewy bodies is most similar to delirium, with fluctuating cognition and attention deficits as important diagnostic criteria (126,127). In dementia with Lewy bodies, the primary neurochemical abnormality is a neocortical cholinergic deficit (128), as opposed to Alzheimer's disease, in which hippocampal cholinergic deficiency predominates early on.

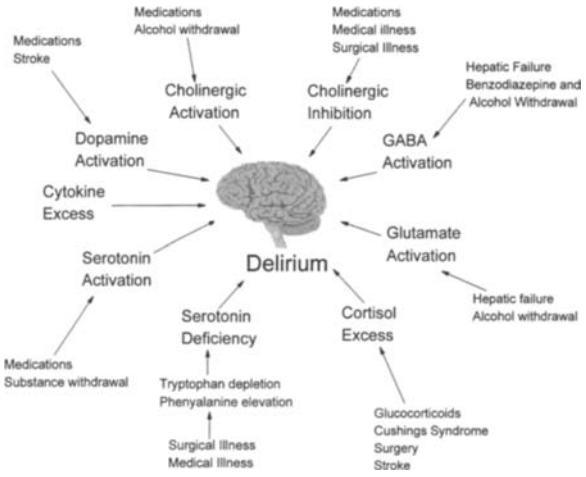

Figure 1. Proposed mechanisms of delirium and possible associated clinical conditions.

Conclusion

This review has pointed out that the theory of "global" cerebral impairment is giving way to the hypothesis that specific disruptions of neurologic pathways and neurotransmitter systems may lead to delirium (Figure 1). Because of the complicated nature of the attentional system of the brain, it is not surprising that failure in several different neurotransmitters should be involved. However, from a clinical perspective, it is clear that some pathophysiologic mechanisms will be more commonly encountered than others. There is probably no final common pathway to delirium, but rather, delirium should be thought of as the final common symptom of a variety of situation-specific neurotransmitter abnormalities. Future studies therefore should focus on target groups of patients with similar primary diagnoses, rather than broad groups of medical/surgical patients with various etiologies of illness. Defining the rela-

tionship between clinical settings and specific mechanisms of functional brain compromise will set the stage for improved understanding of delirium, and lead to more effective therapies for this all too common syndrome.

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REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC: Author; 1994.
2. Naughton BJ, Moran MB, Kadah H, Hemen-Ackah Y, Longano J. Delirium and other cognitive impairments in older adults in an emergency department. *Ann Emerg Med.* 1995;25:751–755.
3. Gustafson Y, Brannstrom B, Norberg A, Bucht G, Winblad B. Under diagnosis and poor documentation of acute confusional states in elderly hip fracture patients. *J Am Geriatr Soc.* 1991;9:760–765.
4. Levkoff SE, Evans EA, Liptzin B, et al. Delirium: The occurrence and persistence of symptoms among elderly hospitalized patients. *Arch Intern Med.* 1992;152;334–340.
5. Thomas R, Cameron D, Fahs M. A prospective study of delirium and prolonged hospital stay. *Arch Gen Psychiatr.* 1988;45:937–940.
6. Rogers MP, Liang MH, Daltroy LH, et al. Delirium after elective orthopedic surgery: risk factors and natural history. *Int J Psychiatry Med.* 1989;19:109–121.
7. Francis J, Kapoor W. Prognosis after hospital discharge of older medical patients with delirium. *J Am Geriatr Soc.* 1992;40:601–602.
8. Murray AM, Levkoff SE, Wetle T, et al. Acute delirium and functional decline in the hospitalized elderly patient. *J Gerontol.* 1993;48:M181–M186.
9. Williams MA, Campbell EB, Raynor WJ, Musholt, MA, Mlynarczyk SM, Crane LF. Predictors of acute confusional states in hospitalized elderly patients. *Res Nurs Health.* 1985;8:31–40.
10. Gustafson Y, Bergrren D, Brannstrom B, et al. Acute confusional states in elderly patients treated for femoral neck fracture. *J Am Geriatr Soc.* 1988;36:525–530.
11. Rockwood K. Acute confusion in elderly medical patients. *J Am Geriatr Soc.* 1989;37:150–154.
12. Francis J, Kapoor W. A prospective study of delirium in hospitalized elderly. *JAMA.* 1990;263:1097–1101.
13. Schor JD, Levkoff SE, Lipsitz LA, et al. Risk factors for delirium in hospitalized elderly. *JAMA.* 1992;267:827–831.
