Une conception multidimensionnelle de l'apathie permet-elle de mieux en comprendre les mécanismes ? : approche cognitive et électrophysiologique

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ÉCOLE DOCTORALE DES SCIENCES DE LA VIE ET DE LA SANTE (ED414)

UMR INSERM U1114 – Neuropsychologie cognitive et Physiopathologie de la Schizophrénie

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soutenue le : **20 octobre 2023**

pour obtenir le grade de : **Docteur de l'université de Strasbourg**

Discipline/ Spécialité : Sciences du vivant / Neurosciences

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Approche cognitive et électrophysiologique

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Remerciements

Messieurs Pessiglione, Raffard et Foucher, je vous remercie grandement d'avoir accepté d'évaluer ce travail. Ce sera un honneur et un plaisir d'échanger avec vous lors de la soutenance.

Anne, je te remercie de m'avoir toujours soutenue et accompagnée durant ces quatre dernières années. Merci de m'avoir laissé « carte blanche » pour élaborer ce projet de thèse, et de m'avoir aussi bien formée à devenir une meilleure chercheuse. Ta confiance m'a été précieuse et je suis ravie du chemin parcouru ensemble ! J'espère que nous pourrons continuer de collaborer sur de futurs projets, toujours plus riches et stimulants !

Anne Giersch, je te remercie pour ton accueil au sein de l'Unité 1114, ta passion communicative pour la recherche, et tes échanges toujours variés, profonds et singuliers.

Bich-Thuy, merci car sans toi ce travail n'aurait pu être réalisé ! Tu as été ma troisième main lors des passations expérimentales. Merci pour ton énergie et tes attentions au quotidien.

Un grand merci aux informaticiens, Julien, Patrick et Ugo, qui m'ont respectivement apporté une aide durant la conception des tâches cognitives, un soutien lors de leur débogage, et une ouverture vers de nouvelles méthodes d'analyses. Ce fut un vrai plaisir d'apprendre à vos côtés !

Je remercie également l'ensemble des membres passés et présents du laboratoire, qui ont rendu le temps de mon doctorat agréable, enrichissant et convivial. Je pense notamment à Ellen, Ugo, Matthieu, Camille, Gabriela, François, Eduardo, Romane, Alana, … J'en profite pour remercier également Estelle, qui a rendu toutes les démarches administratives plus faciles, et Isabelle, pour son stage de master qui a rendu ce doctorat possible !

Je souhaiterais également remercier tous les stagiaires que j'ai accompagnés pour leur investissement et leur curiosité. Je vous souhaite le meilleur pour la suite.

Merci à tous les membres du CEMNIS qui ont facilité le recrutement des patients. Plus particulièrement encore, un immense merci à Ludovic dont les échanges ont toujours été très stimulants et pertinents. Je serais ravie que notre collaboration se poursuive !

Je remercie chaleureusement tous les participants, les patients et leurs familles, ainsi que l'UNAFAM. Sans votre implication et votre contribution, ce projet n'aurait pu aboutir.

Enfin sur une note plus personnelle, je commencerai par une pensée émue pour l'Université de Brest. En particulier, merci à Pierre Bertucci, mon mentor et maintenant ami, qui m'a transmis sa passion pour la recherche et l'enseignement de la psychologie cognitive. Merci pour tes conseils, ton soutien et ta personnalité solaire. Un grand merci aussi à Kader Boudarène, si bienveillant et attentionné, qui m'a permis d'initier la réalisation de mes études dans les meilleures conditions possibles. Sans vous, je n'en serais pas là aujourd'hui.

Je remercie également mes amis pour avoir mis de la joie et des rires dans mon quotidien, en particulier, et ce malgré la distance, Audrey, Mélanie et Marion.

Et pour finir, merci aussi infiniment à ma famille, pour leur amour et leur soutien sans faille. J'en profite pour dédier ce travail à tous ceux que nous aimons mais qui sont partis trop tôt.

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AMS	Aire Motrice Supplémentaire
AVC	Accident Vasculaire Cérébral
AX-CPT	*AX version of the Continuous Performance Test*
BDI	*Beck Depression Inventory*
CCA	Cortex Cingulaire Antérieur
CDSS	*Calgary Depression Scale for Schizophrenia*
CPFdl	Cortex Préfrontal Dorsolatéral
CNV	*Contingent Negative Variation* (ERP)
CxOF	Cortex Orbitofrontal
DAS	*Dimensional Apathy Scale*
DM-TRD	*Dutch Measure for quantification of Treatment Resistance in Depression*
DPX	*Dot-Expectancy Task*
DSM-5	Manuel Diagnostique et Statistique des troubles mentaux et des troubles psychiatriques – 5ème édition
EDM	*Effort-based Decision-Making task*
EEG	Electroencéphalogramme
ERP	*Event-Related Potential*
HC	*Healthy controls*
IE	*Induced Effort task*
IRMf	Imagerie par Résonance Magnétique fonctionnelle
LARS	*Lille Apathy Rating Scale*
LPP	*Late Positive Potential* (ERP)
MD	*Mood disorders*
Méta-analyse ALE	Méta-analyse par estimation de la probabilité d'activation
MID	*Monetary Incentive Delay task*
RDoCs	*Research Domain Criteria*
RewP	*Reward Positivity* (ERP)
rTMS	Stimulation Magnétique Transcrânienne répétitive
TEPS	*Temporal Experience of Pleasure Scale*
SZ	Schizophrénie

Introduction

1. L'apathie unidimensionnelle

1.1. Généralités

1.1.1. Définitions

Étymologiquement, l'apathie se construit sur le grec ancien d'un *a-* privatif pour désigner le manque, l'absence, et de *pathos* la souffrance, les sentiments. En effet, depuis les débuts de la médecine, l'apathie se définit par un manque de motivation (Marin, 1990, 1991). Depuis 2009, une définition comportementale de l'apathie prévaut. Elle est basée sur les résultats d'une commission internationale, révisée en 2018, qui visait à rendre objective la définition de l'apathie (Robert et al., 2009, 2018). Ainsi, aujourd'hui, l'apathie est un symptôme comportemental, qui se définit par une réduction quantitative des comportements volontaires et orientés vers un but, qu'ils soient auto-initiés ou provoqués par l'environnement, comparativement au niveau de fonctionnement habituel de la personne (Robert et al., 2018). Ce symptôme doit être présent pendant plus de quatre semaines et avoir des conséquences sur les dimensions comportementale, cognitive, émotionnelle et/ou sociale. Il ne doit pas être uniquement expliqué par un handicap moteur, un trouble de la conscience, un médicament, ou un changement important dans l'environnement de la personne.

Dans ce travail de thèse, nous nous appuyons sur une approche normativiste de l'apathie, dans la perspective dimensionnelle des *Research Domain Criteria* (RDoCs) (Cuthbert, 2014). En ce sens, l'apathie est définie sur un continuum entre la population normale et les patients. Dès lors, l'apathie ne sera pas étudiée uniquement comme un symptôme, mais également comme un trait, sur le spectre normal - pathologique. Ainsi, le trait apathique peut être un trouble subclinique, c'est-à-dire une position intermédiaire dans le continuum allant de l'absence de trouble au symptôme clinique (Ronald & Pain, 2018). D'ailleurs, l'opposition d'une approche catégorielle (absence / présence d'un trouble) et d'une approche normativiste existe dès les fondements de la médecine. Dans la médecine ancienne occidentale d'Hippocrate, l'apathie est un trait de personnalité non pathologique, reflétant une tranquillité sage et vertueuse pour le stoïcisme et une inaction passive et libertine pour l'aristotélisme (Kapsambelis, 2016), alors qu'à la même période, dans la médecine ancienne orientale d'Avicenne, l'apathie est un symptôme faisant suite à un trouble psychique (Sanagustin, 1995; Sebti, 2000). Au sein de cette approche normativiste, étudier les traits psychopathologiques permettrait d'aider à détecter des facteurs de vulnérabilité à l'apparition d'un symptôme psychopathologique (Knowles & Olatunji, 2020; Rector et al., 2005). Des études récentes ont montré la présence d'un trait apathique chez des sujets sains (sans

pathologie diagnostiquée) qui pourrait être associée au développement futur d'une pathologie neurodégénérative (Roberto et al., 2021; M. Ruthirakuhan et al., 2019; Salem et al., 2023).

1.1.2. Prévalence

L'apathie est un des symptômes neuropsychiatriques les plus fréquents, aussi bien dans les pathologies neurologiques, neurodégénératives que psychiatriques. En effet, plus de 10 millions de personnes sont apathiques aux USA, et environ un patient sur deux vu en clinique présente un symptôme apathique (Chase, 2011). Plus précisément, au sein des troubles neurologiques, le symptôme apathique est présent chez 60% des patients ayant subi un accident vasculaire cérébral (AVC) (Andersson et al., 1999), chez 50% des patients avec un traumatisme crânien (Arnould et al., 2013) et chez 80% des patients après une hypoxie cérébrale (Andersson et al., 1999). Du côté des maladies neurodégénératives, l'apathie est un des symptômes transnosographiques les plus présents (Mulin et al., 2011), touchant 60% des patients souffrant de la maladie d'Alzheimer (Robert et al., 2009) et 75% des patients avec la maladie de Huntington (Craufurd et al., 2001). Dans la maladie de Parkinson, 35% des patients sont apathiques dans les phases précoces et jusqu'à 70% en cas de démence parkinsonienne (Dujardin et al., 2008). En cas de démence mixte, c'est-à-dire l'association d'une maladie neurodégénérative et d'un AVC, l'apathie est présente dans 70% des cas (Mulin et al., 2011). Enfin, concernant les pathologies psychiatriques, environ 50% des patients psychotiques, qu'ils présentent un premier épisode ou souffrent de schizophrénie, sont apathiques (Faerden et al., 2009; Mulin et al., 2011). Pour la dépression, les estimations sont moins précises, avec une prévalence estimée entre 50 et 95% (Ishizaki & Mimura, 2011; Mulin et al., 2011).

L'apathie est également présente chez des personnes saines, c'est-à-dire sans aucune pathologie associée et donc considérées normales sur le spectre normal - pathologique. En effet, environ 2% des sujets sains jeunes présentent un symptôme apathique isolé, comparable à celui des patients neuropsychiatriques (Ang et al., 2017; Pardini et al., 2016). De manière intéressante, une étude longitudinale a montré que la prévalence de l'apathie augmente avec l'âge, avec une augmentation en 5 ans de 6% à 16% chez des personnes âgées de plus de 65 ans sans maladie associée (Brodaty et al., 2010). Enfin, le trait apathique est très fréquent chez les individus sains, puisqu'il est présent chez environ 40% des adultes jeunes (Ang et al., 2017).

1.1.3. Conséquences

Sur le plan personnel, l'apathie est associée à une importante réduction de la qualité de vie (Faerden et al., 2009; Fervaha et al., 2014; Konstantakopoulos et al., 2011). Chez les personnes malades, l'apathie est aussi associée à une altération de la santé générale, à une réduction de la compliance aux traitements et à l'aggravation des maladies associées (Tattan & Creed, 2001; van Reekum et al., 2005). Enfin, l'apathie pourrait être un marqueur comportemental précoce des maladies neurodégénératives (Chase, 2011; Lanctôt et al., 2017). Ce symptôme est effectivement associé à un déclin cognitif et fonctionnel dans toutes les pathologies (Robert et al., 2018; Roth et al., 2004). Sur un plan plus socio-professionnel, l'apathie entraîne de fortes difficultés interpersonnelles, avec une réduction des échanges, un retrait, et/ou une diminution de l'empathie (R. Levy & Dubois, 2006; Lockwood et al., 2017). En outre, les personnes apathiques réduisent voire arrêtent leurs activités, même celles de loisirs (Konstantakopoulos et al., 2011; Yazbek, Raffard, et al., 2014). L'apathie est associée à de moins bons résultats universitaires et à un arrêt précoce de la scolarité (Pluck et al., 2020). Les personnes apathiques sont plus souvent au chômage et quand elles arrivent à garder un emploi, elles sont davantage sujettes à l'absentéisme et ne travaillent que très rarement à temps plein (Jacobs et al., 2018; Tsang et al., 2010; Ventura et al., 2013). L'apathie est donc un symptôme très handicapant, avec des répercussions touchant toutes les sphères de la vie quotidienne et socio-professionnelle, ce qui induit un coût sociétal important (Chase, 2011).

Quelle que soit la pathologie, l'apathie induit également des difficultés pour l'entourage du patient. En effet, les proches présentent davantage de culpabilité et de frustration face à des comportements apathiques (Kos et al., 2016; Lanctôt et al., 2023; Landes et al., 2001). A une période où les proches aidants sont valorisés par le système de santé publique français, l'apathie des patients doit être surveillée et prise en compte puisqu'elle engendre aussi chez les aidants davantage de risques de présenter un épuisement, de la détresse et à long terme des maladies (Guérin, 2016; Leurs et al., 2018).

Enfin, le trait apathique impacterait les mêmes sphères que le symptôme apathique, accentuant l'idée d'une continuité entre trait et symptôme apathique. En effet, plus une personne a un trait apathique important, plus elle tendrait à être dépressive, fatiguée et moins empathique (Lockwood et al., 2017). Elle a aussi davantage tendance à s'isoler, à moins ressentir de plaisir et à rencontrer des difficultés dans son parcours académique (Pluck et al., 2020).

1.2. Limites de la vision unidimensionnelle

La conception unidimensionnelle de l'apathie est encore largement dominante en recherche comme en clinique malgré l'accumulation d'arguments davantage en faveur d'une conception multidimensionnelle (Dickson & Husain, 2022).

1.2.1. Multiplicité des termes cliniques

Une des difficultés majeures de la recherche sur l'apathie concerne les confusions de terminologie, empêchant une étude transnosographique de ce symptôme (Chase, 2011). En effet, de nombreux termes sont utilisés pour décrire le même tableau clinique de perte d'initiation. Par exemple, selon les spécialités de médecine et selon les catégories diagnostiques, la réduction quantitative des comportements volontaires sera nommée apathie, avolition, aboulie, amotivation, apragmatisme, perte de l'auto-activation psychique, symptômes négatifs, … (Laplane et al., 1982; Yazbek et al., 2014 pour une revue). Cette variabilité des terminologies pour décrire une réduction des comportements volontaires apparaît également dans la cinquième version du Manuel diagnostique et statistique des troubles mentaux et des troubles psychiatriques (DSM-5) (American Psychiatric Association, 2013). En effet, un tableau clinique apathique y est décrit dans 19 pathologies psychiatriques, sous des terminologies variées malgré des descriptions identiques de réduction des comportements volontaires (Strauss & Cohen, 2017). Dans une volonté de précision de ces descriptions cliniques en psychiatrie, les troubles de l'initiation sont constatés dans trois principaux domaines : les émotions, l'effort et le social (Bègue et al., 2020; Galderisi et al., 2018).

Le DSM-5 permet également de mettre en lumière la confusion persistante entre symptôme apathique et symptôme dépressif, malgré la double dissociation, clinique et anatomique, entre apathie et dépression (Holthoff et al., 2005; M. L. Levy et al., 1998; R. Levy, 2012; Starkstein, 2005). En effet, aujourd'hui, une perte d'intérêt, associée à une perte d'énergie, une réduction de la capacité de penser et un ralentissement psychomoteur sont à la fois les critères diagnostiques cliniques de l'apathie et de la dépression (American Psychiatric Association, 2013; Robert et al., 2018).

1.2.2. Efficacité limitée des traitements

Actuellement, les pistes thérapeutiques de l'apathie restent insatisfaisantes (Robert et al., 2018).

Sur le plan pharmacologique, de nombreuses molécules ont été testées mais aucun traitement pour l'apathie n'a encore été validé internationalement (J. Cummings, 2021). Dans les pathologies neurodégénératives, les psychostimulants (type méthylphénidate et modafinil) ont été les plus testés mais les effets restent très hétérogènes selon les participants (Herrmann et al., 2008; Mintzer et al., 2021; Padala et al., 2017; P. B. Rosenberg et al., 2013; M. T. Ruthirakuhan et al., 2018). De même, les inhibiteurs de la cholinestérase et la mémantine (antagonistes NMDA) auraient également des effets très hétérogènes (Berman et al., 2012; Harrison et al., 2016; Roth et al., 2007; Sepehry et al., 2017; Teixeira et al., 2021). Les antidépresseurs inhibiteurs sélectifs de la recapture de la sérotonine et les antipsychotiques seraient quant à eux inefficaces, voire pourraient même aggraver l'apathie (Harrison et al., 2016; C. G. Theleritis et al., 2019; Wongpakaran et al., 2006). Dans la schizophrénie, plusieurs méta-analyses ont étudié l'effet des antidépresseurs, des antipsychotiques typiques et atypiques, des traitements glutamatergiques ou antibiotiques sur l'apathie (Brasso et al., 2023; Cerveri et al., 2019). La cariprazine serait à utiliser en première intention, l'amilsulpride en cas d'échec. Néanmoins, l'effet de ces deux antipsychotiques atypiques reste modeste et il y a également une forte hétérogénéité dans la réponse aux traitements chez ces patients (Cerveri et al., 2019; Deakin et al., 2018; Fusar-Poli et al., 2015).

Sur le plan non pharmacologique, quatre méta-analyses ont montré que les psychothérapies et interventions occupationnelles, type art thérapie ou groupe de paroles, n'auraient aucun effet direct sur l'apathie (Cella et al., 2023; Lane-Brown & Tate, 2009; Tan et al., 2022; C. Theleritis et al., 2017). Une de ces méta-analyse a également étudié l'effet des thérapies cognitivo-comportementales, de la remédiation cognitive et des interventions mindfulness. Seule la remédiation cognitive ciblant les fonctions exécutives et le traitement de la récompense aurait un effet modéré sur l'apathie dans la schizophrénie (Cella et al., 2023).

Concernant plus spécifiquement la stimulation cérébrale, des méta-analyses mettent également en évidence des effets très hétérogènes selon les études et les pathologies (Lanctôt et al., 2023; Vacas et al., 2019). Dans la schizophrénie, trois méta-analyses montrent que la stimulation cérébrale par stimulation magnétique transcrânienne répétitive (rTMS) et/ou par stimulation transcrânienne à courant continu (tDCS) sur le cortex préfrontal dorsolatéral permet de réduire modérément l'apathie, tout en soulignant l'hétérogénéité des effets selon les patients et les paramétrages de stimulation (Aleman et al., 2018; Lorentzen et al., 2022; Shi et al., 2014).

Ainsi, quelle que soit la pathologie, aucune thérapeutique n'est efficace chez tous les patients apathiques. Cette forte hétérogénéité dans la réponse aux divers traitements pourrait suggérer qu'une approche unidimensionnelle de l'apathie manque de spécificité pour déterminer l'effet d'un traitement. En ce sens, quelques études ont exploré l'effet de certains traitements avec une approche multidimensionnelle de l'apathie. Par exemple, une étude sur l'effet du méthylphénidate sur l'apathie dans la maladie d'Alzheimer a montré que seulement 40% des patients présentaient une réduction de l'apathie, et que cet effet était corrélé à une forme cognitive de l'apathie (Herrmann et al., 2008). Une deuxième étude sur le méthylphénidate dans la maladie d'Alzheimer a montré des effets variables selon différentes formes d'apathie, avec un effet supérieur dans des formes d'apathie où les symptômes cognitifs prédominent (Padala et al., 2017).

2. L'apathie multidimensionnelle

2.1. Les premiers modèles multidimensionnels

2.1.1. Modèle de Marin (1990)

En 1990, Marin est le premier à distinguer des formes et dimensions dans l'apathie. Il dissocie deux formes d'apathie suite à un trouble motivationnel : l'apathie syndrome (ou apathie primaire) et l'apathie symptôme (ou apathie secondaire) (Marin, 1990). Selon sa classification, l'apathie syndrome est un trouble motivationnel primaire, non attribuable à une détresse émotionnelle, un trouble intellectuel ou une diminution du niveau d'éveil. En revanche, quand une de ces causes peut expliquer l'apathie, il s'agit d'une autre forme d'apathie : l'apathie symptôme. Ainsi, par exemple, un patient schizophrène souffre d'une apathie syndrome puisqu'il présente de forts symptômes négatifs qui sont inhérents à sa pathologie et définissent son comportement au quotidien, tandis qu'un patient dépressif présente un symptôme apathique lorsque son absence de comportements est sous-tendue au premier plan par un trouble émotionnel qui impacte sa motivation. Marin a également précisé les critères cliniques de l'apathie syndrome. Ce trouble primaire de la motivation induit des conséquences simultanées dans trois domaines : (1) une diminution des comportements orientés vers un but, observable par exemple lors d'un manque d'effort, d'initiative ou de socialisation ; (2) une diminution de la cognition orientée vers un but, indiquée par un manque d'intérêt, de curiosité pour les activités, pour soi-même ou pour les autres ; (3) une réduction des émotions lors d'un comportement orienté vers un but, observable par une indifférence ou un manque de réponse émotionnelle aux événements positifs ou négatifs.