14. Williams-Russo P, Urquhart B, Sharrock N, Charlson M. Post-operative delirium: predictors and prognosis in elderly orthopedic patients. *J Am Geriatr Soc.* 1992;40:759–767.
15. Inouye SK, Viscoli CM, Horwitz RI, Hurst LD, Tinetti ME. A predictive model for delirium in hospitalized elderly based on admission characteristics. *Ann Intern Med.* 1993;119:474–481.
16. Marcantonio ER, Goldman L, Mangione CM, et al. A clinical prediction rule for delirium after elective noncardiac surgery. *JAMA.* 1994;271:134–139.
17. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons: predictive model and interrelationship with baseline vulnerability. *JAMA.* 1996;275:852–857.
18. Inouye SK. The dilemma of delirium: clinical and research controversies regarding diagnosis and evaluation of delirium in hospitalized elderly medical patients. *Am J Med.* 1994;97:278–288.
19. Adams RD, Victor M, Ropper AH. The neurology of aging. In: Adams RD, Victor M, Ropper AH, eds. *Principles of Neurology.* New York, NY: McGraw-Hill; 1997:608–620.
20. Coleman PD, Flood DG. Neuron numbers and dendritic extent in normal aging and Alzheimer's disease. *Neurobiol Aging.* 1987;8:521–545.
21. Rupert MP, Eisdorfer C, Lowenstein DA. Normal aging: changes in sensory/perceptual and cognitive abilities. In: Sadavoy J, Lazarus LW, Jarvik LF, Grossberg GT, eds. *Comprehensive Review of Geriatric Psychiatry—II.* Washington, DC: American Psychiatric Press; 1996:113–134.
22. Perry EK, Perry RH. Acetylcholine and hallucinations: disease-related compared to drug-induced alterations in human consciousness. *Brain Cog.* 1995;28:240–258.
23. Lipowski Z. Delirium in the elderly patient. *N Engl J Med.* 1989;320: 578–582.
24. Hall R, Popkin M, McHenry L. Angel's trumpet psychosis: a central nervous system anticholinergic syndrome. *Am J Psychiatr.* 1977;134: 312–314.
25. Granacher R, Baldessarini R, Messner E. Physostigmine treatment of delirium induced by anticholinergics. *Am Fam Physician.* 1976;13:99–103.
26. Trzepacz PT, Leavitt M, Ciongoli K. An animal model for delirium. *Psychosomatics.* 1992;33:404–415.
27. Itil T, Fink M. Anticholinergic drug-induced delirium: experimental modification, quantitative EEG and behavioral correlations. *J Nerv Ment Dis.* 1966;143:492–507.
28. Muller W, Stoll L, Schubert T, Gelbman, C. Central cholinergic functioning and aging. *Acta Psychiat Scand.* 1991;366:(Suppl)34–39.
29. Tune L, Coyle JT. Acute extrapyramidal side effects: serum levels of neuroleptics and anticholinergics. *Psychopharmachology.* 1981;75:9–15.
30. Golinger RC, Peet T, Tune LE. Association of elevated plasma anticholinergic activity with delirium in surgical patients. *Am J Psychiatr.* 1987;144:1218–1220.
31. Tune LE, Damlouji NF, Holland A, Gardner TJ, Folstein MF, Coyle JT. Association of postoperative delirium with raised serum levels of anticholinergic drugs. *Lancet.* 1981;2:651–652.
32. Mondimore FM, Damlouji N, Folstein MF, Tune L. Post-ECT confusional states associated with elevated serum anticholinergic activity. *Am J Psychiatr.* 1983;140:930–931.
33. Mach JR, Dysken MW, Kuskowski M, Richelson E, Holden L, Jilk KM. Serum anticholinergic activity in hospitalized older persons with delirium: a preliminary study. *J Am Geriatr Soc.* 1995;43:491–495.
34. Flacker JM, Cummings V, Mach JR, Bettin K, Keily DK, Wei, J. The association of serum anticholinergic activity with delirium in elderly medical patients. *Am J Geriatr Psychiatr.* 1998;6:31–41.
35. Tune L, Carr S, Hoag E, Cooper T. Anticholinergic effects of drugs commonly prescribed for the elderly: potential means of assessing risk of delirium. *Am J Psychiatr* 1992;149;1393–1394.
36. Tune L. Anticholinergic effect of drugs for the elderly. (Letter.) *Am J Psychiatr.* 1993;150:1757.
37. Coffman J, Dilsaver S. Cholinergic mechanisms in delirium. (Letter.) *Am J Psychiatr.* 1988;145:382–383.
38. Thienhaus OJ, Allen A, Bennett JA, Chopra YM, Zemlan FP. Anticholinergic serum levels and cognitive performance. *Eur Arch Psychiatry Clin Neurosci.* 1990;240:28–33.
39. Flacker JM, Lipsitz LA. Serum anticholinergic activity changes with acute illness in elderly medical patients. *J Gerontol Med Sci.* 1999;54A:M12–M16.
40. Hu J, El-Fakahany E. Allosteric interaction of dynorphin and myelin basic protein with muscarinic receptors. *Pharmacology.* 1993;47:351–359.
41. Hu J, Wang S, Forray C, El-Fakahany E. Complex allosteric interaction of cardiac muscarinic receptors by protamine: potential model for putative endogenous ligands. *Mol Pharmacol.* 1992;42:311–324.
42. Marcantonio ER, Juarez G, Goldman L, et al. The relationship of postoperative delirium with psychoactive medications. *JAMA.* 1994;272:1518–1522.
43. Ratcheson R, Blank A, Ferendilli J. Regionally selective metabolic effects of hypoglycemia in the brain. *J Neurochem.* 1981;36:1952–1958.
44. Smythies JR, Gottfries C, Regland B. Disturbances of one-carbon metabolism in neuropsychiatric disorders: a review. *Biol Psychiatr.* 1997;41:230–233.
45. van der Mast RC, van den Broek WW, Fekkes D, Pepplinkhuizen L, Roest FHJ. Delirium after cardiac surgery: the possible role of tryptophan in relation to other neutral amino acids. In: Filippini GA, ed. *Recent Advances in Tryptophan Research.* New York: Plenum Press; 1996:93–96.
46. Trzepacz PT, Ho V, Mallavarapu H. Cholinergic delirium and neurotoxicity associated with tacrine for alzheimer's disease. *Psychosomatics.* 1996;37:299–301.
47. Imperato A, Dazzi L, Carta G, Colombo G, Biggio G. Rapid increase in basal acetylcholine release in the hippocampus of freely moving rats induced by withdrawal from long-term ethanol intoxication. *Brain Res.* 1998;347–350.
48. Kelly J. Cranial nerve nuclei, the reticular formation, and biogenic amine-containing neurons. In: Kandel E, Schwartz J, eds. *Principles of Neural Science.* New York: Elsevier; 1985:539–561.
49. Denoble V, Schrack L, Reigel A, Denoble K. Visual recognition in squirrel monkeys: effects of serotonin antagonists on baseline and hypoxia induced performance deficits. *Pharmacol Biochem Behav.* 1991;39:1991–1996.

50. Pope HG, Jonas JM, Hudson JI, Kafka MP. Toxic reactions to the combination of monoamine ocidase inhibitors and tryptophan. *Am J Psychiatr.* 1985;142:491–492.
51. Steiner W, Fontaine R. Toxic reaction following the combined administration of fluoxetine and L-tryptophan: five case reports. *Biol Psychiatr.* 1986;21:1067–1071.
52. Feighner JP, Boyer WF, Tyler DL, Neborsky RJ. Adverse consequences of fluoxetine-MAOI combination therapy. *J Clin Psychiatr.* 1990;51:222–225.
53. Sternbach H. The serotonin syndrome. *Am J Psychiatr.* 1991;148:705–713.
54. Gerson S, Baldessarini R. Motor effects of serotonin in the central nervous system. *Life Sci.* 1980;27:1435–1451.
55. Koponen H, Leopola U, Leinonen E. A long-term follow-up study of cerebrospinal fluid 5-hydroxyindolacetic acid in delirium. *Eur Arch Psychiatry Clin Neurosci.* 1994;244:131–134.
56. Banki J, Vojnik M. Comparative simultaneous measurement of cerebrospinal fluid 5-hydroxyindolacetic acid and blood serotonin levels in delirium tremens and clozapine- induced delirious reaction. *J Neurol Neurosurg Psychiatr.* 1978;41:420–424.
57. van der Mast RC, Fekkes D, Moleman P, Pepplinkhuizen L. Is postoperative delirium related to reduced plasma tryptophan? *Lancet.* 1991;338:851–852.