2.1.2. Modèle de Stuss et al. (2000)

En 2000, l'équipe de Stuss, sur la base de son modèle des fonctions du lobe frontal, propose un modèle avec différentes formes d'apathie. Chaque forme y est associée à une présentation clinique et des substrats neuroanatomiques distincts (Stuss et al., 2000). En effet, ils identifient sept symptômes apathiques, qui sont liés à des dysfonctionnements de différentes régions au niveau frontal et sous-cortical (Figure 1). Ces symptômes peuvent se regrouper en deux grandes familles : l'apathie liée à une perturbation de l'éveil et différentes apathies liées à un dysfonctionnement du système frontal. Pour Stuss et ses collègues, il existe une apathie sous-tendue par des troubles de l'éveil, sans trouble de la conscience, suite à des dysfonctionnements de l'activité de la formation réticulaire du tronc cérébral. Cette forme d'apathie d'éveil correspond au mutisme akinétique, où les patients n'ont plus de réactions

spontanées à l'exception de certains mouvements oculaires. Au niveau du système frontal, une première forme d'apathie, appelée apathie sociale, est sous-tendue par des dysfonctionnements au niveau des lobes frontaux antérieurs et de ses connexions limbiques. Cette apathie sociale, fréquente dans le syndrome de Capgras et les troubles de l'humeur, serait liée à des troubles de la conscience de soi et sociale. Une personne souffrant de cette forme d'apathie saurait réaliser un mouvement, aurait l'intention d'agir mais il lui manquerait l'image de soi pour s'organiser selon ses propres intérêts. Les auteurs décrivent également cinq formes différentes d'apathie exécutive, liées à des dysfonctionnements spécifiques au sein des circuits fronto-sous-corticaux. Au sein de ces apathies exécutives, ils distinguent deux apathies motrices et trois apathies comportementales. Les apathies motrices sont sous-tendues par des déficits au niveau du circuit oculomoteur et de l'aire motrice supplémentaire (AMS) : (1) un dysfonctionnement cérébral du circuit oculomoteur, souvent associé à une héminégligence, peut entraîner une incapacité à initier une réponse visuelle ou motrice du côté controlatéral à la lésion ; (2) les dysfonctionnements de l'AMS peuvent entraîner une réduction de la fluence verbale, souvent associée à des lésions frontales dorsolatérales gauches, ou le symptôme de la main étrangère, trouble neurologique avec une incapacité de bouger volontairement la main controlatérale. Les trois apathies comportementales sont respectivement dues à des dysfonctionnements du cortex préfrontal dorsolatéral (CPFdl), orbitofrontal latéral (CxOF), ou du cortex cingulaire antérieur (CCA) : (1) l'apathie du cortex préfrontal dorsolatéral se caractérise par une réduction de la fluence verbale et un trouble de la sélection exécutive volontaire des actions ; (2) l'apathie du cortex orbitofrontal latéral entraîne des changements voire un émoussement de personnalité, avec une incapacité à anticiper la sélection d'une réponse motivationnelle ; (3) l'apathie du cortex cingulaire antérieure est très sévère, surtout en cas de lésions bilatérales. Devant les tableaux cliniques variés et la richesse des connexions au niveau du cortex cingulaire antérieur, trois sous-types d'apathie du cortex cingulaire antérieur ont été proposés : (i) si les dysfonctionnements du cortex cingulaire antérieur sont en lien avec l'amygdale, l'apathie sera caractérisée par une placidité affective ; (ii) si les dysfonctionnements se situent dans le gyrus cingulaire antérieur, l'apathie sera caractérisée par des troubles de la sélection des réponses ; (iii) si les dysfonctionnements sont en lien avec l'AMS, l'apathie sera caractérisée par des troubles de l'exécution des mouvements.

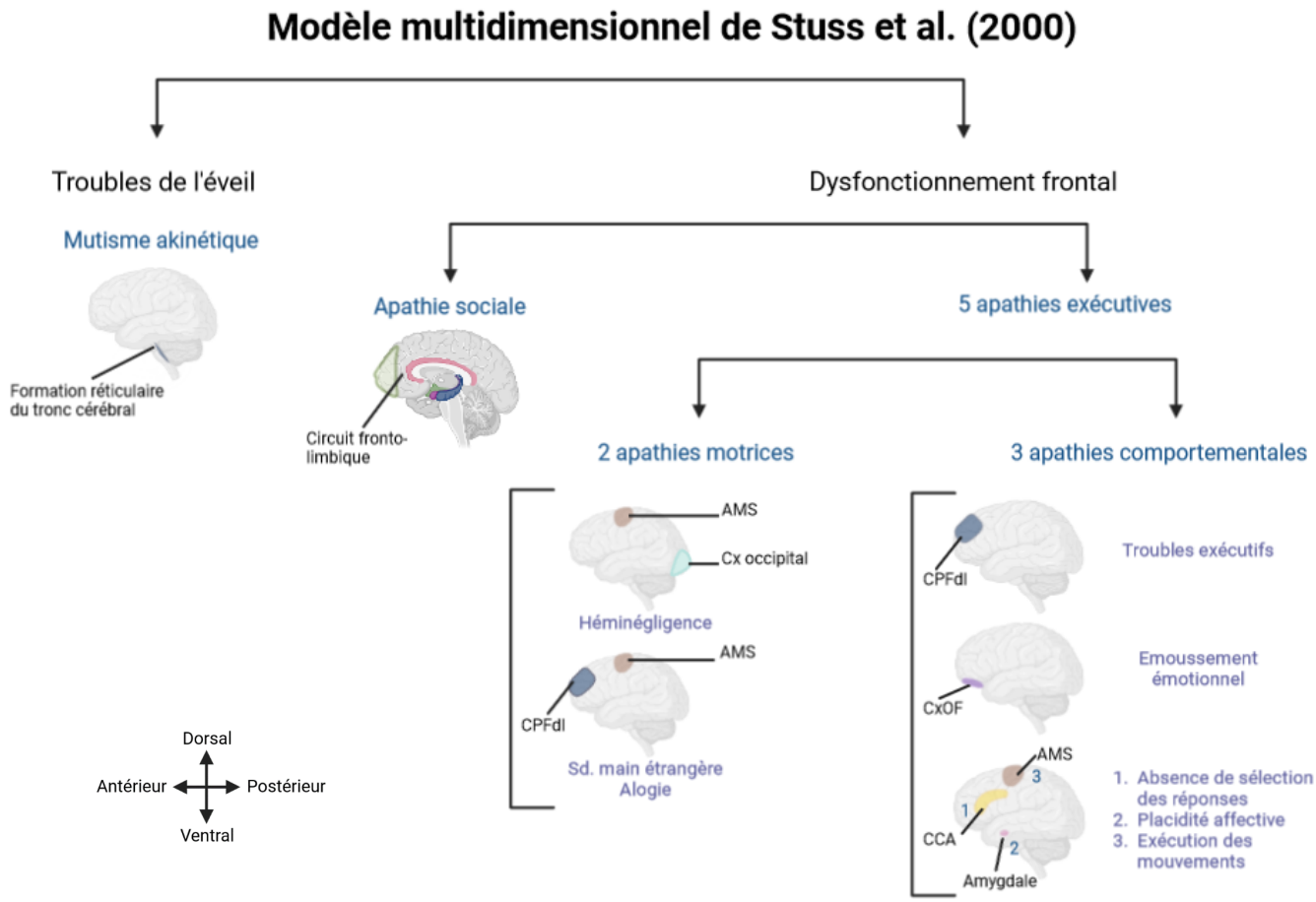

Figure 1 : Synthèse du modèle multidimensionnel de Stuss et al. (2000).

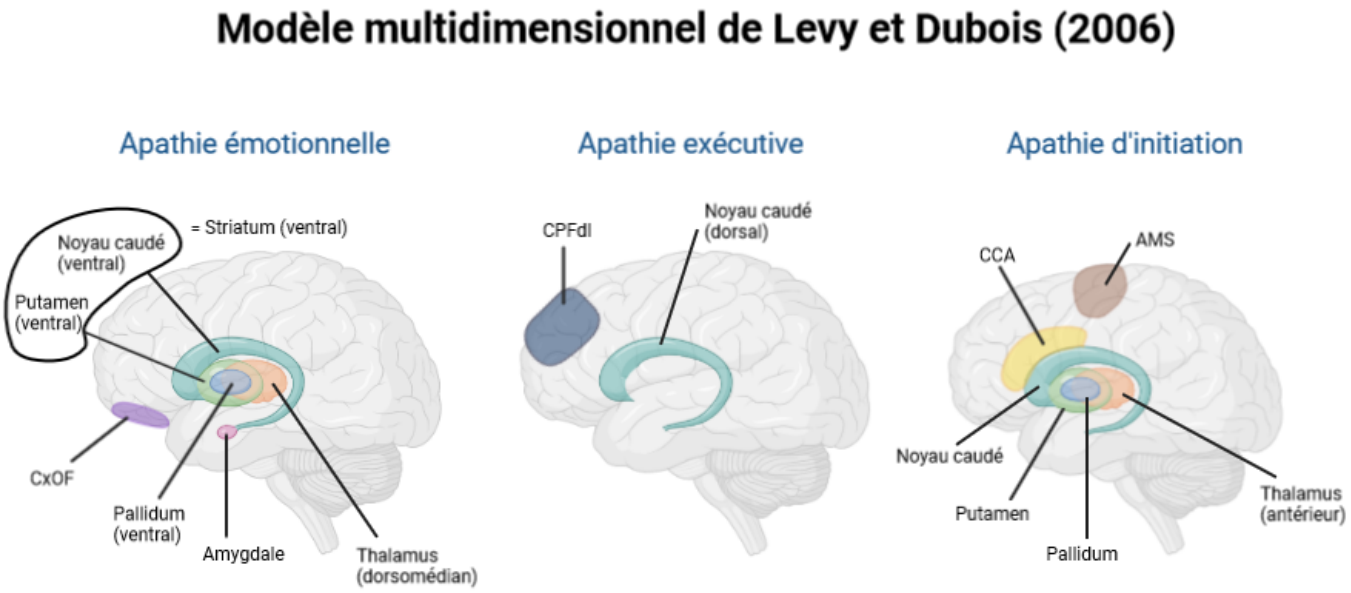

Figure 2 : Synthèse du modèle multidimensionnel de Levy et Dubois (2006).

2.2. *Le modèle multidimensionnel de Levy et Dubois (2006)*

2.2.1. *Généralités*

En 2006, Levy et Dubois proposent un modèle multidimensionnel de l'apathie basé sur une définition purement comportementale de ce symptôme. L'apathie correspond à une réduction quantitative des comportements orientés vers un but. Les comportements dirigés vers un but sont définis par un ensemble de processus qui permettent l'achèvement d'un but à travers la réalisation d'une action volontaire (Brown & Pluck, 2000). Le but peut être physique ou cognitif, réalisable immédiatement ou à long terme. Le terme dirigé ou orienté implique que l'action est sous-tendue par la connaissance d'un lien entre l'action et le résultat attendu. Différentes étapes sont nécessaires à la réalisation de ces comportements orientés vers un but : l'intention d'agir, l'élaboration d'un plan d'action, l'initiation de l'action, son exécution et le contrôle de la réponse comportementale (R. Levy & Dubois, 2006). Ces étapes sont possibles grâce à l'intégration fonctionnelle de facteurs émotionnels, motivationnels, cognitifs et moteurs (Wallis, 2007). Plus précisément, trois facteurs principaux sont nécessaires pour mener à bien un comportement volontaire orienté vers un but : la motivation, le contrôle cognitif et la prise de décision basée sur le calcul coût / bénéfice (A. J. Culbreth et al., 2018b; Kring & Barch, 2014). Ainsi, l'altération d'un de ces trois facteurs pourrait sous-tendre une réduction des comportements orientés vers un but, et donc l'apathie (R. Levy & Dubois, 2006; Robert et al., 2018). A partir d'études expérimentales (anatomiques, électrophysiologiques et fonctionnelles) et d'observations cliniques chez des patients atteints de troubles neurologiques, Levy et Dubois ont élaboré un modèle avec trois formes d'apathies : l'apathie émotionnelle / affective, l'apathie cognitive (exécutive) et l'apathie d'auto-activation (d'initiation). Les trois formes d'apathie sont sous-tendues par des dysfonctionnements de réseaux entre le cortex préfrontal et les ganglions de la base (Figure 2). Les auteurs font également l'hypothèse de mécanismes distincts pour chaque forme d'apathie, au niveau des systèmes de génération et de contrôle des mouvements volontaires auto-initiés.

Ce modèle plus récent a également servi de bases théoriques pour l'élaboration d'un auto-questionnaire : le *Dimensional Apathy Scale* (DAS) (Radakovic & Abrahams, 2014). Ce questionnaire permet de quantifier la sévérité des trois formes d'apathie de Levy et Dubois, simplifiées sous les termes d'apathie exécutive, émotionnelle et d'initiation. Ce questionnaire a été largement testé et validé dans différentes populations de différentes cultures et dans des pathologies différentes (Kawagoe et al., 2020; Quang et al., 2022; Radakovic & Abrahams, 2018; Santangelo, Raimo, et al., 2017). La DAS a également permis de mettre en évidence des profils d'apathie spécifiques dans les pathologies neurodégénératives : l'apathie exécutive

est dominante dans la maladie de Parkinson (Radakovic et al., 2018) ; l'apathie émotionnelle est la plus fréquente dans la démence fronto-temporale à variante comportementale (Radakovic et al., 2020) ; l'apathie d'initiation est majoritaire dans la sclérose latérale amyotrophique (Radakovic et al., 2016). En revanche, toutes les pathologies n'ont pas une forme dominante : c'est notamment le cas de la maladie de Huntington, bien que les conséquences associées à chaque forme y soient différentes (Atkins et al., 2021). En psychiatrie, une étude montre une prévalence plus importante des formes exécutive et initiative dans la schizophrénie (Barek et al., 2021). Enfin, l'implication des réseaux sous-tendant les trois formes d'apathie du modèle a été testée et confirmée chez l'homme dans plusieurs pathologies neurodégénératives. Par exemple, une méta-analyse a confirmé l'implication de ces réseaux neuronaux sous-jacents à chacune des trois formes d'apathie dans la maladie de Parkinson (Pagonabarraga et al., 2015). En revanche, à notre connaissance, aucune étude fonctionnelle n'a testé ce modèle dans les pathologies psychiatriques.

2.2.2. L'apathie émotionnelle

2.2.2.1. Arguments cliniques et fonctionnels

Certains patients apathiques présentent un tableau clinique dominé par des troubles émotionnels et motivationnels. Par exemple, ils ne sont plus intéressés par les activités qui leur plaisaient et les motivaient auparavant, ils semblent indifférents à ce qui leur arrive et à leur environnement et dans les rares cas où ils réagissent à un événement, leurs réactions sont faibles en intensité et très brèves. Au niveau structural, l'apathie émotionnelle / affective est sous-tendue par des dysfonctionnements au niveau de la boucle émotionnelle entre le cortex préfrontal orbital et médian et la partie ventrale des ganglions de la base (noyau caudé, striatum, pallidum) (Bechara et al., 2000; Bhatia & Marsden, 1994; Eslinger & Damasio, 1985; Öngür & Price, 2000; Rosen et al., 2002). Le thalamus dorso-médian et l'amygdale pourraient être également impactés (Fudge et al., 2002; Haber, 2003; Russchen et al., 1985). Ainsi, l'apathie émotionnelle / affective serait potentiellement due à une incapacité d'associer des signaux émotionnels et affectifs à des comportements présents ou futurs. En effet, les émotions et affects sont nécessaires pour décoder le contexte d'un comportement donné et lui fournir une valeur motivationnelle. Ainsi, un changement dans le couplage émotion / affect – comportement pourrait conduire à l'apathie, soit par réduction de la volonté à réaliser ou maintenir des actions (perte de motivation, perte des buts, émoussement émotionnel, insensibilité à la récompense), soit en diminuant la capacité d'évaluer les conséquences de ces futures actions (R. Levy, 2012; R. Levy & Dubois, 2006).

2.2.2.2. Potentiel mécanisme impliqué

Pour réaliser une action orientée vers un but, il est primordial d'avoir envie de faire l'action, et donc d'être motivé à atteindre le but fixé (Berridge & Aldridge, 2008; M. J. F. Robinson et al., 2016). Dès 1993, Robinson et Berridge dissocient deux processus motivationnels interconnectés mais distincts : le *liking* et le *wanting* (T. E. Robinson & Berridge, 1993). Les comportements orientés vers un but reposent sur l'intégrité de ces deux processus motivationnels, qui permettent d'initier, de maintenir et de changer de comportement adapté parmi différentes options disponibles dans l'environnement, tout en optimisant l'allocation des ressources cérébrales nécessaires pour atteindre ces buts (Berridge & Kringelbach, 2013). Le *liking* est le processus responsable du plaisir hédonique, c'est-à-dire un ressenti émotionnel au moment de l'obtention d'une récompense ou d'une punition. Par ce ressenti hédonique, le *liking* module la motivation des prochains comportements orientés vers un but, en ajoutant une valeur affective à la prochaine action à atteindre (Dickinson & Balleine, 2010). Le *wanting* est le processus responsable de l'envie (désir motivé) d'aller chercher une récompense ou un plaisir et/ou d'éviter une punition, par le traitement de la saillance motivationnelle (T. E. Robinson & Berridge, 1993). La valeur motivationnelle donnée à la récompense à atteindre (alimentaire, monétaire, affective) peut s'étendre aux indices et objets liés à la récompense ou permettant sa récupération, en les transformant en incitations "voulues" (Pool et al., 2016; M. J. F. Robinson et al., 2016). Le *wanting* se manifeste par une préparation attentionnelle majorée pour les indices en lien avec la récompense à atteindre dans l'environnement et par une préparation motrice améliorée pour favoriser la probabilité d'obtenir cette récompense lors de l'action (Berridge et al., 2009; M. J. F. Robinson et al., 2016).

Les processus de *liking* et *wanting* sont sous-tendus par les mêmes structures au niveau du système de récompense (Berridge et al., 2009) (Figure 3). En effet, ces deux processus sont contenus dans des structures mésolimbiques communes : le striatum ventral, le pallidum ventral, ainsi que le cortex orbitofrontal (Berridge & Kringelbach, 2013; Berridge & Robinson, 2003, 2016). Plus spécifiquement, les structures du *liking*, aussi appelées « *hot spots* hédoniques », ne sont que de petites sous-régions de ces structures mésolimbiques, notamment au niveau du striatum ventral (noyau accumbens médian) et du pallidum ventral (Berridge et al., 2009; Berridge & Robinson, 2003). Le pallidum ventral est le seul site à sous-tendre également le « *disliking* », c'est-à-dire le ressenti déplaisant en cas de punition ou d'absence de récompense (Berridge & Kringelbach, 2013; Berridge & Robinson, 2016). Les systèmes opioïde et endocannabinoïde sous-tendent le *liking*, tandis que le système dopaminergique sous-tend le *wanting* (Berridge & Robinson, 2016; Smith & Berridge, 2007).