58. Wurtman RJ, Hefti F, Melamed E. Precursor control of neurotransmitter synthesis. *Pharmacol Rev.* 1981;32:315–335.
59. Fernstrom JD, Wurtman RJ. Brain serotonin content: physiologic regulation by plasma neutral amino acids. *Science.* 1972;178:414–416.
60. Milakofsky L, Hare TA, Miller JM. Rat plasma level of amino acids and related compounds during stress. *Life Sci.* 1985;36:753–761.
61. Smith KA, Fairburn CG, Cowen PJ. Relapse of depression after rapid depletion of tryptophan. *Lancet.* 1997;349:915–919.
62. Hebenstreit GF, Fellerer GF, Twerdy B, Pfeiffer KP, Zadravec S, Ferdinand P. L-tryptophan bei pradeliranten und delianten zustandsbildern. *Infusionstherapie.* 1989;16:92–96.
63. Guttler F, Lou H. Dietary problems of phenylketonuria: effect on CNS transmitters and their possible role in behaviour and neuropsychological function. *J Inher Metab Dis.* 1986;9 (Suppl 2):169–177.
64. Krause W, Halminski M, Dembure P, Salvo R, Freides D, Elsas L. Biochemical and neuropsychological effects of elevated plasma phenylalanine in patients with treated phenylketonuria. *J Clin Invest.* 1985;75:40–48.
65. Krause W, Epstein C, Averbook A, Dembure P, Elsas L. Phenylalanine alters the mean power frequency of electroencephalograms and plasma L-dopa in treated patients with phenylketonuria. *Pediatr Res.* 1986;20:1112–1116.
66. Kaufman S. An evaluation of the possible neurotoxicity of metabolites of phenylalanine. *J Ped.* 1989;114:895–900.
67. Takezawa J, Taenaka N, Nishijima MK, et al. Amino acids and thiobabituric acid reactive substances in cerebrospinal fluid and plasma of patients with septic encephalopathy. *Crit Care Med.* 1983;11:876–879.
68. Mizok B. Branched-chain amino acids in sepsis and hepatic failure. *Arch Intern Med.* 1985;145:1284–1288.
69. Cascino A, Cangiano C, Fiaccadori F, et al. Plasma and cerebrospinal fluid amino acid patterns in hepatic encephalopathy. *Dig Dis Sci.* 1982;27:828–832.
70. Birkmayer W. Toxic delirium after L-dopa medication. *J Neural Transm.* 1978;14(Supp):163–166.
71. Cummings J. Behavioral complications of drug treatment of Parkinson's disease. *J Am Geriatr Soc.* 1991;39:708–716.
72. Golden RN, James SP, Sherer MA, Rudorfer MV, Sack DA, Potter WZ. Psychoses associated with buproprion treatment. *Am J Psychiatr.* 1985;142:1459–1462.
73. Pycock CJ, Carter CJ, Kerwin, RW. Effect of 6-hydroxy-dopamine lesions of the medial prefrontal cortex on neurotransmitter systems in subcortical sites in the rat. *J Neurochem.* 1980;34:91–99.
74. Kramer TAM, Merriam A, Harvey P, Lisoskie MD. Acquired brain lesions and psychiatric illness: possible role of dopaminergic systems. *Mt Sinai J Med.* 1991;58:324–327.
75. Jones E, Skolnick P, Gammal S, Basile A, Mullen K. The gamma-aminobutyric acid A ($GABA_A$) receptor complex and hepatic encephalopathy. *Ann Intern Med.* 1989;110:532–546.
76. Basile A, Jones A, Skolnick P. The pathogenesis and treatment of hepatic encephalopathy: evidence for involvement of benzodiazepine receptor ligands. *Pharmacol Rev.* 1991;43:27–71.
77. Unseld E, Ziegler G, Gemeinhar A, Janssen U, Klotz U. Possible interaction of fluroquinilones wih the benzodiazepine-$GABA_A$-receptor complex. *Br J Clin Pharmacol.* 1990;30:63–70.
78. Farrington J, Stoudmire A, Tierney J. The role of ciprofloxacin in a patient with delirium due to multiple etiologies. *Gen Hosp Psychiatry.* 1995;17:47–53.
79. Ross CA. CNS arousal systems: possible role in delirium. *Int Psychogeriatr.* 1991;3:353–371.
80. Carlsson M, Carlsson A. Schizophrenia: a subcortical neurotransmitter imbalance syndrome? *Schizophr Bull.* 1990;16:426–432.
81. Mousseau DD, Butterworth RF. Current theories on the pathogenesis of hepatic encephalopathy. *Proc Soc Exp Med.* 1994;206:329–344.
82. Tsai G, Coyle JT. The role of glutamatergic neurotransmission in the pathophysiology of alcoholism. *Ann Rev Med.* 1998;49:173–184.
83. Sara S. Noradrenergic modulation of selective attention: its role in memory retrieval. *Ann NY Acad Sci.* 1985;444:178–193.
84. McCann UD, Penetar DM, Shaham Y, et al. Sleep deprivation and impaired cognition: possible role of brain catecholamines. *Biol Psychiatr.* 1992;31:1082–1097.
85. Siejsjo B. Brain energy metaboplism and catecholaminergic activity in hypoxia, hypecapnia, and ischemia. *J Neural Transm.* 1978;14(Supp):17–22.
86. Giocobini E, Izikowitz S, Wegmann A. Norepinephrine and epinephrine excretion in delirium tremens. *Arch Gen Psychiatr.* 1960;3:289–296.
87. Ackenheil M, Athen D, Beckmann H. Pathophysiology of delirious states. *J Neural Transm.* 1978;14(Supp):167–175.
88. Picotte-Prillmayer D, Dimaggio JR, Baile WF. H_2 blocker delirium. *Psychosomatics.* 1995;36:74–76.
89. Mogelnicki SR, Walter JL, Finlayson DC. Physostigmine reversal of cimetidine-induced mental confusion. *JAMA.* 1979;241:826–827.
90. Goff DC, Garber HJ, Jenike MA. Partial resolution of ranitidine-associated delirium with physostigmine: case report. *J Clin Psychiatr.* 1985;46:400–401.
91. Koponen H, Reinihainen K, Reikkinen P. Cerebrospinal fluid somatostatin in delirium II. Changes at the acute stage and at one year follow-up. *Psychol Med.* 1990;20:501–505.
92. Koponen H, Leinonen E, Lepola U, Reikkinen P. A long-term follow-up study of cerebrospinal fluid somatostatin in delirium. *Acta Psychiatry Scand.* 1984;89:178–193.
93. McIntosh TK, Bush H.L, Yetson NS, et al. Beta-endorphin, cortisol, and postoperative delirium: a preliminary report. *Psychoneuroendocrinology.* 1985;10:303–313.
94. Pickar D, Dubois M, Cohen MR. Behavioral change in a cancer patient following intrathecal beta endorphin administration. *Am J Psychiatr.* 1984;141:103–104.
95. Koponen H, Reikkinen P. A longitudinal study of cerebrospinal fluid beta-endorphin-like immunoreactivity in delirium: chages at acute stage and one-year follow-up. *Acta Psychiatr Scand.* 1990;82:323–326.
96. Kiraly SJ, Ancill RJ, Dimitrovsa G. The relationship of endogenous cortisol to psychiatric disorder: a review. *Can J Psychiatr.* 1997;42:415–420.
97. DeKloet E, Veldhuis H. Adrenocortical hormone action. *Handbook Neurochem.* 1985;8:47–91.
98. Uno H, Eisele S, Sakai A, et al. Neurotoxicity of glucocorticoids in the primate brain. *Horm Behav.* 1994;28:336–348.
99. van der Lely A, Foeken K, van der Mast RC, Lamberts SWJ. Rapid reversal of acute psychosis in the cushing syndrome with the cortisol-receptor antagonist mifepristone (RU 486). *Ann Intern Med.* 1991;114:143–144.
100. Koponen H, Steinback U, Riekkinen PJ. Delrium and the DST in the aged. *Nord Psykiatr Tidsskr.* 1987;43:203–207.
101. McKieth IG. Clinical use of the DST in a psychogeriatric population. *Br J Psychiatr.* 1984;145:389–393.
102. O'Keeffe ST, Devline JG. Delirium and the dexamethasone supression test in the elderly. *Neuropsychobiology.* 1994;30:153–156.
103. Miller AH, Sastry G, Speranza AJ, et al. Lack of association between cortisol hypersecretion and nonsuppression on the DST in patients with Alzheimer's disease. *Am J Psychiatr.* 1994;151:267–270.
104. Gustafson Y, Olsson T, Asplund K, Hagg E. Acute confusional state (delirium) soon after stroke is associated with hyperscortisolism. *Cerebrovasc Dis.* 1993;3:33–38.