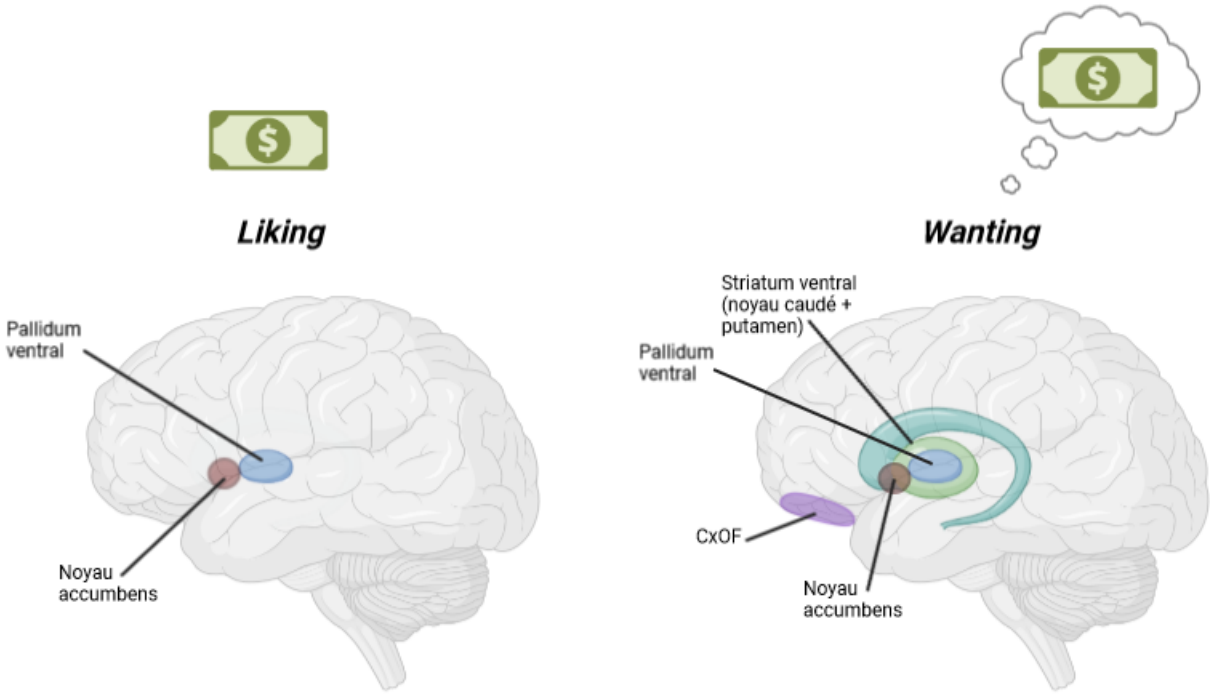

Figure 3 : Synthèse des réseaux associés au *liking* et au *wanting*.

La *Monetary Incentive Delay* (MID) *task* (Knutson et al., 2000) est une tâche de détection visuelle dans laquelle la motivation est manipulée. Les sujets doivent répondre le plus rapidement possible, en appuyant sur un bouton réponse, à la présentation d'une cible précédée soit d'un indice motivant (gain ou perte monétaire) soit d'un indice neutre (voir Figure page 60 - Article 2). Après chaque réponse, un feedback (positif ou négatif), relatif à la rapidité de la réponse, informe le sujet de sa potentielle récompense : dans les essais où l'indice motivant est un gain, un feedback positif indique un gain monétaire réel, tandis qu'un feedback négatif indique l'absence de gain ; dans les essais où l'indice motivant est une perte monétaire, un feedback positif indique l'absence de perte monétaire, tandis qu'un feedback négatif indique une perte monétaire réelle. La MID permet de dissocier les processus motivationnels de *wanting* (engagés après la présentation de l'indice et avant la cible) et de *liking* (engagés après la présentation du feedback) (Knutson et al., 2000).

2.2.2.3. État de la littérature – Impact de la motivation sur l'apathie dans la schizophrénie et les troubles dépressifs

L'analyse porte sur l'ensemble des études d'imagerie par résonance magnétique fonctionnelle (IRMf) explorant le lien entre apathie et processus motivationnels, via la MID, chez des patients souffrant de schizophrénie et de dépression unipolaire ou bipolaire.

Dans la schizophrénie, aucune des études ne montre de lien entre dysfonctionnement du *liking* et apathie. En effet, dans trois de ces études, l'hypoactivation du striatum ventral était positivement corrélée aux symptômes dépressifs ou dissociatifs, mais en aucun cas à l'apathie (Kirschner et al., 2016; Schlagenhauf et al., 2009; Simon et al., 2010). La dernière montrait une corrélation négative entre le score d'apathie et l'activation de structures non motivationnelles, à savoir le gyrus frontal et le cortex cingulaire antérieur qui permettent la mise à jour de la représentation des récompenses pour permettre la prochaine prise de décision (Waltz et al., 2010). Dans la dépression, la seule étude suggère une corrélation négative entre la sévérité de l'apathie et l'hypoactivation du noyau accumbens gauche et du noyau caudé dorsal bilatéral (Pizzagalli et al., 2009).

S'agissant du *wanting*, dix études menées avec des patients souffrant de schizophrénie ont mis en évidence une corrélation négative entre le score d'apathie et l'activation du striatum ventral (Arrondo et al., 2015; Burrer et al., 2020; Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006; Juckel, Schlagenhauf, Koslowski, Wüstenberg, et al., 2006; Kirschner et al., 2016, 2019; Kluge et al., 2018; Simon et al., 2010; Stepien et al., 2018; Waltz et al., 2010). Une étude a montré que ce résultat existait aussi dans le continuum psychotique : les patients schizophrènes ayant une apathie et une hypoactivation du striatum ventral plus importantes que les sujets sains avec un trait psychotique, qui eux-mêmes avaient une apathie et une hypoactivation plus importantes que les sujets sains sans trait psychotique (Simon et al., 2015). En revanche, deux études avec la même méthodologie n'ont pas mis en évidence de lien entre troubles du *wanting* et apathie dans la schizophrénie (Kirschner et al., 2018; Nielsen et al., 2012). Au niveau transnosographique, une étude comparant la schizophrénie et la bipolarité a montré que l'activation du striatum ventral était négativement corrélée à la sévérité de l'apathie dans la schizophrénie, alors que l'hypoactivation de structures non motivationnelles était associée à l'apathie dans la bipolarité (Kirschner et al., 2019). En outre, une étude comparant la schizophrénie et la dépression a montré que les patients schizophrènes et dépressifs présentaient tous les deux un dysfonctionnement du *wanting* reflété par une hypoactivation du striatum ventral, mais que cette hypoactivation était positivement corrélée à l'apathie uniquement dans la schizophrénie (Arrondo et al., 2015). En revanche, une étude menée chez des patients dépressifs a montré l'intégrité du *wanting*, avec une activité du striatum ventral comparable à celle de sujets sains (Pizzagalli et al., 2009).

2.2.3. L'apathie exécutive

2.2.3.1. Arguments cliniques et fonctionnels

Certains patients apathiques présentent un tableau clinique dominé par des troubles cognitifs. Par exemple, ils présentent souvent un ralentissement psychomoteur, des troubles attentionnels (« la tête ailleurs »), ils ne savent plus planifier ou organiser une activité complexe et ils semblent perdus quand plusieurs événements se produisent simultanément. Au niveau neuropsychologique, ces patients présentent une inertie cognitive, c'est-à-dire un syndrome dysexécutif comprenant des difficultés pour maintenir et manipuler des objectifs, générer des stratégies et s'adapter en passant d'une action à une autre. Au niveau structural, l'apathie cognitive est sous-tendue par des dysfonctionnements au niveau de la boucle cognitive entre le cortex préfrontal dorsolatéral et le noyau caudé dorsal (Bhatia & Marsden, 1994; Godefroy, 2003; Kumral et al., 1999; Luria, 1966; Mendez et al., 1989). Ainsi, l'apathie cognitive serait potentiellement due à des déficits des fonctions cognitives nécessaires à l'élaboration d'un plan et à l'exécution d'un comportement orienté vers un but. Ainsi, plusieurs fonctions pourraient être impactées : la planification, la mémoire de travail et la flexibilité (R. Levy, 2012; R. Levy & Dubois, 2006).

2.2.3.2. Potentiel mécanisme impliqué

Le contrôle cognitif correspond à l'ensemble des processus cognitifs qui permettent de mener à bien un comportement orienté vers un but (A. J. Culbreth et al., 2018b). Ces processus permettent au quotidien de maintenir un but en mémoire, d'avoir la capacité de planifier et sélectionner une séquence d'actions ou de pensées en adéquation avec ce but, de l'initier, ainsi que de savoir adapter cette séquence aux imprévus et changements de l'environnement (Miller & Cohen, 2001). Tous ces processus de contrôle peuvent être opérés de manière proactive en anticipant les situations pour atteindre le but, ou de manière réactive en explorant l'environnement et en s'adaptant à de nouvelles opportunités pour atteindre le but (Notebaert & Braem, 2015). Le regroupement de ces processus, sur la base de leur dynamique temporelle d'engagement, a été théorisé dans le modèle *Dual Mechanisms of Control* (DMC) qui distingue un mode de contrôle proactif et un mode de contrôle réactif (Braver, 2012; Braver et al., 2007). Plus spécifiquement, le mode de contrôle proactif permet le maintien actif du but et du contexte afin de pouvoir anticiper les demandes cognitives pour faciliter la réalisation du comportement orienté vers un but. Le contrôle proactif facilite donc le traitement des informations contextuelles pertinentes pour atteindre le but visé, en orientant stratégiquement les processus cognitifs nécessaires pour préparer au mieux la réalisation d'un

comportement orienté vers un but. Le contrôle proactif repose sur l'activation maintenue et anticipée du cortex préfrontal dorsolatéral et de ses projections vers le cortex pariétal inférieur et le gyrus fusiforme (Figure 4), ainsi que sur l'activation phasique des neurones dopaminergiques (Braver et al., 2009; Lopez-Garcia et al., 2016). A contrario, le contrôle réactif correspond à un engagement des processus cognitifs en réaction à un événement. Le contrôle réactif permet un traitement non différencié de toutes les informations de l'environnement, pertinentes ou non pour atteindre le but, afin de pouvoir détecter et résoudre les conflits ou interférences et réajuster le comportement au besoin. Ce mode réactif est sous-tendu par une activation transitoire du cortex préfrontal latéral et du cortex cingulaire antérieur, ainsi que par l'activation transitoire des neurones dopaminergiques (Botvinick, 2007; Braver et al., 2009).

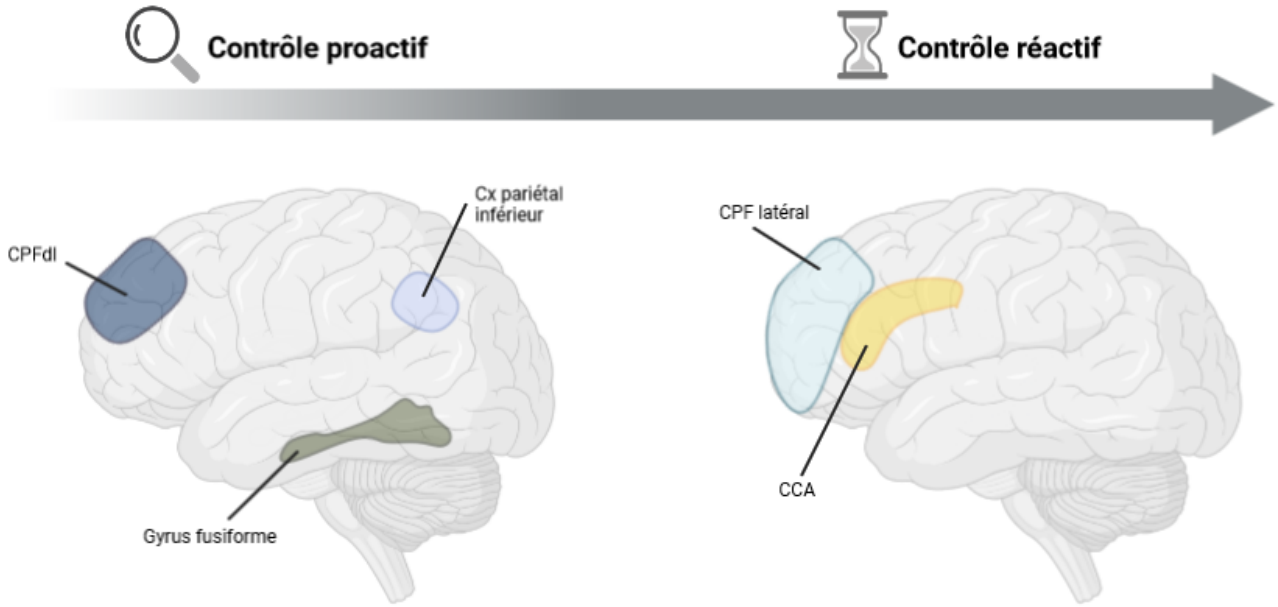

Figure 4 : Synthèse des réseaux associés au contrôle cognitif proactif et réactif.

La *Continuous Performance Test* (AX-CPT) (Servan-Schreiber et al., 1996) et la *Dot-Expectancy Task* (DPX) (Henderson et al., 2012) sont deux tâches classiquement utilisées pour étudier ces deux modes de contrôle. Plus précisément, il s'agit de deux tâches de détection visuelle (voir Figure page 59 - Article 2). Dans la CPT-AX, les stimuli sont des lettres alphabétiques, dans la DPX des lettres en braille (Lopez-Garcia et al., 2016). Chaque essai est composé d'une paire de lettres. La première, constitue la lettre indice (A ou B), la seconde, la lettre cible (X ou Y). Les sujets doivent détecter une séquence indice-cible en appuyant sur un bouton réponse à l'apparition de chaque cible. Dans le cas d'une séquence indice A – cible X, le sujet doit répondre en appuyant sur le bouton réponse droit, et sur le bouton réponse

gauche dans tous les autres cas (séquences AY, BX et BY). La séquence AX représente 70% des séquences présentées (contre 12 % pour les séquences AY et BX et 6 % pour les séquences BY). La prise en compte du contexte (*i.e.*, de l'indice) va se traduire, à la présentation de l'indice A, par l'activation du schéma de réponse associé à la séquence AX. L'analyse combinée des performances aux différents essais et des indicateurs électrophysiologiques évoqués respectivement par l'indice et la cible permettra d'étudier le recours privilégié à un mode de contrôle proactif ou réactif.

2.2.3.3. État de la littérature – Impact du contrôle cognitif sur l'apathie dans la schizophrénie et la dépression

L'analyse porte sur l'ensemble des études comportementales ou d'IRMf examinant le lien entre apathie et contrôle cognitif, à l'aide de la CPT-AX ou de la DPX, chez des patients souffrant de schizophrénie et de dépression unipolaire ou bipolaire.

Dans la schizophrénie, les résultats sont très hétérogènes selon la méthodologie utilisée. Trois études comportementales ont montré une corrélation positive entre le score d'apathie et le nombre d'erreurs BX chez des patients avec ou sans traitement psychotique (Barch et al., 2003; Chun et al., 2018; Frydecka et al., 2014). En IRMf, l'hypoactivation du cortex préfrontal dorsolatéral est associée à la sévérité de l'apathie dans une seule étude (Edwards et al., 2010), et à l'intensité des symptômes de désorganisation dans six études (Lesh et al., 2013; MacDonald et al., 2005; Poppe et al., 2016; Smucny et al., 2018; Yoon et al., 2008, 2012). Au niveau transnosographique, deux études comparant la schizophrénie et la bipolarité ont montré que dans la bipolarité, le dysfonctionnement du proactif était corrélé à la sévérité de l'apathie dans une étude (Smucny et al., 2018), et des symptômes dépressifs dans l'autre (Frydecka et al., 2014). Concernant la dépression, aucune étude n'a étudié spécifiquement le lien entre apathie et troubles du contrôle cognitif. En revanche, de manière indirecte, une étude comportementale a montré que la présence de symptômes dépressifs était associée à un trouble du contrôle proactif (Msetfi et al., 2009). En outre, les ruminations et l'apathie étant deux traits majeurs de la dépression, une étude électrophysiologique a permis de montrer que la présence de ruminations n'était pas associée à une altération du contrôle cognitif (Muscarella et al., 2020).

2.2.4. L'apathie d'initiation

2.2.4.1. Arguments cliniques et fonctionnels

Enfin, certaines personnes apathiques présentent un « vide mental », c'est-à-dire qu'elles ne se disent à l'initiative d'aucune pensée volontaire. Elles semblent également avoir perdu toute spontanéité, aussi bien physique, mentale qu'émotionnelle. En revanche, bien qu'elles n'initient aucune action dans leur vie quotidienne, elles sont capables de réaliser aisément des actions automatisées ou initiées par quelqu'un d'autre. L'apathie d'auto-activation est sous-tendue par des dysfonctionnements au niveau des territoires limbiques et associatifs des ganglions de la base (pallidum et striatum bilatéral, noyau caudé, thalamus antérieur), ainsi que du cortex préfrontal médian, principalement le cortex cingulaire antérieur dorsal et l'aire motrice supplémentaire (Godefroy et al., 1992; Jenkins et al., 2000; Katz et al., 1989; Lugaresi et al., 2008; Strub, 1989; van Domburg et al., 1996). En clinique, l'apathie d'auto-activation est la forme la plus sévère d'apathie, proche des diagnostics d'athymhormie ou de syndrome d'auto-activation en neurologie (Laplane et al., 1982; Laplane & Dubois, 2001; Starkstein et al., 1990). Elle serait potentiellement due à une difficulté à activer des réponses cognitives et émotionnelles ou à initier le programme moteur nécessaire pour compléter un comportement volontaire. Ainsi, l'apathie d'auto-activation reflète soit l'altération simultanée des processus cognitifs et émotionnels, soit une altération spécifique à une étape non motrice ultérieure permettant l'initiation des comportements volontaires (R. Levy, 2012; R. Levy & Dubois, 2006).

2.2.4.2. Potentiel mécanisme impliqué

Le processus de prise de décision correspond à la dernière étape non motrice avant l'action. La prise de décision basée sur l'effort et la récompense correspond aux estimations mentales qu'une personne réalise afin de quantifier l'effort nécessaire pour obtenir une récompense. L'initiation d'un comportement orienté vers un but est possible grâce à la prise de décision d'investir de l'effort pour le réaliser, aux vues des bénéfices possibles que l'accomplissement de ce but pourrait générer (Higgins, 2006).

Les modèles neuroéconomiques considèrent que trois paramètres principaux sont nécessaires pour prendre une décision : l'évaluation de la valeur de la récompense attendue, l'évaluation du coût cognitif et physique, en terme d'effort, et la probabilité de succès (Kool & Botvinick, 2014; Shenhav et al., 2017). Le choix sera effectué après un calcul de la différence entre le bénéfice et le coût. Cette différence sera également modulée par la possibilité de réussir à obtenir cette récompense (Salamone et al., 2016; Wallis, 2007).

Un modèle neurocognitif considère que ces estimations entre la valeur de la récompense et de l'effort, cognitif ou physique, sont modulées par quatre facteurs principaux : le *liking*, le *wanting*, le contrôle cognitif et les pensées défaitistes (A. J. Culbreth et al., 2018a).

Au niveau fonctionnel, la prise de décision, basée sur l'évaluation du coût associé à l'engagement dans un effort, physique et/ou cognitif et sur l'estimation de la récompense à obtenir, est sous-tendue par l'activité du cortex cingulaire antérieur (Kool et al., 2017; Shenhav et al., 2013; Verguts et al., 2015) (Figure 5). L'évaluation de l'effort cognitif est sous-tendue par le cortex préfrontal dorsolatéral, le cortex cingulaire antérieur et le cortex pariétal inférieur, tandis que l'effort physique est sous-tendu par le cortex sensorimoteur et le putamen postérieur ; l'évaluation de la récompense est sous-tendue par l'activité du cortex préfrontal ventral, du striatum ventral et du pallidum ventral (Schmidt et al., 2012). Au niveau neurochimique, la prise de décision coût / bénéfice est sous-tendue par l'activité des neurones dopaminergiques situés entre le cortex cingulaire antérieur et le striatum (Cools, 2008; Cools et al., 2019).

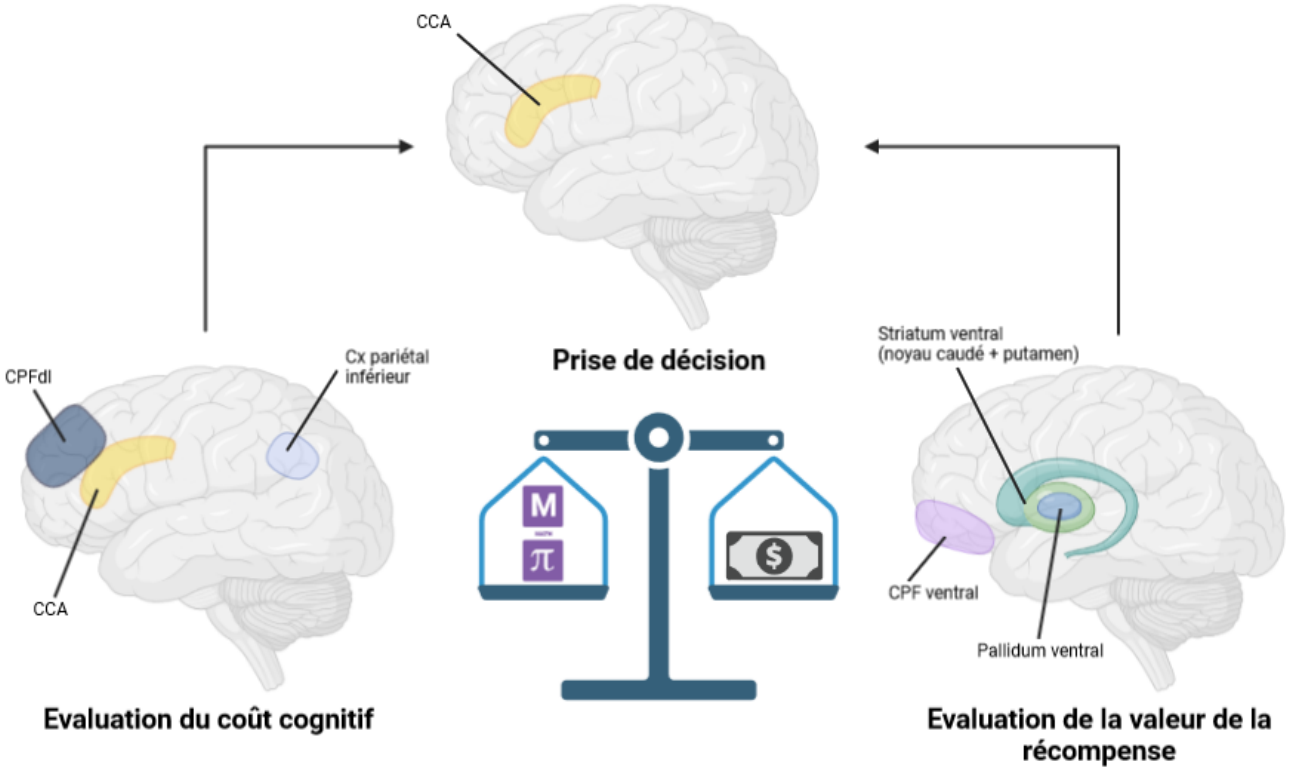

Figure 5 : Synthèse des réseaux associés à la prise de décision.

Aucune tâche consensuelle n'existe pour évaluer la prise de décision basée sur l'effort, qu'il soit physique ou cognitif (Hartmann-Riemer et al., 2018). En revanche, de nombreuses tâches ont été proposées, basées sur la perception du coût de l'effort et l'évaluation de la quantité d'effort qu'une personne est prête à exercer pour obtenir un certain niveau de récompense (Green et al., 2015; Reddy et al., 2015).

2.2.4.3. État de la littérature – Impact de la prise de décision sur l'apathie dans la schizophrénie et les troubles dépressifs

L'analyse porte sur l'ensemble des études comportementales ou fonctionnelles explorant le lien entre apathie et prise de décision, chez des patients souffrant de schizophrénie, de dépression ou de bipolarité.

Dans la schizophrénie,17 études ont montré un lien entre apathie et trouble de la prise de décision : 11 études basées sur l'effort physique (Barch et al., 2014; Chang et al., 2019; A. J. Culbreth et al., 2023; Gold et al., 2013; Hartmann et al., 2015; Horan et al., 2015; Moran et al., 2017; Serper et al., 2017; Strauss et al., 2016; Treadway et al., 2015; J. Wang et al., 2015) et 6 études basées sur l'effort cognitif (A. Culbreth et al., 2016; A. J. Culbreth et al., 2020, 2023; Reddy, Horan, et al., 2018; Reddy, Reavis, et al., 2018; Wolf et al., 2014). Comparativement à des sujets contrôles, plus les patients schizophrènes sont apathiques, moins ils ont envie d'exercer un effort, physique ou cognitif quand la récompense potentielle à obtenir est élevée. En effet, les patients schizophrènes ne font pas des choix optimaux, car ils arrêtent de choisir des options difficiles uniquement quand le gain potentiel associé est élevé. En revanche, 6 études mettent en évidence un évitement de l'effort et des troubles de la prise de décision, mais non liés à l'apathie : 4 études basées sur l'effort physique (Docx et al., 2015; Fervaha et al., 2013, 2015; J. Huang et al., 2016) et 2 études sur l'effort cognitif (Gold et al., 2015; Horan et al., 2015). Cette corrélation avec l'apathie n'est pas non plus retrouvée sur le continuum psychotique, chez des personnes souffrant d'expérience psychotiques occasionnelles (Ermel et al., 2019). Une possible explication à ces résultats contradictoires malgré des méthodologies similaires pourrait être que le lien entre trouble de la prise de décision et apathie ne serait présent que chez les patients schizophrènes avec des pensées défaitistes importantes (Reddy, Horan, et al., 2018).

Dans deux études transnosographiques, avec des sujets sains, des sujets schizophrènes et des sujets dépressifs unipolaires et/ou bipolaires, les troubles de la prise de décision basée sur l'effort physique n'étaient pas liés à la présence d'apathie quelle que soit la pathologie (Saperia et al., 2020; Zou et al., 2020). En revanche, dans une autre étude transnosographique avec des patients schizophrènes et des patients dépressifs, unipolaires et bipolaires, les patients schizophrènes présentaient des troubles de la prise de décision,

avec une réduction de l'effort physique pour les fortes récompenses corrélée positivement à la sévérité de l'apathie, alors que les patients dépressifs présentaient les mêmes prises de décision que les sujets contrôles (Yang et al., 2021). Enfin, une étude transnosographique en IRMf a montré que l'apathie était corrélée à une réduction de l'activité du putamen, en fonction de la récompense chez les patients schizophrènes, et en fonction de l'effort chez les patients dépressifs (Park et al., 2017). Autrement dit, les patients schizophrènes ne sont motivés que par les récompenses facilement accessibles alors que les patients dépressifs ne sont motivés que par les essais difficiles (où la présence d'un possible échec est plus probable).

Concernant la dépression, deux études ont montré un coût de l'effort, physique et/ou cognitif, supérieur chez des patients avec des troubles dépressifs unipolaires et bipolaires, par rapport à des sujets sains (Hershenberg et al., 2016; Vinckier et al., 2022). Cette augmentation de la sensibilité à l'effort était corrélée positivement à la sévérité de l'apathie. Deux études ont montré que plus des patients présentant une dépression chronique ou subclinique sont anhédoniques, moins ils ont envie d'exercer un effort physique quand la récompense potentielle à obtenir est élevée (Tran et al., 2020; Treadway et al., 2012; Yang et al., 2014). En revanche, une de ces études a montré que l'anhédonie n'impactait pas les efforts cognitifs (Tran et al., 2020). En outre, une étude a montré que les patients dépressifs ne modulent pas leur effort physique en fonction d'un possible gain financier, non pas à cause de l'apathie mais en raison d'une augmentation de l'effort subjectif à déployer pour obtenir cette récompense (M.-L. Cléry-Melin et al., 2011). Enfin, une étude liant effort et motivation a montré que chez les sujets contrôles, le niveau de *liking* d'une récompense prédit la motivation à fournir de l'effort pour aller rechercher à nouveau cette récompense, alors que chez des patients dépressifs, l'apathie est liée à un faible *wanting*, induisant une faible motivation à fournir de l'effort (Sherdell et al., 2012).

3. Les objectifs de la thèse

L'objectif principal de ce travail de thèse est de mieux caractériser les mécanismes sous-tendant chacune des trois formes d'apathie de l'approche multidimensionnelle : l'apathie émotionnelle, exécutive et d'initiation. Dans cette perspective, une approche phénotypique (études 1 à 3) et transnosographique (méta-analyse et étude 4) ont été utilisées.

Plus précisément, l'étude 1 vise à rendre compte de la prévalence des trois formes d'apathie dans une population jeune et à identifier d'éventuels prédicteurs spécifiques à chacune d'entre elles (Lafond-Brina, G. & Bonnefond, A. (2022). The stability of multidimensional subclinical apathy during a pandemic and its relations to psycho-behavioral factors. *Scientific Reports*, *12*(1), 2931). A l'issue de cette enquête, la sélection de sujets sains présentant un phénotype spécifique d'apathie permet d'étudier dans les études expérimentales 2 et 3 les mécanismes sous-tendant les trois formes d'apathie. L'étude 2 étudie les processus motivationnels et cognitifs sous-tendant respectivement l'apathie émotionnelle et l'apathie exécutive (Lafond-Brina, G., Pham, B. T. & Bonnefond, A. (under review). Specific mechanisms underlying executive and emotional apathy: A phenotyping study. *Psychiatric Research*). A la suite de ces résultats, des analyses complémentaires permettent de tester le caractère spécifique des mécanismes altérés dans l'apathie émotionnelle et l'apathie exécutive, ainsi que d'étudier l'hypothèse d'une forme mixte dans l'apathie d'initiation. L'étude 3 étudie les mécanismes d'effort cognitif et de prise de décision dans l'apathie d'initiation (Lafond-Brina, G., Pham, B. T. & Bonnefond, A. (2023). Initiative apathy trait underlies individual differences in the ability to anticipate and expend cognitive effort in cost-benefit decision-making tasks. *Cerebral Cortex*, 33(12), 7714-7726).

La méta-analyse et l'étude 4, ont été menées dans une perspective transnosographique. L'une et l'autre explorent l'apathie dans la schizophrénie et les troubles dépressifs. La méta-analyse par estimation de la probabilité d'activation (ALE) en IRMf explore les réseaux sous-tendant l'activation des processus motivationnels et de contrôle cognitif chez les patients schizophrènes et dépressifs, afin de pouvoir étudier la possibilité de formes dominantes d'apathie distinctes dans ces deux pathologies. Elle s'appuie sur l'ensemble des études publiées avec des sujets contrôles, des patients schizophrènes et/ou des patients dépressifs, et ayant utilisé les mêmes tâches cognitives que celles de l'étude 2 (Lafond-Brina, G., Dormegny-Jeanjean, L. & Bonnefond, A. (en préparation). A systematic review and ALE meta-analysis of cognitive control and motivation in schizophrenia and mood disorders: implications for multidimensional apathy). L'étude 4 (encore en cours) permet de tester le caractère transnosographique des mécanismes précédemment identifiés et associés à chaque sous-forme d'apathie.

Méthodes

1. Les sujets

Les caractéristiques de l'ensemble des participants sont résumées par étude dans le tableau 1. L'étude 1 correspond à l'enquête en ligne, proposée aux étudiants de l'Université de Strasbourg à deux reprises : à tous les étudiants en février 2020 puis aux nouveaux inscrits en février 2021. Les études expérimentales 2 à 4 combinent mesures électrophysiologiques (électroencéphalogramme - EEG), mesures comportementales (performances) et mesures cliniques subjectives (questionnaires). Dans les études 2 et 3, les sujets sains avec un phénotype spécifique d'apathie ont été sélectionnés afin de présenter des caractéristiques d'âge et de sexe similaires à celles des trois sous-groupes d'apathie présents dans la population générale (étude 1). Les sujets sains non apathiques ont été sélectionnés sur des critères d'âge, de sexe et de niveau d'études, de façon à obtenir un groupe comparable sur ces facteurs sociodémographiques aux trois autres groupes. Dans l'étude 4, les patients schizophrènes et les patients dépressifs ont été sélectionnés sur la base de la présence d'un trait ou d'un symptôme apathique. Les sujets sains non apathiques ont été sélectionnés de façon à obtenir pour les trois groupes de sujets, des distributions comparables en âge, sexe et niveau d'éducation.

Tableau 1 : Résumé des caractéristiques des participants. Les valeurs sont données en moyenne (écart-type).

	Étude 1		Études 2 et 3 - Sujets sains				Étude 4 - Patients		
	Session 1	Session 2	Apathie exécutive	Apathie émotionnelle	Apathie d'initiation	Sans apathie	Schizophrénie	Dépression	Sujets contrôles
Nombre de sujets	N= 4 467		N=91				N=31		
(N)	2789	1678	22	22	23	24	7	10	14
Âge (années)	20.8 (2.2)	19.2 (1.4)	21.4 (1.71)	21.4 (2.13)	20.7 (2.22)	22 (1.73)	39.3 (11.0)	42 (6.78)	37.1 (8.15)
Sexe (% d'hommes)	26.1	38.6	27.27	63.63	30.43	41.66	71.4	50	50
Niveau d'études (années)	13.75 (1.34)	12 (1.2)	13.68 (1.58)	13.86 (1.46)	13.17 (1.64)	14.58 (1.41)	13.14 (2.91)	14.25 (2.55)	14.9 (1.52)
DAS exécutive Trait : [16;20] Symptôme : [21;24]	11.86 (4.75)	12.14 (5.07)	19.1 (1.87)	7.23 (4,89)	11.61 (3.47)	8.63 (3.79)	12.57 (4.35)	16.40 (4.06)	5.36 (2.73)
DAS émotionnelle Trait : [12;16] Symptôme : [17;24]	7.65 (4.31)	7.79 (4.35)	6,64 (2.87)	16,3 (3.40)	6.13 (2.98)	6.25 (2.59)	13.43 (2.51)	10.70 (3.83)	7.36 (2.90)
DAS d'initiation Trait : [14;17] Symptôme : [18;24]	10.38 (4.10)	9.71 (4.15)	9.45 (2,26)	7.09 (2.91)	15.04 (1.36)	7.54 (2.95)	12.71 (2.81)	17.00 (4.11)	7.43 (3.03)

1.1. Profils d'apathie multidimensionnelle dans la population jeune (étude 1)

Étant donné le grand nombre de participants, l'échantillon pouvait être assimilé à une représentation de la population jeune étudiante. Ainsi, à partir de la moyenne et de l'écart-type de l'échantillon à l'échelle d'apathie DAS, des cut-offs traits et symptômes ont pu être calculés pour chaque sous-forme d'apathie : exécutive, émotionnelle et d'initiation. Le cut-off trait correspond au score seuil à partir duquel un sujet a un score qui dévie de plus d'un écart-type de la moyenne de la population, tandis que le cut-off symptôme correspond au score seuil à partir duquel un sujet a un score qui dévie de plus de deux écarts-types de la moyenne de la population (Muneaux, 2018).

A partir de ces cut-offs, des phénotypes spécifiques ont pu être observés pour chaque forme d'apathie. Nous avons considéré qu'un sujet présentait une forme spécifique d'apathie quand son score d'apathie était supérieur au cut-off de la population jeune pour cette forme et que ses scores aux deux autres formes étaient inférieurs aux cut-off de la population. Ainsi, dans notre échantillon de 4 467 personnes, 30.01% présente une seule forme d'apathie, 12,55% présente deux formes d'apathie et 2,10% présente les trois formes associées. Sur les 30.01% de personnes présentant une seule forme d'apathie, 42.7% ont uniquement une apathie exécutive, 36.4% une apathie émotionnelle et 20.9% une apathie d'initiation. En revanche, sur les 12.55% de participants présentant simultanément deux formes d'apathie, 86.97% présentent une apathie d'initiation associée à une autre forme.

Les participants à l'enquête en ligne avaient la possibilité de laisser leurs coordonnées (mail ou téléphone) s'ils souhaitaient être recontactés pour une éventuelle participation à une étude expérimentale rémunérée (études 2-3) (autorisation n°381 de la Commission Nationale de l'Informatique et des Libertés (CNIL)).

1.2. Recrutement des participants des études 2 et 3

Le critère principal de sélection des participants pour constituer les groupes des études 2 et 3 était leurs scores d'apathie aux trois sous-échelles de la DAS lors de l'enquête en ligne. Le but était de recruter des phénotypes spécifiques pour chaque forme d'apathie. Des troubles métaboliques, du sommeil, neurologiques ou psychiatriques ont été associés à une prévalence élevée d'apathie (Barber et al., 2018; Jurado-Flores et al., 2022). De même, la présence de troubles psychiatriques chez les parents, frères et sœurs, ou enfants, est associée à des particularités cognitives et neuronales (Weissman, 2006; Whitfield-Gabrieli et al., 2009; Williamson et al., 2004). Ainsi, la présence d'un de ces troubles était un critère d''exclusion, de même que la présence, chez le participant, d'un retard mental.

Chaque participant a complété la DAS lors de l'enquête en ligne puis à nouveau lors de l'étude expérimentale. Les scores aux trois formes étaient stables entre ces deux mesures faites entre 3 mois et un an d'intervalle. Cette stabilité suggère que le score d'apathie ne reflétait pas un état dépendant du contexte mais plutôt la mesure d'un trait, sur un continuum allant d'une absence d'apathie à la présence d'un symptôme apathique. Au final, le groupe d'apathie exécutive est constitué de 63% de trait et de 37% de symptôme apathique, le groupe d'apathie émotionnelle de 54% de trait et de 46% de symptôme et le groupe d'apathie d'initiation à 100% de trait.

1.3. Recrutement des sujets de l'étude patients (étude 4)

Les patients ont été recrutés aux Hôpitaux Universitaires de Strasbourg au sein du centre de neuromodulation non invasive et du service de psychiatrie, ainsi qu'au sein de la délégation Bas-Rhin de l'Union nationale de familles et amis de personnes malades et/ou handicapées psychiques (UNAFAM). Les sujets contrôles ont été recrutés par voie d'affichage. Les patients schizophrènes et dépressifs ont été diagnostiqués selon le DSM-5 et étaient tous stabilisés depuis au moins deux mois. Les patients schizophrènes ne devaient pas présenter de symptômes dépressifs majeurs associés et les patients dépressifs ne devaient pas présenter de schizophrénie associée. Les autres critères d'exclusion étaient semblables à ceux des études 2 et 3.

Tous les patients devaient présenter un trait ou un symptôme apathique undimensionnel, observé cliniquement par un médecin psychiatre et confirmé par un score égal ou supérieur à -23 à la Lille Apathy Rating Scale (LARS) (Sockeel et al., 2006; Yazbek, Norton, et al., 2014). Pour éviter les biais de sélection, l'apathie n'était évaluée de manière multidimensionnelle, à l'aide de la DAS, que lors de la première visite expérimentale.

Contrairement aux études 2 et 3 qui se déroulaient en une session expérimentale unique pour chaque sujet, l'étude 4 s'est déroulée en deux ou trois temps : une visite d'inclusion (pour les patients uniquement), permettant de caractériser leur trouble psychiatrique, et deux sessions expérimentales, espacées d'une semaine au minimum. Lors de chaque session expérimentale, les participants répondaient à des questionnaires (listés dans le tableau 3) puis réalisaient deux tâches cognitives associées à un enregistrement EEG. La présentation des questionnaires et des tâches cognitives a été contrebalancée entre les sujets.

Lors de la visite d'inclusion, les symptômes des patients ont été évalués à l'aide de plusieurs échelles cliniques administrées par deux psychiatres expérimentés. L'ensemble de ces échelles a été administré à chaque patient :

- deux échelles de dépression : la Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979) et la Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990), qui prend en compte les spécificités de la symptomatologie psychotique et la possible présence d'effets extrapyramidaux dus aux antipsychotiques chez les patients schizophrènes ;
- deux échelles pour les symptômes positifs et négatifs de la schizophrénie : les Scales for the Assessment of Positive and Negative Symptoms (SAPS et SANS) (Andreasen, 1989, 1984) ;
- une échelle pour les symptômes maniaques : la Young Mania Rating Scale (YMRS) (Young et al., 1978) ;
- une échelle pour explorer la résistance au traitement dans la dépression : la Dutch Measure for quantification of Treatment Resistance in Depression (DM-TRD) (Peeters et al., 2016).