105. Rosenberg S, Loetz M, Yang J. Experience with the use of high-dose interleukin-2 in the treatment of 652 cancer patients. *Ann Surg.* 1989;210:474–484.
106. Denicoff K, Rubinow DR, Papa MZ, et al. The neuropsychiatric effects of treatment with interleukin-2 and lymphocyte-activated killer cells. *Ann Intern Med.* 1987;107:293–300.
107. Fenner M, Hanninen E, Kirchner H, Poliwoda H, Atzpodien J. Neuropsychiatric symptoms during treatment with interleukin-2 and interferon-alpha [Letter]. *Lancet.* 1993;341:372.
108. Goodin D, Starr A, Chippendalc T, Squires K. Sequential changes in the P3 componant of the auditory evoked potential in confusional states and dementing illness. *Neurology.* 1983;1215– 1218.

109. Hammond E, Meador K, Aung-din R, Wilder B. Cholinergic modulation of human P3 event-related potentials. *Neurology*. 1987;37:346–350.
110. Caraceni A, Martini C, Belli F, et al. Neuropsychological assessment of the central effects of interleukin-2 administration. *Eur J Cancer*. 1992;29A:1266–1269.
111. Saris SC, Patronas NJ, Rosenberg SA, et al. The effect of interleukin-2 on brain water content. *J Neurosurg*. 1989;71:169–174.
112. Tearo A, Matssamura H, Saito M. Interleukin-1 induces slow-wave sleep at the prostaglandin D2-sensitive sleep-promoting zone in the rat brain. *J Neurosci*. 1998;18:6599– 6607.
113. Urade Y, Hayaishi O, Matsumura H, Watanabe K. Molecular mechanism of sleep regulation by prostaglandin D_2. *J Lipid Med Cell Signal*. 1996;14:71–82.
114. Evans P. Free radicals in brain metabolism and pathology. *Br Med Bull*. 1993;49:577–587.
115. Jeppson B, Freund H, Gimmon Z, James J, von Mayenfeldt M, Fischer J. Blood-brain barrier derangement in sepsis: cause of septic encephalopathy? *Am J Surg*. 1981;141:136–142.
116. Crossen J, Goldman D, Neuweldt E. Neuropsychological assessment of nonacquired immunodeficiency syndrome patients with primary central nervous system lymphoma before and after blood-brain barrier disruption chemotherapy. *Neurosurgery*. 1991;30:23–29.
117. Knudsen G, Schmidt J, Almdal T, Paulson O, Vilstrup H. Passage of amino acids and glucose across the blood brian barrier in patients with hepatic encephalopathy. *Hepatology*. 1993;17:987–992.
118. Engel GL, Romano J. Delirium: a syndrome of cerebral insufficiency. *J Chron Dis*. 1959;9:260–277.
119. Blass JP, Plum F. Metabolic encephalopathies in older adults. In: Katzman R, Terry RD, eds. *The Neurology of Aging*. Philadelphia: FA Davis; 1983:189–220.
120. Geshwind N. Disorders of attention. *Philos Trans R Soc Lond Biol*. 1982;298:173–185.
121. Benbadis SR, Sila CA, Cristea RL. Mental status changes and stroke. *J Gen Intern Med*. 1994;9:485–497.
122. Mach JR, Kabat V, Olsen D, Kuzkowski M. Delirium and right hemisphere dysfunction in cognitively impaired older persons. *Int Psychogeriatr*. 1996;8:373–382.
123. Trzepacz PT, Sclabassi RJ, van Thiel DH. Delirium: a subcortical phenomenon? *J Neuropsychiatr*. 1989;1:283–290.
124 Trzepacz PT. The neuropathogenesis of delirium: a need to focus our research. *Psychosomatics*. 1994;35:374–391.
125. Jacobson SA. Delirium in the elderly. *Psych Clin North Am*. 1997;20:91–110.
126. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathological diagnosis of dementia with lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology*. 1996;47;1113–1124.
127. Perry EK, Irving D, Kerwin JM, et al. Cholinergic transmitter and neurotropic activities in lewy body dementia: similarity to Parkinson's and distribution from Alzheimer's disease. *Alz Dis Assoc Dis*. 1993;7:69–79.
128. Perry EK, Marshall E, Kerwin JM, et al. Evidence of a monaminergic: cholinergic imbalance related to visual hallucinations in lewy body dementia. *J Neurochem*. 1990;55:1454–1456.

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