Il nous paraissait important d'inclure des patients qui soient le plus représentatif possible des patients rencontrés en pratique clinique quotidienne. De fait, les patients sélectionnés prenaient souvent un traitement médicamenteux. Ils étaient inclus tant que leur traitement était bien toléré et pris depuis plus de 8 semaines consécutives. Lors de la visite d'inclusion, il était également vérifié que l'émergence de l'apathie n'était pas liée au début de la prise d'un traitement, suite à l'apparition de signes extrapyramidaux et/ou d'une sédation-somnolence (Kirschner et al., 2017). Afin de tester l'effet éventuel des médicaments sur les résultats, une équivalence en chlorpromazine a été calculée selon le consensus international sur les médicaments psychotiques pour les patients schizophrènes (Gardner et al., 2010) et, une équivalence en fluoxetine pour les patients dépressifs (consensus international sur les médicaments antidépresseurs) (Furukawa et al., 2019; Hayasaka et al., 2015). L'influence des médicaments sur les résultats, encore très préliminaires et en cours d'analyse, n'est pas présentée dans le manuscrit. Les caractéristiques psychopathologiques des patients sont résumées dans le tableau 2.

Tableau 2 : Résumé des caractéristiques psychopathologiques des patients de l'étude 4. Les valeurs sont données en moyenne (écart-type).

	Schizophrénie	Dépression
Lille Apathy Rating Scale (LARS) Cut-off : -23	-12.66 (8.50)	-1.8 (13.36)
Montgomery Asberg Depression Rating Scale (MADRS)	10.33 (8.5)	24.8 (8.64)
Calgary Depression Scale for Schizophrenia (CDSS)	4.33 (3.21)	11.4 (3.51)
Scale for the Assessment of Positive Symptoms (SAPS)	10.33 (5.86)	0.83 (2.23)
Scale for the Assessment of Negative Symptoms (SANS)	52.66 (8.73)	42.2 (18.86)
Young Mania Rating Scale (YMRS)	0	3 (5.08)
Dutch Measure for quantification of Treatment Resistance in Depression (DM-TRD)	-	5.8 (8.18)
Equivalence en chlorpromazine (mg)	570 (25.5)	1096.66 (2409.33)
Equivalence en fluoxetine (mg)	0	36.83 (70.71)

2. Les questionnaires et tests neuropsychologiques

Les questionnaires et tests neuropsychologiques utilisés sont listés par étude dans le tableau 3. Le questionnaire DAS en version française est également disponible en Annexe 1.

Tableau 3 : Liste des questionnaires et tests neuropsychologiques utilisés dans chaque étude.

	Études 1, 2 et 3 Sujets sains	Étude 4 Patients et sujets sains
Apathie	DAS	DAS LARS
Dépression	BDI *The Beck Depression Inventory (Beck et al., 1988)*	QIDS-SR16 *The 16 item Quick inventory of depressive symptomatology self-report (Rush et al., 2003)*
Bipolarité		MDQ *The Mood Disorder Questionnaire (Hirschfeld et al., 2000)*
Anxiété		STAI versions état et trait *The State-Trait Anxiety Inventory (Spielberger, 1966)*
Estime de Soi	*Rosenberg Self-Esteem Scale (M. Rosenberg, 1965)*	*Rosenberg Self-Esteem Scale*
Motivation	TEPS *Temporal Experience of Pleasure Scale (Gard et al., 2006)*	TEPS BIS BAS *A behavioral inhibition system (BIS) and a behavioral activation system (BAS) scales (Carver & White, 1994)*
Qualité de vie		WHODAS 2.0 *World Health Organization Disability Assessment Schedule 2.0 (Buist-Bouwman et al., 2008)*
Somnolence		*The Epworth Sleepiness Scale (Johns, 1991)*
Estimation intelligence		fNART *French version of the National Adult Reading Test (Mackinnon & Mulligan, 2005)*
Mémoire de travail	Mémoire des chiffres WAIS-III *(Wechsler, 1997)*	Mémoire des chiffres WAIS-III

Les scores aux questionnaires et tests neuropsychologiques des participants des études sujets sains sont présentés dans les articles 1 à 3 (pages 42, 63 et 94). Les scores des participants de l'étude 4 sont résumés dans le tableau 4.

Tableau 4 : Résumé des différentes mesures issues des questionnaires et tests neuropsychologiques réalisés par les participants de l'étude 4. Les valeurs sont données en moyenne (écart-type).

	Contrôles N= 14	Schizophrénie N= 7	Dépression N= 10	p-value
LARS Cut-off: ≥-23		-12.66 (8.50)	-1.8 (13.36)	p<.27
DAS exécutive Cut-off: ≥16	5.36 (2.73)	12.57 (4.35)	16.40 (4.06)	**p<.001**
DAS émotionnelle Cut-off: ≥12	7.36 (2.90)	13.43 (2.51)	10.70 (3.83)	**p<.001**
DAS initiative Cut-off: ≥14	7.43 (3.03)	12.71 (2.81)	17.00 (4.11)	**p<.001**
QIDS-SR16	9.64 (5.02)	21.4 (9.62)	42.3 (12.4)	**p<.001**
MDQ (% en faveur d'un trouble bipolaire)	0%	28.57%	60%	p<.20
BAS *drive*	11.4 (1.34)	10.9 (3.48)	10.9 (2.28)	p<.83
BAS *fun seeking*	8.36 (1.78)	10.3 (3.20)	9.40 (3.13)	p<.31
BAS *reward response*	7.71 (1.49)	9.71 (2.81)	10.7 (4.11)	p<.07
BIS	15.4 (3.25)	15.6 (2.82)	13.7 (4.69)	p<.57
TEPS Plaisirs anticipatoires	42.9 (4.85)	39.6 (8.22)	37.8 (7.25)	p<.18
TEPS Plaisirs consommés	41.0 (5.13)	35.1 (7.29)	35.4 (7.12)	p<.08
Rosenberg SES	24.4 (2.59)	26.4 (1.81)	26.0 (3.16)	p<.13
STAI état	26.4 (5.35)	35.1 (4.18)	42.8 (11.7)	**p<.001**
STAI trait	32.7 (5.84)	40.9 (9.58)	57.0 (6.58)	**p<.001**
WHODAS	0.04 (0.04)	0.25 (0.12)	0.44 (0.15)	**p<.001**
Epworth Sleepiness Scale	7.86 (3.51)	7.86 (4.91)	10.3 (4.99)	p<.43
fNART (estimation du QI)	108 (4.90)	108 (6.19)	104 (7.19)	p<.27
Mémoire à court terme – empan endroit	6.57 (0.94)	6.14 (0.69)	6.80 (1.40)	p<.37
Mémoire de travail – empan envers	5.07 (1.27)	5.00 (1.29)	5.50 (1.27)	p<.67

3. Les tâches cognitives

Un aperçu très général des tâches cognitives utilisées dans les études expérimentales mais aussi lors des analyses complémentaires et de la méta-analyse sont présentées dans le tableau 5. Le descriptif précis de chaque tâche est fait dans la méthodologie des différentes études (page 59 pour la MID, page 58 pour la DPX, et page 93 pour l'IE et l'EDM).

Tableau 5 : Aperçu général des tâches cognitives utilisées.

Mécanismes explorés	Nom de la tâche	Études
Motivation	Monetary Incentive Delay task (MID)	Étude 2 Analyses complémentaires Méta-analyse Étude 4
Contrôle cognitif	Dot Pattern Expectancy task (DPX)	Étude 2 Analyses complémentaires Méta-analyse Étude 4
Effort	Induced Effort task (IE)	Étude 3
Prise de décision	Effort-based Decision-Making task (EDM)	Étude 3

4. Le module d'évaluation écologique de l'apathie

Un module d'évaluation écologique de l'apathie est utilisé dans l'étude patients (étude 4). En effet, les questionnaires classiques reposent essentiellement sur les souvenirs que les sujets ont de leurs habitudes quotidiennes et de leurs activités lors des semaines ou mois passés. Dans la mesure où les patients avec des troubles psychiatriques ont souvent des difficultés mnésiques ou une mauvaise conscience de leurs troubles, ces méthodes diagnostiques de l'apathie peuvent parfois se révéler inexactes (Barch & Ceaser, 2012). Pour pallier ce problème, une des solutions est d'interroger les proches ou d'utiliser des outils d'évaluation plus écologiques (c'est-à-dire ancrés dans le quotidien). Par exemple, des alertes sur le téléphone portable permettent de recueillir, sur le moment, des données relatives à l'activité des patients (Moran et al., 2017).

Cette évaluation à domicile a pour objectif de tester les liens potentiels entre la perception subjective que les patients ont de leurs difficultés au quotidien, les déficits objectivés grâce aux études expérimentales et aux évaluations cliniques faites par les psychiatres lors de la visite d'inclusion. Elle permet également d'évaluer dans quelle mesure les difficultés des patients à bien fonctionner au quotidien peuvent être reliées à chaque forme d'apathie. Concrètement, cet outil, inspiré de Moran et al. (2017), permet de demander en temps réel l'activité en cours des sujets, leur niveau de motivation, de plaisir, de planification et d'effort fourni pendant l'activité, grâce à des alertes envoyées sur un téléphone portable (Annexe 2). Les sujets doivent répondre à 4 questionnaires par jour pendant 7 jours consécutifs, envoyés aléatoirement entre 10h et 19h. Dès réception d'un message, les sujets disposent de 15 minutes pour répondre à 5 questions (en moyenne, le questionnaire est complété en une minute). Les réponses sont uniquement des cases à cocher, pour limiter les difficultés d'utilisation et les risques d'abandon.

A ce jour, tous les patients et sujets contrôles ont bien accepté le module, avec un fort taux de participation (plus de 75% de réponses pour tous). Les résultats de ce module, encore très préliminaires et en cours d'analyse, ne sont pas présentés dans le manuscrit.

Résultats

Étude 1

Lafond-Brina, G., & Bonnefond, A. (2022). The stability of multidimensional subclinical apathy during a pandemic and its relations to psycho-behavioral factors. *Scientific Reports*, *12*(1), 2931.

L’annexe 3 présente le matériel supplémentaire de l’étude 1.

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The stability of multidimensional subclinical apathy during a pandemic and its relations to psycho-behavioral factors

Giulia Lafond-Brina[1,2]✉ & Anne Bonnefond[1,2]

Apathy is a clinical symptom prevalent in many neuropsychiatric pathologies. Subclinical apathy is found in 35% of the general population. Despite high prevalence and negative consequences, underlying mechanisms are poorly understood, perhaps because the concept of apathy is one-dimensional. The current investigation aims to address the incidence of multidimensional apathetic trait in three distinct forms in a student population, to specify its determinants and to evaluate its stability during a global pandemic. Two online surveys, conducted 1 year apart on two separate cohorts of university students, with qualitative measures and validated scales. The final analysis included, respectively, 2789 and 1678 students. The three forms of apathetic trait were present, with the same debilitating consequences as apathetic symptom but independent determinants. Executive apathy was predicted by depressive symptoms, emotional apathy by motivational deficit and initiative apathy comprised a mixed executive-emotional form and a pure deficit of action initiation. The three forms of subclinical apathy remained similar in the context of increased depressive symptoms due to a global pandemic. This study confirmed the presence and independence of three forms of subclinical apathy in healthy students, which remained similar even in the light of increased depressive scores. These results shed light on cognitive and neuronal mechanisms underlying multidimensional apathy, allowing new, targeted treatments.

Did you ever hear a teacher call a lazy student 'apathetic'? Or a psychologist call a patient 'apathetic' when they seem indifferent? In everyday language, it can be used in many contexts, but the term 'apathy' also refers to a clinical symptom[1]. Specifically, apathy is defined by quantitative decrease in goal-directed activity in comparison to the person's previous level of functioning (International consensus group—Robert et al.[2]). Different terms, depending mainly on the pathology, are used ('avolition', 'aboulia', 'apragmatism'…) but all describe the same clinical symptom[3,4]. Apathy is a transnosographic symptom, prevalent in many neurological and psychiatric pathologies, and almost half of patients suffer from it[5]. It is an important source of burden, affecting both personal and occupational life[6–8].

In the general population, about 2% of healthy young people[9] and about 6% of healthy older people[10] suffer from apathy, and show apathy scores similar to those of patients (i.e., more than two standard deviations from the population mean) and the same disability. In a recent article from Ang et al.[11], about 35% of a sample of healthy adults presented a milder apathy, often described as subclinical apathy (more than one standard deviation from the mean)[11]. This may represent a trait: i.e., a middle position between asymptomatic healthy people and patients with disabling symptoms. Figure 1 illustrates the differences of subclinical and clinical concepts. Interestingly, it has been shown that subclinical apathy negatively impacts the same personal and occupational dimensions as the clinical symptom: the stronger the apathetic trait, the greater the depression, fatigue and isolation, and the lower the hedonia, empathy and academic success[12,13].

However, despite its high prevalence and negative consequences, no pharmacological or non-pharmacological treatments exist[14], and the underlying mechanisms of apathy are poorly understood[2,15]. One reason for this may be an overlap in diagnostic criteria between apathy and depressive symptoms, which remains a source of confusion. Yet there is evidence that apathy and depressive symptoms are distinct. Clinically, people can suffer from apathy without being depressed or present depressive symptoms without apathy[4]. Neuroimaging results point in the same direction, revealing the involvement of distinct cerebral networks in apathy and depressive

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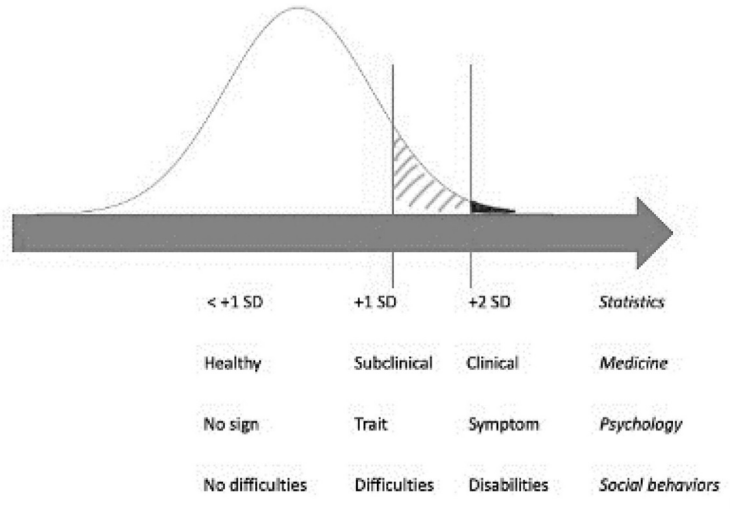

Figure 1. Differences of subclinical and clinical concepts in four fields: statistics, medicine, psychology, and social behaviors.

symptoms[16,17]. A further explanation may be that a one-dimensional concept of apathy still prevails[18,19], despite clinical observations and fMRI findings in brain-damaged patients that both support the idea that apathy is multidimensional[20–22].

In light of these results, Levy and Dubois[23] proposed a multidimensional model of apathy, distinguishing three forms: cognitive/executive, emotional and auto-activation/initiative. According to this model, executive disorders underlie the cognitive form of apathy. Patients with executive apathy report difficulty in planning new action, switching between tasks and focusing on an activity. It may be related to lesions of the dorsolateral prefrontal cortex and the cognitive territory of the basal ganglia. Emotional apathy, characterized by difficulty in expressing and experiencing emotion, empathy, and interest, could be due to motivational disorder. Dysfunctions or lesions in the orbital and medial prefrontal cortex and limbic territories of the basal ganglia may underlie this. Finally, the initiative form, associated with more severe symptoms, is often described as mental emptiness with difficulty in thinking of new things, being spontaneous and initiating social contact, and may be a mixed form, with both motivational and executive difficulties. Lesions or dysfunctions may affect both the cognitive and limbic territories of the basal ganglia or the anterior cingulate cortex.

Although this multidimensional concept was confirmed in patients suffering from neurodegenerative disease[15,24,25] and schizophrenia[26], no studies addressed the three distinct forms of apathetic trait in a healthy population. Confirming its presence in healthy people (i.e., without other associated pathology) and identifying specific determinants for each form would help specify and investigate the respective neural mechanisms.

From this perspective, the present investigation was divided into two studies. The first study had three main aims: (1) to assess the presence of the three forms of apathy (executive, emotional and initiative) in a young and healthy population; (2) to assess links between each form and various factors relating to sociodemographic characteristics, past and ongoing education, general functioning, and psychopathology and (3) to determine which of these factors best predicts each form of apathy. Following the conclusions given by the first study and the emergence of COVID-19 pandemic, we conducted a second study, with three main purposes: (1) to confirm the stability across a year of the distribution of multidimensional subclinical apathy tested in a different sample of young students; (2) to replicate two major predictors (depression and gender) highlighted in Study 1 and (3) to evaluate the contextual stability of subclinical apathy and how it differs from depression in a student population, considering the pandemic context, which is known to be associated with increased depression in young populations[27–29].

Results

The present investigation was based on two studies conducted 1-year apart. Its objectives were to address the incidence of apathetic trait in three distinct forms (executive, emotional and initiative) in a young and healthy student population and to evaluate its stability over time and during a global pandemic. The first study also determined the correlates and predictors of each form from several factors relating to sociodemographic characteristics, past and present education, general functioning, and psychopathology.

Questionnaire	Mean ± standard deviation	Minimum–maximum
DAS total	29.07 ± 8.70	6–64
BDI-II	8.31 ± 6.45	0–38
RSE	27.5 ± 6.21	10–40
TEPS anticipatory	44.8 ± 7.30	10–60
TEPS consummatory	37.2 ± 6.22	8–48

Table 1. Descriptive results of the validated questionnaires. *DAS* The Dimensional Apathy Scale (Radakovic and Abrahams[47]), *BDI-II* The Beck Depression Inventory II (Beck et al. [52]), *RSE* The Rosenberg Self-Esteem Scale (Rosenberg [53]), *TEPS* The Temporal Experience of Pleasure Scale (Gard et al. 2006).

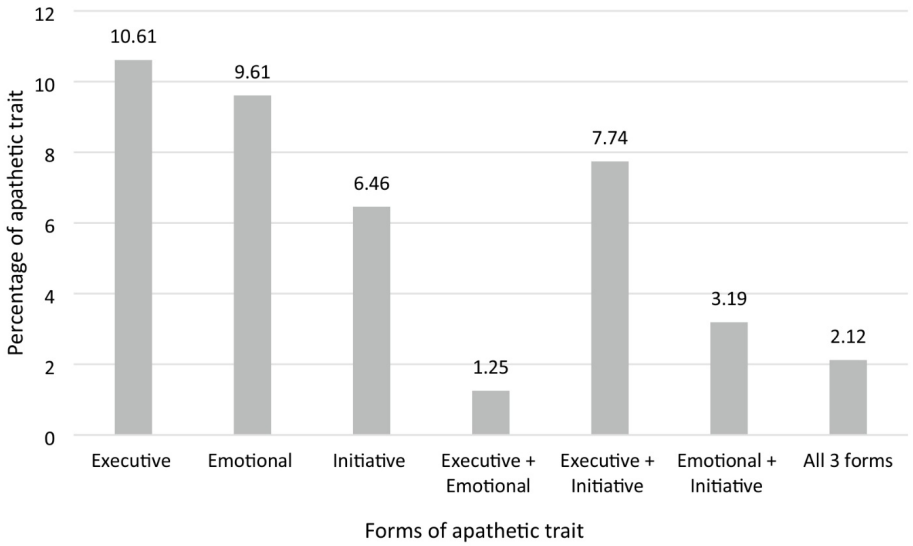

Figure 2. Combinations of multidimensional apathetic trait in the sample.

Study 1. *Presence of the three forms of apathy.* Mean executive apathy score was 11.43 ± 4.77 (range: 0–24). Mean emotional apathy score was 7.46 ± 4.24 (range: 0–24). Mean initiative apathy score was 10.20 ± 3.94 (range: 0–24). The other results on the validated questionnaires are summarized in Table 1.

Among the respondents, 21.2% had an executive apathy trait (cut-off: 16), 16.2% an emotional apathy trait (cut-off: 12) and 20.9% an initiative apathy trait (cut-off: 14); 3.2% had an executive apathy symptom (cut-off: 21), 4.8% an emotional apathy symptom (cut-off: 16) and 3.6% an initiative apathy symptom (cut-off: 18) (see Supplementary data 1 online).

Specifically, 28.68% of respondents presented a single form of apathetic trait, 11.68% combined two forms, and 2.12% had all three forms. Figure 2 illustrates the percentage of combinations for the three forms of apathetic trait.

Among the respondents, 9.44% presented a single form of apathetic symptom (2.55% executive, 4.20% emotional and 2.69% initiative apathy), 1.08% had mixed symptoms (0.18% executive and emotional forms, 0.43% executive and initiative forms, and 0.47% emotional and initiative forms), and none (0.00%) presented all three symptoms together.

Analyses of correlations between the three forms of apathetic trait showed that executive and emotional apathy were no correlated ($r = -0.065$; $p > 0.05$), whereas initiative apathy was positively correlated with both executive ($r = 0.405$; $p < 0.001$) and emotional apathy ($r = 0.205$; $p < 0.001$).

Identification of variables correlated with each form of apathy. Executive apathy. *Sociodemographic* ANOVAs on executive apathy scores revealed that no sociodemographic factor showed a significant, practical effect.

Education ANOVAs on executive apathy scores revealed significant, small effects of type of field ($F(4,2784) = 20.8$; $p < 0.001$; $\eta^2 = 0.029$), level of study ($F(5,2783) = 9.81$; $p < 0.001$, $\eta^2 = 0.017$), Bachelor's degree with honours ($F(5,2783) = 7.26$; $p < 0.001$; $\eta^2 = 0.013$) and choice of field ($F(3,2785) = 26.6$; $p < 0.001$; $\eta^2 = 0.028$). More precisely, Bonferroni tests showed that executive apathy scores were higher for students in the arts and literature field than for those in the other fields ($t(2784) = 8.687$; $p < 0.001$; $d = 0.16$), for first- and second-year undergraduates than PhD degree students ($t(2783) = 5.94$; $p < 0.001$; $d = 0.11$), for students without honours

than for those with honours in their Bachelor's degree ($t(2783) = 4.51$; $p < 0.001$; $d = 0.09$) and for students in a field they had chosen but did not like, compared to those who had chosen their field and liked it ($t(2785) = 8.77$; $p < 0.001$; $d = 0.17$).

General functioning ANOVAs on executive apathy scores revealed significant, large effects of daily pleasure ($F(3,2785) = 148$; $p < 0.001$; $\eta^2 = 0.137$) and dynamism ($F(1,2787) = 324$; $p < 0.001$; $\eta^2 = 0.104$); moderate effects of isolation ($F(2,2786) = 82.1$; $p < 0.001$; $\eta^2 = 0.056$) and small effects of number of initiated social contacts ($F(3,2785) = 23.6$; $p < 0.001$; $\eta^2 = 0.025$), independence ($F(1,2787) = 51.7$; $p < 0.001$; $\eta^2 = 0.018$) and leisure ($F(1,2787) = 47.5$; $p < 0.001$; $\eta^2 = 0.017$). Indeed, executive apathy scores were higher in participants who felt less pleasure in daily life, were less dynamic and suffered from their isolation. They were also socially inhibited and did not perform leisure activities.

Psychopathology Correlation analyses showed that executive apathy scores were strongly positively correlated with depressive symptom score on BDI ($r = 0.548$; $p < 0.001$; 95%confidence interval CI[0.521,0.573]) and negatively correlated with self-esteem score (SES) ($r = -0.489$; $p < 0.001$; 95%CI[− 0.516,− 0.460]).

ANOVAs on executive apathy scores revealed significant, large effects of level of subjective fatigue ($F(3,2785) = 195$; $p < 0.001$; $\eta^2 = 0.174$), moderate effects of self-perceived anxiety ($F(1,2787) = 215$; $p < 0.001$; $\eta^2 = 0.072$) and psychiatric disorder ($F(1,2787) = 171$; $p < 0.001$, $\eta^2 = 0.058$) and small effects of use of psychotropics ($F(1,2787) = 53.6$; $p < 0.001$; $\eta^2 = 0.019$), presence of psychiatric disorders in first-degree relatives ($F(1,2787) = 41.2$; $p < 0.001$; $\eta^2 = 0.015$) and somatic disorder ($F(1,2787) = 40.7$; $p < 0.001$; $\eta^2 = 0.014$). Thus, executive scores were higher in respondents who were exhausted, anxious, had a psychiatric disorder, used psychotropics, had a first-degree relative with psychiatric disorders, or had a somatic disorder themselves.

Emotional apathy. *Sociodemographic* ANOVAs on emotional apathy scores revealed that gender was the only sociodemographic variable to have a large, significant effect ($F(2,2786) = 218$; $p < 0.001$; $\eta^2 = 0.135$). Bonferroni tests revealed that men had higher scores than women ($t(2786) = 20.85$; $p < 0.001$; $d = 0.39$), while there was no difference between men and trans individuals or between women and trans individuals.

Education ANOVAs on emotional apathy scores revealed significant, small effects of type of field ($F(4,2784) = 8.07$; $p < 0.001$; $\eta^2 = 0.010$) and of level of study ($F(5,2783) = 6.21$; $p < 0.001$; $\eta^2 = 0.010$). More precisely, Bonferroni tests showed that emotional apathy scores were higher in the technical and sciences field than the other fields ($t(2784) = 5.08$; $p < 0.001$; $d = 0.09$) and for first years than Master's degree students ($t(2783) = 3.71$; $p < 0.02$; $d = 0.07$).

General functioning ANOVAs on emotional apathy scores revealed small, significant effects of isolation ($F(2,2786) = 39.1$; $p < 0.001$; $\eta^2 = 0.027$), daily pleasure ($F(3,2785) = 17.6$; $p < 0.001$; $\eta^2 = 0.019$), number of social contacts initiated ($F(3,2785) = 17.2$; $p < 0.001$; $\eta^2 = 0.018$) and dynamism ($F(1,2787) = 49.3$; $p < 0.001$; $\eta^2 = 0.017$). Indeed, emotional apathy scores were higher in participants who did not suffer from their isolation, felt less pleasure in daily life and were also socially inhibited and less dynamic.

Psychopathology Correlation analyses showed that emotional apathy scores were negatively correlated with anticipatory pleasure ($r = -0.340$; $p < 0.001$; 95%CI[− 0.372,− 0.306]) and consummatory pleasure ($r = -0.257$; $p < 0.001$; 95%CI[− 0.292,− 0.222]), measured by the Temporal Experience of Pleasure Scale (TEPS).

ANOVAs on emotional apathy scores revealed significant, small effects of anxiety ($F(1,2787) = 27.9$; $p < 0.001$; $\eta^2 = 0.010$). Indeed, emotional apathy scores were higher in respondents who were less anxious.

Initiative apathy. *Sociodemographic* ANOVAs on initiative apathy scores revealed that gender was the only sociodemographic variable to have a significant, small effect ($F(2,2786) = 13.7$; $p < 0.001$; $\eta^2 = 0.010$). Bonferroni tests revealed that men had higher scores than women ($t(2786) = 4.89$; $p < 0.001$; $d = 0.10$), while there was no difference between men and trans individuals or between women and trans individuals.

Education ANOVAs performed on scores of initiative apathy revealed a significant, small effect of honours at Bachelor degree level ($F(5,2783) = 13.0$; $p < 0.001$; $\eta^2 = 0.023$), type of field ($F(4,2784) = 15.0$; $p < 0.001$; $\eta^2 = 0.021$), choice of field ($F(3,2785) = 17.7$; $p < 0.001$; $\eta^2 = 0.019$) and number of repeated class ($F(7,2781) = 5.90$; $p < 0.001$; $\eta^2 = 0.015$). More precisely, Bonferroni tests showed that initiative apathy scores were higher for students without than with honours on their Bachelor's degree ($t(2783) = 6.12$; $p < 0.001$; $d = 0.11$), for students in the arts and literature field rather than in law or health ($t(2786) = 5.55$; $p < 0.001$; $d = 0.10$), for students in a field they had chosen but did not like compared to those who had chosen their field and liked it ($t(2785) = 7.01$; $p < 0.001$; $d = 0.13$) and for students that had repeated three class rather than none ($t(2781) = 4.32$; $p < 0.001$; $d = 0.08$).

General functioning ANOVAs on initiative apathy scores revealed significant, large effects of dynamism ($F(1,2787) = 803$; $p < 0.001$; $\eta^2 = 0.224$), daily pleasure ($F(3,2785) = 194$; $p < 0.001$; $\eta^2 = 0.173$) and number of initiated social contacts ($F(3,2785) = 124$; $p < 0.001$; $\eta^2 = 0.118$); moderate effects of isolation ($F(2,2786) = 127$; $p < 0.001$; $\eta^2 = 0.083$) and frequency of social evenings ($F(3,2785) = 52.3$; $p < 0.001$; $\eta^2 = 0.053$) and small effects of leisure ($F(1,2787) = 100$; $p < 0.001$; $\eta^2 = 0.035$), curiosity ($F(1,2787) = 92.5$; $p < 0.001$; $\eta^2 = 0.032$), independence ($F(1,2787) = 35.1$; $p < 0.001$; $\eta^2 = 0.012$) and frequency of household cleaning ($F(1,2787) = 34.5$; $p < 0.001$; $\eta^2 = 0.012$). Indeed, initiative apathy scores were higher in participants who were less dynamic, felt less pleasure in daily life, were socially inhibited and isolated. They also had fewer social engagements, did not perform leisure activities, were less curious, were more dependent and cleaned their home less frequently.

Psychopathology Correlation analyses showed that initiative apathy scores were positively correlated with depressive symptoms (BDI) ($r = 0.401$; $p < 0.001$; 95%CI[0.370,0.432]) and negatively correlated with self-esteem (SES) ($r = -0.396$; $p < 0.001$; 95%CI[− 0.427,− 0.365]), anticipatory pleasure (TEPS) ($r = -0.366$; $p < 0.001$; 95%CI[− 0.398,− 0.333]) and consummatory pleasure (TEPS) ($r = -0.254$; $p < 0.001$; 95%CI[− 0.279,− 0.210]).

ANOVAs on initiative apathy scores revealed significant, moderate effects of fatigue ($F(3,2785) = 47.2$; $p < 0.001$; $\eta^2 = 0.048$) and small effects of anxiety ($F(1,2787) = 64.3$; $p < 0.001$; $\eta^2 = 0.023$) and psychiatric disorder

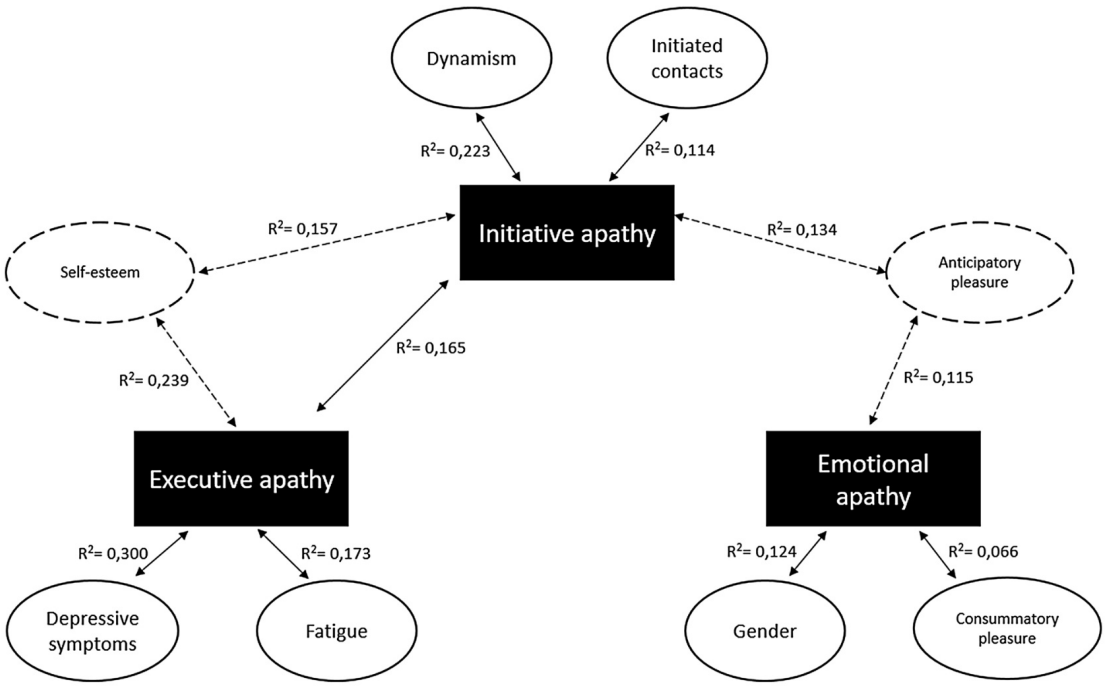

Figure 3. Predictors for the three forms of apathy.

($F(1,2787) = 51.6$; $p < 0.001$; $\eta^2 = 0.018$). Indeed, initiative apathy scores were higher in respondents who felt exhausted, felt anxious and had a psychiatric disorder.

Identification of the predictors of each form of apathy. Figure 3 summarizes survey variables that best predicted each form of apathy.

In a linear regression model with executive DAS score as the dependent variable, depression ($B = 0.210$; $SE = 0.018$; 95%CI[0.175,0.246]; $\beta = 0.284$; $t = 11.58$; $p < 0.001$), initiative apathy ($B = 0.252$; $SE = 0.020$; 95%CI[0.212,0.291]; $\beta = 0.208$; $t = 12.50$; $p < 0.001$), fatigue ($B = 1.038$; $SE = 0.109$; 95%CI[0.822,1.253]; $\beta = 0.168$; $t = 9.45$; $p < 0.001$) and self-esteem ($B = -0.093$; $SE = 0.017$; 95%CI[− 0.128,− 0.058]; $\beta = -0.121$; $t = -5.26$; $p < 0.001$) explained 37.0% of the variance in executive apathy scores ($F(4,2784) = 407$; $p < 0.001$; $AIC = 15,356$).

In a linear regression model with emotional DAS score as the dependent variable, gender ($B = -2.737$; $SE = 0.161$; 95%CI[− 3.052,− 2.422]; $\beta = -0.292$; $t = -17.02$; $p < 0.001$), anticipatory pleasure ($B = -0.135$; $SE = 0.011$; 95%CI[− 0.157, − 0.114]; $\beta = -0.234$; $t = -12.54$; $p < 0.001$) and consummatory pleasure ($B = -0.084$; $SE = 0.012$; 95%CI[− 0.109, − 0.059]; $\beta = -0.124$; $t = -6.73$; $p < 0.001$) explained 21.3% of the variance in emotional apathy scores ($F(3,2785) = 253$; $p < 0.001$; $AIC = 15,284$).

In a linear regression model with initiative DAS score as the dependent variable, dynamism ($B = -2.159$; $SE = 0.145$; 95%CI[− 2.445,− 1.873]; $\beta = -0.548$; $t = -14.81$; $p < 0.001$), executive apathy ($B = 0.194$; $SE = 0.014$; 95%CI[0.166,0.222]; $\beta = 0.235$; $t = 13.61$; $p < 0.001$), self-esteem ($B = -0.059$; $SE = 0.011$; 95%CI[− 0.081,− 0.036]; $\beta = -0.093$; $t = -5.15$; $p < 0.001$), anticipatory pleasure ($B = -0.119$; $SE = 0.008$; 95%CI[− 0.136, − 0.103]; $\beta = -0.221$; $t = -14.08$; $p < 0.001$) and number of contacts initiated ($B = -0.821$; $SE = 0.076$; 95%CI[− 0.970,− 0.673]; $\beta = -0.169$; $t = -10.82$; $p < 0.001$) explained 39.0% of the variance in initiative apathy scores ($F(5,2783) = 356$; $p < 0.001$; $AIC = 14,198$).

Study 2. *Confirmation of the presence of the three forms of apathy.* Of the respondents, 26.5% had an executive apathy trait (cut-off:16), 19.4% an emotional apathy trait (cut-off:12) and 18.4% an initiative apathy trait (cut-off:14); 5.6% had an executive apathy symptom (cut-off:21), 5.8% an emotional apathy symptom (cut-off:16) and 4.1% an initiative apathy symptom (cut-off:18).

Specifically, 31.34% of respondents presented a single form of apathetic trait (14.36% executive, 11.56% emotional and 5.42% initiative apathy), 13.41% combined two forms, and 2.09% had all three forms. Figure 4 illustrates a comparison of the percentage of combinations for the three forms of apathetic trait in first-years students, in both studies.

Among the respondents, 12.22% presented a single form of apathetic symptom (4.41% executive, 5.24% emotional and 2.56% initiative apathy), 1.66% had mixed symptoms (0.18% executive and emotional forms,

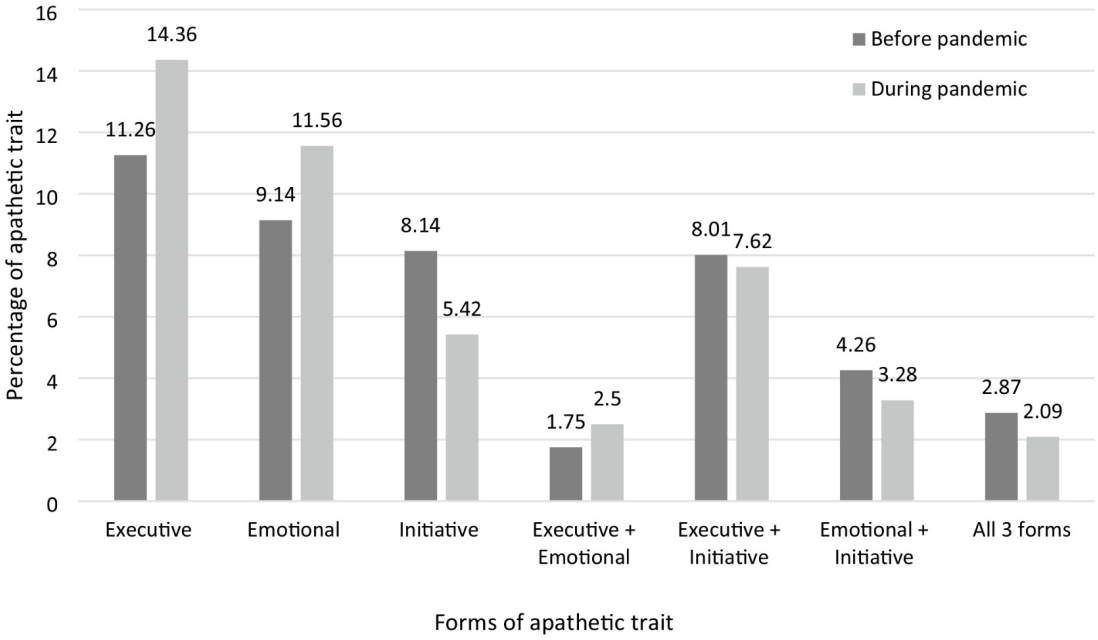

Figure 4. Comparison of combinations of multidimensional apathetic trait in first-year students between before and during the COVID-19 pandemic.

1.07% executive and initiative forms, and 0.42% emotional and initiative forms), and none (0.00%) presented all three symptoms together.

Analyses of correlations between the three forms of subclinical apathy showed that executive and emotional apathy were still not correlated in the second study ($r = -0.037$; $p > 0.05$), whereas initiative apathy was still positively correlated with both executive ($r = 0.459$; $p < 0.001$) and emotional apathy ($r = 0.181$; $p < 0.001$).

Interests of two main predictors: gender and depression. ANOVAs on executive and initiative apathy scores revealed that gender had no significant effect. ANOVAs on emotional apathy scores revealed that gender had a medium, significant effect ($F(1,1676) = 161$; $p < 0.001$; $\eta^2 = 0.088$). Bonferroni tests revealed that men had higher scores than women ($1676) = 12.7$; $p < 0.001$; $d = 0.31$).

Correlation analyses showed that depressive symptom score on the BDI were positively correlated with executive apathy scores ($r = 0.286$; $p < 0.001$; 95%CI[0.242,0.330]) and initiative apathy scores ($r = 0.178$; $p < 0.001$; 95%CI[0.131,0.224]).

In a linear regression model with executive DAS score as the dependent variable, initiative apathy ($B = 0.515$; $SE = 0.026$; 95%CI[0.464,0.566]; $\beta = 0.422$; $t = 19.70$; $p < 0.001$) and depression ($B = 0.423$; $SE = 0.043$; 95%CI[0.339,0.507]; $\beta = 0.211$; $t = 9.86$; $p < 0.001$) explained 25.5% of the variance in executive apathy scores ($F(2,1675) = 286$; $p < 0.001$; $AIC = 9720$).

In a linear regression model with emotional DAS score as the dependent variable, gender ($B = -2.585$; $SE = 0.206$; 95%CI[−2.988,−2.182]; $\beta = -0.594$; $t = -12.58$; $p < 0.001$) and initiative apathy ($B = 0.178$; $SE = 0.024$; 95%CI[0.130,0.225]; $\beta = 0.169$; $t = 7.35$; $p < 0.001$) explained 11.6% of the variance in emotional apathy scores ($F(2,1675) = 110$; $p < 0.001$; $AIC = 9499$).

In a linear regression model with initiative DAS score as the dependent variable, executive apathy ($B = 0.383$; $SE = 0.017$; 95%CI[0.349,0.417]; $\beta = 0.467$; $t = 22.08$; $p < 0.001$) and emotional apathy ($B = 0.189$; $SE = 0.020$; 95%CI[0.150,0.229]; $\beta = 0.199$; $t = 9.38$; $p < 0.001$) explained 25.0% of the variance in initiative apathy scores ($F(2,1675) = 280$; $p < 0.001$; $AIC = 9062$).

Stability of the three forms of apathy. For first-year students, Table 2 presents a comparison of the scores of the three forms of subclinical apathy and depressive symptoms, in 2020 and 2021. Only BDI–II score showed a large significant difference in the new cohort tested 1 year later, with an increase of 5.37 points (BDI 2021–2020 = 14.52–9.15).

Discussion

The results revealed the presence and stability of the three forms of apathetic trait in students over a year and identified form-specific determinants, confirming their independence. In addition, by revealing for the first time a specific link between one form of apathy (the executive form) and depressive symptoms, they shed new light

Questionnaire	February 2020		February 2021		Stats
	Mean ± standard deviation	Minimum–maximum	Mean ± standard deviation	Minimum–maximum	
DAS total	29.89 ± 9.11	8–64	29.64 ± 9.28	7–60	Student's t(2475) = 0.63; p = 0.528
					Cohen's d = 0.03; 95% CI [− 0.057;0.111]
DAS executive	11.86 ± 4.75	1–23	12.14 ± 5.07	0–24	Welch's t(1663) = − 1.34; p = 0.180
					Cohen's d = − 0.06; 95% CI [− 0.141;0.028]
DAS emotional	7.65 ± 4.31	0–24	7.79 ± 4.35	0–24	Student's t(2475) = − 0.786; p = 0.432
					Cohen's d = − 0.03; 95% CI [− 0.118;0.050]
DAS initiative	10.38 ± 4.10	0–24	9.71 ± 4.15	0–24	Student's t(2475) = 3.81; p < 0.01
					Cohen's d = 0.164; 95% CI [0.078;0.248]
BDI–II	9.15 ± 6.80	0–38	14.52 ± 2.53	2–36	Welch's t(905) = − 21.6; p < 0.001
					Cohen's d = − 1.22; 95% CI [− 1.33;− 1.12]

Table 2. Comparison of scores of the validated questionnaires for first-year students, in 2020 and 2021. *DAS* The Dimensional Apathy Scale (Radakovic and Abrahams[47]), *BDI-II* The Beck Depression Inventory II (Beck et al.[52]).

on the overlap between apathy and depression that continues to cause confusion. Taken together, the present results open new avenues to explore to develop new, targeted therapeutic treatments.

Subclinical apathy was present in three distinct forms in a student population and associated with the same debilitating consequences as apathetic symptom. The present investigation, based on two studies involving, respectively, 2789 and 1678 students, confirmed the presence of subclinical apathy in three distinct forms in a student population. About 40% of respondents presented an apathetic trait, in agreement with the 35% found in the only other study in a similar population[11]. About 10–14% of respondents presented an apathetic symptom, which was far above the 2% found in other studies with young people[9]. However, in these studies, no distinction was made between the three forms of apathy and the scales used were different: 2% may correspond to participants with the most severe form of apathy (i.e., initiative apathy).

An exploration of factors related to education and general functioning clearly revealed, in agreement with some other studies, that subclinical apathy, of whichever form, was associated with debilitating consequences in academic and daily life[13]. Initiative apathy was the most debilitating form in daily life, and emotional apathy specifically in social life. As previously shown, all negative repercussions were similar, although perhaps differing in intensity, to those of the apathetic symptom[19,30]. The present results are thus completely consistent with the usual definition of apathy and support keeping the overarching term "apathy" for all three forms, despite their not having the same underlying mechanisms.

Regarding the population of students, our results show that the dominant form of apathy differed according to field of study, suggesting that course choices may be related to the difficulties associated with the specific form of apathy affecting a student. Students with executive or initiative apathy were more often studying art and literature whereas students with emotional apathy more often studied technical subjects and sciences. This question, as yet unexplored, could be an interesting object of investigation for educational scientists.

From the independence of the three forms of apathy to a better characterization of each. Our results provide strong evidence for the independence of the three forms of apathy. This is because they highlight that the majority of participants with a subclinical apathy presented a single form of apathy. They also show the existence of specific correlates or predictors for each of the three forms. Of the respondents with apathetic trait, 10–15% had only executive apathy, 10% only emotional apathy and 5–8% only initiative apathy. We expected a lower prevalence of the third form in a young healthy population because it is the most severe form, associated with greater disability[31].

Most factors specifically linked to a form of apathy concerned psychopathology. Regarding executive apathy, our results suggest that it may be a secondary form. It was the only form specifically linked to psychiatric or somatic disorders and the only one to be predicted by depressive symptoms and fatigue. Executive apathy may

therefore be secondary to another disorder, potentially modulated by executive deficits. In the literature, executive apathy has been linked to deficits in executive functions (Alzheimer: Perri et al.[25]; Schizophrenia: Raffard et al.[26]), executive deficits which also correlate with depression[32,33] and fatigue[34,35]. These results cast doubt on the nature of executive apathy, but also shed light on the confusion between apathetic and depressive symptoms, suggesting that the overlap may be specific to the executive form.

Emotional apathy, in contrast, was the only form to be predicted by the two motivational components: consummatory and anticipatory pleasure. However, only consummatory pleasure was specific to emotional apathy; anticipatory pleasure also predicted the initiative apathy. Emotional apathy was therefore the only form linked to a deficit of hedonic pleasure in the moment. To our knowledge, the only link previously highlighted between apathy and motivation was non-specific: a link between deficit of anticipatory pleasure and one-dimensional apathy[36]. Our results revealed the importance of considering all the components of motivation to improve understanding of apathy in its multidimensional form.

Finally, and interestingly, our results may suggest the presence of two subtypes of initiative apathy: a mixed form with both executive and emotional deficits, and a specific deficit. Initiative apathy was correlated with the two other forms of apathy over 2 years. Moreover, in 60–70% of cases, initiative apathy was present in association with another form. This mixed form hypothesis is also supported by neuroanatomical and clinical studies in patients with neurodegenerative disease, especially Parkinson's and Alzheimer's[25,37,38]. These studies showed a combination of cognitive and emotional deficits and the presence of lesions characteristic of the two other forms. The second subtype of initiative apathy could be a pure deficit in action initiation, the last step before action is taken. Although the percentage was low, the fact remains that 5–8% of our sample had initiative apathy without any other associated form. Such pure initiative apathy has previously been highlighted in amyotrophic lateral sclerosis, confirming the existence of this pure form as a symptom[39,40] related to specific cerebral regions (anterior cingulate cortex and supplementary motor area) in patients[24,41] and in healthy people[31,42].

The stability of subclinical apathy and the effects of the COVID-19 pandemic. The three dimensions of subclinical apathy were stable under different circumstances. Indeed, before and during a global pandemic, there were no major variations of means, standard variations, correlates, predictors and cut-off for apathetic trait and symptom. Only initiative apathy as a pure deficit of action initiation showed a slight decrease in the second study. However, social distancing and lockdown could explain this reduction, by changed social norms and reduced everyday activities for everyone.

Furthermore, the stability of apathy contrasts with the sharp increase in depression. One year later, depression was still a specific predictor of executive apathy. However, in the second study, the rise of depression during the COVID-19 pandemic allowed us to improve our knowledge of the link between executive apathy and depression. Depressive symptoms doubled over 1 year in students, probably because of lockdowns, curfews and psychological difficulties induced by the COVID-19 pandemic[43,44], but executive apathy remained stable. Thus, even if depressive symptoms are a strong predictor of executive apathy, it appears that executive apathy remains a separate symptom with other explanatory factors.

What role do gender and self-esteem play in apathy? To our knowledge, no other studies explored the link between gender and a specific form of apathy. However, others have revealed a positive correlation between male gender and one-dimensional apathy[30,45]. Our results showed more precisely that men presented more emotional apathy than women and trans individuals whereas transgender experienced more executive apathy than cisgender (male and female). The male gender was still a predictive factor of emotional apathy 1 year later. Although no real explanation for this association is yet apparent, controlling for gender seems important for studying apathy.

The identification of self-esteem as a predictor for executive and initiative apathy may offer new perspectives for non-pharmacological therapeutic interventions focused on enhancing self-esteem when these two forms of apathy are present. Two previous studies, involving patients with traumatic brain injury[41] and psychotic disorders[36], showed that low self-esteem, by inducing demotivating beliefs, may prevent people from undertaking new or complex tasks, thereby inducing apathy.

Conclusion

This study confirmed the existence and stability of multidimensional subclinical apathy in young healthy students under different circumstances (global pandemic vs not) and showed that apathetic trait was associated with the same debilitating consequences in all spheres of daily life as apathetic symptom. By identifying specific characteristics for three forms of apathy, the present results may aid exploration of the mechanisms underlying multidimensional apathy (especially self-esteem, anticipation, and motivation) in healthy people and in various pathologies to propose new, targeted therapies.

Methods

The current investigation, based on two studies, aims to address the incidence of multidimensional apathetic trait in three distinct forms (executive, emotional and initiative) in a student population, to specify its determinants and to evaluate its stability during a global pandemic. Two online surveys, conducted 1 year apart, tested 2789 and 1678 different university students, with qualitative measures and validated scales.

Participants. Participants were recruited in a French University. All registered students received an email giving them the opportunity to participate in an online survey about 'Personality in university students', created on LimeSurvey. To participate, the only criteria were to be a student, aged between 18 and 28 years and to

	Study 1 (2020)	Study 2 (2021)
Number	2789 participants	1678 participants
Gender	729 males (26.1%), 2040 females (73.1%), 20 trans individuals (0.7%)	648 males (38.6%), 1030 females (61.4%)
Age	20.8 years (± 2.2); range 18–28	19.2 years (± 1.4); range 18–22
Level of study	First year: 799 (28.6%)	First year: 1678 (100%)
	Second year: 596 (21.4%)	
	Third year: 460 (16.5%)	
	Fourth year: 483 (17.3%)	
	Fifth year: 338 (12.1%)	
	PhD: 113 (4.1%)	
Field of study	Arts, literature, languages: 382 (13.7%)	–
	Law, economy, politics: 599 (21.5%)	
	Health: 434 (15.6%)	
	Humanities and social: 728 (26.1%)	
	Technological sciences: 646 (23.2%)	

Table 3. Sociodemographic characteristics of the sample.

be a native French-speaker. All participants gave electronic informed consent, and the study was approved by the University review board (UNISTRA/CER/2020-13) and the French data protection authority (CNIL). They weren't paid for their participation.

In total, for study 1, 3144 students (26.5% male) completed the survey. After eliminating 355 respondents who did not match the criteria, 2789 students constituted the study sample. For study 2, 1678 new first-year students (38.6% male) constituted the study sample (see Table 3 for sociodemographic characteristics of the studies).

Online survey. For Study 1, the survey was divided in four parts: sociodemographic characteristics, education, general functioning, and psychopathology (see Supplementary data 2 online). All these factors were assessed with qualitative measures. Four validated scales were added to complete the assessment of psychopathology. The names and themes of the four questionnaires were not specified online.

(1) The Dimensional Apathy Scale (DAS)[47] is a 24-item scale assessing the severity of the 3 forms of apathy (Executive, Emotional and Initiative apathy). Items are scored on a 4-point Likert scale based on the frequency of occurrence of the apathetic symptoms in the previous month. 3 scores are obtained, one for each form of apathy (based on 8 items each). A high score (maximum, 24) indicates a severe form of apathy.
(2) The Beck Depression Inventory II (BDI-II) (Beck et al.[52]) is a 13-item scale assessing the severity of depressive symptoms. Each item is score from 0 to 3. A high global score (maximum, 39) indicates severe depression.
(3) The Rosenberg Self-Esteem Scale (RSE) (Rosenberg[53]) is a 10-item scale assessing self-esteem. Each item is score from 1 to 4. A low global score (minimum, 10) indicates severe self-esteem disorder.
(4) The Temporal Experience of Pleasure Scale (TEPS) (Gard et al. 2006) is an 18-item scale assessing anticipatory (10 items) and consummatory (8 items) pleasure. Each item is score from 1 to 6. Anticipatory pleasure refers to pleasure due to active search for or anticipation of a pleasant activity (score range: 10 to 60). Consummatory pleasure refers to pleasure directly due to accomplishing a pleasant activity (score range: 8 to 48). A low score for each subscale indicates pleasure disorder[46].

For study 2, the survey was divided into two parts: sociodemographic characteristics and psychopathology. Two validated questionnaires were used to assess the psychopathology: the DAS[47] and the BDI-II (Beck et al.[52]).

See Supplementary data 3 online for correlations between all the questionnaires for both studies.

Statistical analysis. Each participant had three DAS subscores: one for each form of apathy.

To determine the percentage of participants with a subclinical apathy, a cut-off was calculated for each subscore, based on the mean and the standard deviation of studies samples (Study 1, 2789 students, Study 2, 1678 first-year students). The suggested cut-offs were + 1 standard deviation from the mean for subclinical apathy/apathetic trait and + 2 standard deviation from the mean for clinical apathy / apathetic symptom[11,39,48].

Both studies had large sample size, so according to the Central Limit Theorem, data could be approximated by a normal distribution and parametric tests were used[49].

Pearson correlation tests were implemented between DAS scores.

To identify variables correlating with each form of apathy, Pearson correlation tests were implemented with continuous variables; ANOVAs and Bonferroni post-hoc tests were used with categorical variables.

Exploratory approach was used for regressions analyses since the selection of predictor variables was not based on a priori hypotheses. Predictors of each form of apathy were specified by multiple linear regression analyses, using one DAS score as reference and all the other variables from the online survey as possible regressors of interest (see Supplementary data 4 online). The purpose was to determine which variables in the survey

most influenced each form of apathy, thanks to the Akaike Information Criterion (AIC). The smaller the AIC value, the better the model fit, using the fewest possible variables. R-square values (the percentage variation of the reference explained by the regressor of interest) were calculated.

In study 2, to compare questionnaire scores across time, Student's t test was used when there was an assumption of equal variances with Levene's test ($p > 0.05$); Welch's t test was used when there was a violation of the assumption of equal variances with Levene's test ($p < 0.05$).

The statistical significance level was set at 0.05. As both studies have a large sample size, effect size measures were always added, to prevent big data bias and to analyze only practical effects[50,51]. For correlation squared (R^2 and η^2) used in regressions and ANOVA, practical effect was small around 0.01, medium around 0.06 and large from 0.14. For correlation coefficient (r) used in correlations, practical effect was small around 0.10, medium around 0.30 and large from 0.50. For standardized mean difference (d) used in t-test, practical effect was small around 0.20, medium around 0.50 and large from 0.80. Only practical significant results are described in the Results section below.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation (Research ethics committee of the University of Strasbourg—UNISTRA/CER/2020-13) and with the Helsinki Declaration of 1975, as revised in 2008.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Received: 11 November 2021; Accepted: 4 February 2022
Published online: 21 February 2022

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Author contributions

Both authors designed the study. G.L-B. did the statistical analysis and wrote the first draft of the manuscript. Both authors were involved in the writing of this draft.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors, except a ministerial PhD scholarship.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-022-06777-5.

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Résumé des principaux résultats

Les deux enquêtes en ligne, auxquelles 4 467 étudiants ont répondu, ont permis de mettre en évidence l'existence des trois sous-formes d'apathie du modèle multidimensionnel de Levy et Dubois (2006) dans la population jeune. Concernant le trait apathique, les phénotypes purs d'apathie exécutive et d'apathie émotionnelle sont les plus fréquents, respectivement 12.4 % et 10.58 %. Le symptôme apathique (intensité clinique équivalente à celle rapportée par des patients) est, quant à lui, présent chez 2 à 5 % des participants. En termes de conséquences, quelle que soit la forme d'apathie, le trait est associé à des difficultés académiques et dans la vie quotidienne, qui sont accentuées en cas de symptôme. L'apathie d'initiation est la forme associée aux difficultés les plus sévères. 6 % des participants ont un phénotype pur d'apathie d'initiation, tandis que 11 % ont une apathie d'initiation associée à une autre forme. L'apathie d'initiation est également la seule forme d'apathie corrélée avec les deux autres formes.

Concernant les prédicteurs - bien que certains soient communs à l'apathie d'initiation et aux deux autres formes -, la mise en évidence de prédicteurs spécifiques à chaque forme met en exergue la relative indépendance nosologique de ces trois formes d'apathie. L'apathie exécutive est prédite par des symptômes dépressifs et la fatigue, ce qui pourrait suggérer que l'apathie exécutive soit secondaire à une vulnérabilité psychologique induisant des difficultés de contrôle cognitif. Malheureusement, aucune mesure de contrôle cognitif n'a été faite dans cette étude. L'apathie émotionnelle est prédite par des troubles motivationnels, de *liking* et de *wanting*, ce qui confirme bien l'intérêt d'aller explorer ces processus. Le genre masculin est également un prédicteur de l'apathie émotionnelle. Enfin, l'apathie d'initiation est prédite par des difficultés sociales et un manque de dynamisme, ce qui correspond à la définition même de cette forme mais apporte peu d'éléments quant aux mécanismes sous-jacents.

Étude 2

Lafond-Brina, G., Pham, B. T., & Bonnefond, A. (under review). Specific mechanisms underlying executive and emotional apathy: A phenotyping study. *Psychiatric Research*.

L'annexe 4 présente le matériel supplémentaire de l'étude 2.

Specific mechanisms underlying executive and emotional apathy: A phenotyping study

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Abstract

Apathy is a behavioral symptom prevalent both in neuropsychiatric pathologies and in the healthy population. However, the knowledge of the cognitive and neural mechanisms underlying apathy is still very limited, even if clinical and fMRI data support the existence of three forms of apathy (executive, emotional, initiative). These forms could be explained by the alteration of specific mechanisms. This present study's aim is to specify the cognitive and neuronal mechanisms of executive and emotional apathy. We used an EEG study conducted on 68 subjects comprising two groups of young people with specific executive or emotional phenotypes of apathy and one group with no apathy. Despite having symptom of apathy, participants were free of any neurological, metabolic, or psychiatric diagnoses and with high education. Two tasks were used: the DPX for cognitive control and the MID for motivation. Our results showed that distinct mechanisms underlie these two forms of apathy, and, for the first time, we specified these mechanisms. A deficit of the proactive control mode, reflected by a reduced probe-N2 amplitude in AY trials, underlies the executive form of apathy ($p<.03$), whereas liking motivational blunting, highlighted by a reduced LPP amplitude for financial loss, characterizes the emotional form ($p<.04$). The main limit of the results is that generalizability to the general population may be reduced since the apathetic samples were chosen for having a specific form of apathy. To conclude, better knowledge of these mechanisms informs new, more targeted treatments, both pharmacological and non-pharmacological, necessary for reducing the debilitating consequences of apathy.

Keywords

Motivation; Cognitive control; EEG; Avolition; Executive functions; Treatments

Introduction

Apathy is a clinical symptom defined by a quantitative decrease in an individual's goal-directed activity compared to their previous level of functioning (International consensus group - Robert et al., 2018). This symptom is transnosographic, prevalent in many neurological, neurodegenerative, and psychiatric pathologies. For example, apathy affects about 40-50% of patients suffering from stroke, multiple sclerosis, Parkinson, Alzheimer or schizophrenia (Manera et al., 2019; Mulin et al., 2011). It is also a significant personal and professional burden (Tsang et al., 2010; van Reekum et al., 2005). Apathy can also occur in the healthy population, where it is less frequent but associated with the same debilitating consequences in all spheres of daily life. Indeed, about 2% of young people and 6% of older people have apathy scores similar to those of patients (i.e., scores higher than two standard deviations from the population mean) (Brodaty et al., 2010; Pardini et al., 2016). Furthermore, along a continuum from healthy behavior to apathetic symptom, milder apathy trait, often described as subclinical apathy (i.e., scores higher than one standard deviation from the population mean), has even been reported in about 30%-40% of the general population, stable at one-year intervals (Ang et al., 2017; Lafond-Brina & Bonnefond, 2022). Despite apathy's high prevalence and negative consequences, the scientific knowledge of the cognitive and neural mechanisms underlying apathy is very limited (Radakovic & Abrahams, 2018; Robert et al., 2018). However, its improvement is essential for the development of new, more targeted treatments, both pharmacological and non-pharmacological, in order to help to reduce the debilitating consequences of apathy.

The limited knowledge we have about the mechanisms of apathy is undoubtedly linked to the prevailing one dimensional concept of apathy (Dickson & Husain, 2022). However, clinical and fMRI data, mainly collected from studies on patients suffering from brain damage and neurodegenerative diseases (Bhatia & Marsden, 1994; J. L. Cummings, 1993; Dickson & Husain, 2022; Pagonabarraga et al., 2015; Radakovic & Abrahams, 2018; Stuss et al., 2000), support the existence of at least three forms of apathy: executive/cognitive, emotional and initiative/auto-activation apathy. The alteration of specific mechanisms could underly these different forms of apathy (R. Levy & Dubois, 2006). Executive apathy manifests as difficulty in planning new action, switching between tasks, or focusing on an activity. It is related to dysfunctions of the dorso/ventrolateral prefrontal cortex and cognitive territory of the basal ganglia (mainly the dorsal caudate nucleus) and may be caused by executive/cognitive control disorders (Miller & Cohen, 2001; Nejati et al., 2018). Emotional apathy is characterized by difficulty in experiencing and expressing emotion, empathy, and interest. It is associated with dysfunctions of the orbital and ventromedial prefrontal cortex, and the limbic territories of the

basal ganglia (especially the ventral striatum) and may be underpinned by motivational deficits (Kringelbach, 2005; Kringelbach & Rolls, 2004; Zald, 2007). Finally, initiative apathy is often described as mental emptiness with difficulty in thinking of new things, being spontaneous, and initiating social contact. It is associated with dysfunctions affecting interconnected regions associated with executive and emotional apathy and/or the anterior cingulate cortex and it may be a mixed form of apathy (Le Heron et al., 2018). This hypothesis for specific mechanisms underlying each form of apathy has never been directly tested.

To date, only studies using neuropsychological tests, known to have strong psychometric properties but low process specificity, and/or validated questionnaires have confirmed that impairments of specific cognitive processes underpin executive and emotional forms of apathy, whereas initiative apathy is underpinned by the sum of the cognitive processes altered in the two other forms [in patients suffering from neurodegenerative diseases (Perri et al., 2018), schizophrenia (Raffard et al., 2016), and in subclinical apathy in the healthy population (Cuvillier & Bayard, 2021; Lafond-Brina & Bonnefond, 2022)]. Only the unidimensional approach of apathy has been used to explore neural mechanisms of apathy. Yet, several electrophysiological correlates of cognitive control or motivational processes, and more precisely cognitive event-related evoked potentials (ERP), have previously been linked to the severity of unidimensional apathy. In cognitive tasks allowing the exploration of cognitive control processes, especially the proactive and reactive modes, some specific ERP, like the cue-P3b and probe-P3a, had seen their amplitude negatively correlated with the severity of unidimensional apathy (Daffner et al., 2000, 2001; Mathis et al., 2014; Yamagata et al., 2004). However, the P3b results were heterogeneous between the pathologies (Davis et al., 2022; Vignapiano et al., 2016; Yamagata et al., 2004). In the same way, in motivational tasks allowing the exploration of wanting and liking motivational processes, relatives respectively to the anticipation of a rewarded cue and the hedonic treatment of a rewarded feedback, the amplitude of two ERP had been linked to the severity of unidimensional apathy : the feedback-P3a in healthy subjects (Takayoshi et al., 2018) and the LPP in Parkinson disease (Dietz et al., 2013). Finally, the heterogeneity of the ERP linked to unidimensional apathy could be due to differences between pathologies, but also to specificities associated with each form of apathy (Kos et al., 2016).

Therefore, this present study's main aim is to specify the cognitive and neuronal mechanisms underlying executive and emotional forms of apathy using experimental cognitive and motivational paradigms combined with EEG. We hypothesize specific altered processes in the executive and emotional forms of apathy: a specific impairment of the proactive control process in executive apathy and a specific impairment of the wanting and/or liking motivational components in emotional apathy.

Method

Subjects

68 university students', native French speakers aged between 18 and 28 years, were recruited based on their specific phenotypes of multidimensional apathy. Three groups of participants were created: one group of 22 participants with an executive apathy phenotype, one group of 22 participants with emotional apathy phenotype, and one group of 24 participants with non-apathy. Participants with a history of neurological, metabolic, sensorial, or psychiatric disorders; a history of psychiatric disorders in first-degree relatives; consumption of psychoactive drugs and cannabis during the last three months; or general anesthesia in the past three months were excluded based on a self-administered clinical questionnaire and then, a short interview with a certified neuropsychologist. Moreover, students with mild or severe depressive symptoms, as determined by the self-report Beck Depression Inventory II (BDI-II; score ≥16) (Beck et al., 1996), were excluded. No participant dropped out. The study protocol was approved by the local ethics committee (University review board: UNISTRA/CER/2020-13) and the selected subjects were paid for their participation.

The executive and emotional apathy participants were included because they specifically presented one form of apathy but not the two other forms of apathy (see Table 1 for the criteria). To do that, participants completed the self-report Dimensional Apathy Scale (DAS) (Radakovic & Abrahams, 2014). The DAS is a 24-item scale assessing the severity of executive, emotional, and initiative apathy. Items are scored on a 4-point Likert scale based on the frequency of occurrence of apathy symptoms in the previous month (1 = "hardly ever"; 4 = "almost always"). For each subscore, a cut-off based on the mean and the standard deviation of the total sample was calculated (Lafond-Brina & Bonnefond, 2022). Cut-offs were +1 standard deviation from the mean for trait apathy and +2 standard deviation from the mean for symptom apathy, as recommended (Angus et al., 2017; Muneaux, 2018).

A part the DAS and the BDI, they also completed another self-report questionnaire: the Temporal Experience of Pleasure Scale (TEPS) (Gard et al., 2006). The TEPS is an 18-item scale designed to measure motivational trait dispositions in both anticipatory and consummatory experiences of pleasure. For a brief neuropsychological measure of their working memory, the digit span task from the WAIS-III was realized by a certified neuropsychologist (Wechsler, 1997).

Table 1: Criteria for the constitution of the three groups of participants. Values are the cut-offs used for each questionnaire (the DAS, the Dimensional Apathy Scale; the BDI-II, the Beck Depression Inventory II).

Cut-offs	Controls	Executive apathy	Emotional apathy
DAS executive	< 16	Trait [16;20] Symptom [21;24]	< 16
DAS emotional	< 12	< 12	Trait [12;16] Symptom [17;24]
DAS initiative	< 14	< 14	< 14
BDI-II	< 16	< 16	< 16

Tasks and behavioral measures

The participants completed in a counterbalanced order the Dot Pattern Expectancy (DPX) task (MacDonald III et al., 2005) and the Monetary Incentive Delay (MID) task (Knutson et al., 2000). The DPX is a dot-pattern cue-probe detection task that allows for the exploration of cognitive control processes in a dual time framework, proactive and reactive modes, corresponding respectively to anticipatory and adaptive control modes (Boudewyn et al., 2019; Braver et al., 2009). The MID task is a simple detection task that allows the study of the motivational "wanting" and "liking" components, which reflect, respectively, the anticipation of a reward and the feeling of pleasure when obtaining that reward (Angus et al., 2017; Berridge et al., 2009; Gard et al., 2006). Both tasks lasted about 30 minutes and were divided into three blocks of 100 trials. These blocks were separated by short breaks and preceded by a training of a few minutes until the participants achieved success in six consecutive trials.

The DPX is a dot-pattern cue-probe detection task in which dots combinations are presented one by one on the screen: black dots combinations (A or B dot cues) alternated with blue dots combinations (X or Y dot probes) (Figure 1). The subjects had to respond after the blue probes by pressing the right button in cases presenting the target sequence ("A cue – X probe" dots combination trials). In all other cases, they had to press the left button. Thus, four types of trials were differentiated: AX, AY (where Y is any other blue dot combination apart from X), BX (where B is any other black dot combination apart from A), and BY trials. The target sequence (AX) was more frequent (70% of trials) than the other sequences (12% for AY, 12% for BX and 6% for BY), leading participants to develop a strong expectation of making a "match" in response to probes following 'A' cues, and to 'X' probes generally.

For each type of trial, reaction times (RT) and the rate of false alarms (FA) (i.e., pressing on the wrong button) were calculated. The total number of omissions (absence of response) and the Behavioral Shift Index (for RT and for rates of FA, BSI = (AY-BX)/(AY+BX)) were also

calculated. Another comparison was made to evaluate more specifically the goal maintenance; the z-transform of the FA in AX and BX trials, Z(FA $_{AX}$)+Z(FA $_{BX}$), was compared to the z-transform of FA in AY trials, Z(FA $_{AY}$). Subjects with a good goal maintenance should have few FA on AX and BX trials and more on AY trials, because they will use the information provided by the cue to prepare their response. In contrast, subjects with poor goal maintenance should have the opposite profile (i.e., few FA on AY trials and more on AX and BX trials) because they will not take into account the cue and thus will tend to respond target to the X.

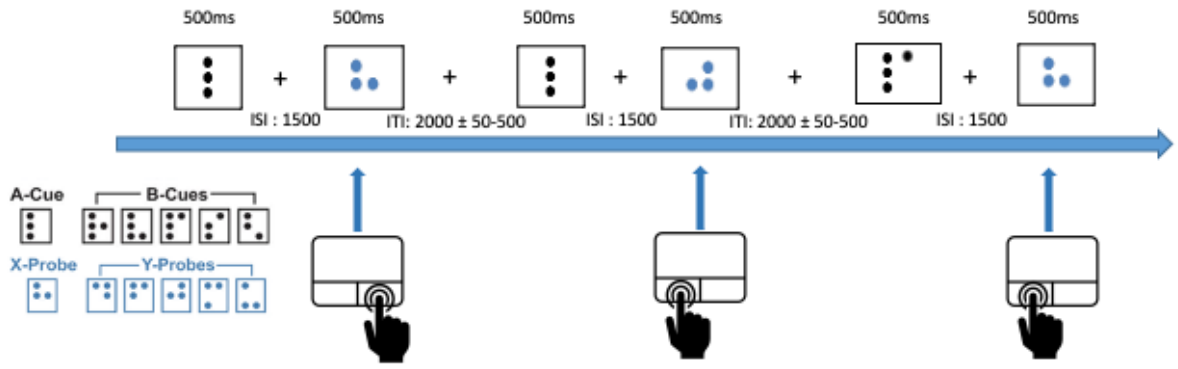

Figure 1: The DPX task

The MID is a visual detection task in which subjects are required to respond as quickly as possible by pressing a response button at the presentation of the probe (a blue cross) (Figure 2). An incentive (win or loss of 15 cents) or neutral cue (no win and no loss) is presented before the probe. In each block, the three types of cues (win, loss, neutral) are presented in a random order and in similar proportions (33%, 33% and 34%, respectively). Either positive (a green disc) or negative (a red disc) feedback is given after the response. It informs the subject if his or her response was completed with enough speed. This performance feedback also informs the participant about the obtained reward in case of incentive cues. After a win cue, positive feedback indicates an actual monetary win, whereas negative feedback indicates the absence of a monetary win. After a loss cue, positive feedback indicates the absence of monetary loss, whereas negative feedback indicates an actual monetary loss. After a neutral cue, positive and negative feedback indicates no monetary variation. The feedback judgment criterion is adjusted to the individual average detection speed throughout the task, allowing approximatively 60% of positive feedback (mean success rate: 61.44%).

RT, rate of anticipations (response before the presentation of the probe) and number of omissions (absence of response) were calculated for the three types of cues.

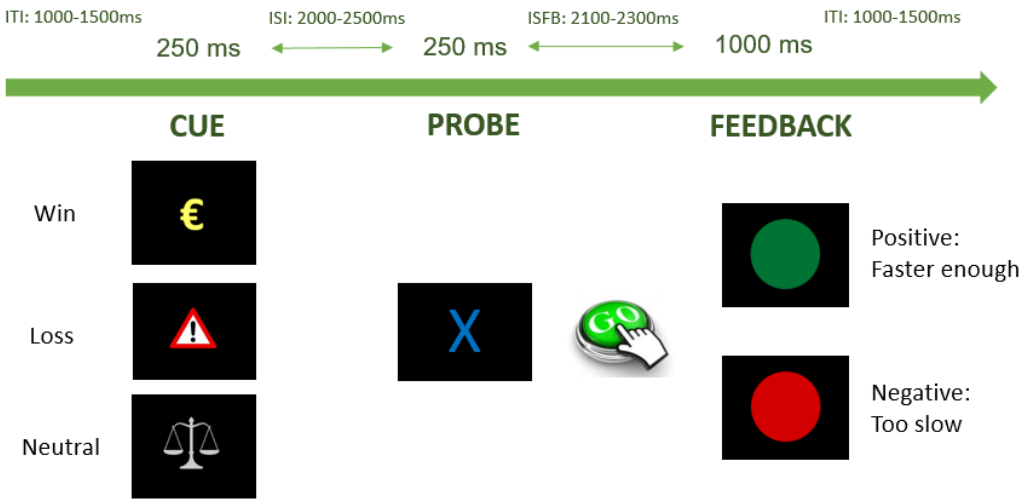

Figure 2: The MID task

Electrophysiology

1) *Electrophysiological preprocessing*

Electroencephalograms (EEGs) were recorded using 64 Ag/AgCl BioSemi ActiveTwo System (Amsterdam, Netherlands) electrodes mounted on an elastic cap according to the standard 10-10 system and with a 0.01-500 Hz band-pass filter. BrainVision Analyzer 2.1 software was used to analyze the data offline at 2048 Hz with a 0.05 Hz off-line high-pass filter, a 30 Hz off-line low-pass filter and a 50 Hz notch filter. EEGs were re-referenced to the average monopolar reference (Offner, 1950). Blinks and horizontal eye movements were removed using a regression algorithm (Gratton et al., 1983). The noisy scalp channel was defined as an amplitude exceeding ± 100 μV throughout the recording and was interpolated by the average of the four nearest spatial electrodes.

2) *Event-Related Potential analysis (ERP)*

For the DPX, cue- and probe-locked ERP were analyzed. The cue-locked EEG was segmented from -250 to 5000 msec relative to cue onset, while the probe-locked EEG was segmented from -3000 to 3000 msec relative to probe onset. For the MID task, cue- and feedback-locked ERP were analyzed. The cue-locked EEG was segmented from -250 to 4500 msec relative to cue onset and from -200 to 1500 msec relative to feedback onset.

All EEG data were visually inspected for artefacts using a semi-automatic procedure. The EEG segments were rejected based on the following criteria: a maximum voltage difference of less than 0.5 μV within 100 msec intervals; a voltage step of more than 50 μV between sample points; a maximum of 100 μV; a minimum of -100 μV; and a voltage difference of 100 μV within a given trial. Additional artifacts were identified visually. The EEG data was then transformed using current-source density (CSD) analysis. In both tasks, the ERP were averaged separately for each trial and were baselined to a pre-stimulus interval of -200 to 0 msec.

The ERP parameters chosen for analysis were determined by the literature and our own data. All ERP were extracted at the electrode where the maximum amplitude was observed. In the DPX task, the cue-locked ERP were the difference P2/N2, the P3b and the CNV. The difference P2/N2, interpreted as reflecting proactive task goal reconfiguration, was computed at FCz, where the minimum (trough) of the N2 was subtracted from the maximum (peak) of the P2. The P2 was defined within a 20 msec latency window centered on the peak latency, between 145 and 205 msec after the cue, whereas the N2 was defined within a 40 msec latency window centered on the peak latency, between 210 and 340 msec after the cue. The P3b, assumed to reflect attentional stimulus processing, was computed at Pz, in the time range between 400 and 600 msec after the cue. The CNV, which reflected response motor preparation, was computed at CPz, in the time range between 1750 and 2000 msec after the cue. The probe-locked ERP were the N2 and the P3a, both of which were extracted at electrode FCz. The N2, interpreted as reflecting conflict detection, was defined within a 35 msec latency window centered on the peak latency, between 140 and 270 msec after the probe. The P3a, which reflected attentional processing for conflict resolution, was defined within a 40 msec latency window centered on the peak latency, between 220 and 320 msec after the probe. For the MID task, the ERP were all scored using time-window averages. The cue-locked ERP were the P3b and the CNV. The P3b was computed at Pz, in the time range between 300 and 600 msec after the cue. The CNV was computed at CPz, in the time range between 2100 and 2300 msec after the cue. The feedback-locked ERP were the RewP, the P3a and the LPP. The RewP, assumed to reflect reward sensitivity, was computed at Fz, in the time range between 170 and 220 msec after the feedback. The P3a, which reflected attentional processing to surprising or unfavorable outcomes as well as response inhibition, was computed at Cz, in the time range between 330 and 360 msec after the feedback. The LPP, which reflected affective processing, was computed at CPz, in the time range between 500 and 700 msec after the feedback.

Statistical analysis

A two-tailed significance level of 0.05 and a trend level of 0.10 were used for all tests. Effect sizes were calculated using a partial eta square (η_p^2).

Assumption tests were realized on behavioral and electrophysiological data. ANOVA's. See Supplementary Data Table S1 for the detailed results. ANOVAs were used when data were normally distributed (Shapiro–Wilk $p>.05$). Analysis of Variance of Aligned Rank Transformed Data (ART-ANOVA) were performed when data were not normally distributed (Shapiro–Wilk $p<.05$) (Elkin et al., 2021; Wobbrock et al., 2011).

In the DPX task, behavioral data were subjected to ART-ANOVAs, including the within-subject factor Trial (AX, AY, BX) and the between-subject factor Group (control, executive apathy, emotional apathy). For cue-locked ERP, ART-ANOVAs or ANOVAs were performed, including the within-subject factor Cue (A, B) and the between-subject factor Group. For probe-locked ERP, ANOVAs were performed, including the within-subject factor Trial and the between-subject factor Group.

In the MID task, behavioral data and cue-locked ERP were subjected to ART-ANOVAs or ANOVAs, including the within-subject factor Cue (win, loss, neutral) and the between-subject factor Group. Regarding feedback-locked ERP, the ANOVAs performed included the between-subject factor Group and the within-subject factor Feedback. According to the process being evaluated, the modalities compared were as follows:

- actual win *versus* actual loss, in order to assess reward positivity (RewP);
- actual win (or loss) *versus* neutral trial, in order to assess potential modulation of attention by rewards (or punishments) (P3a);
- actual win (or loss) *versus* absence of win (or loss), in order to assess affective treatment of rewards (or punishments) (LPP)
- neutral trials with positive *versus* negative feedback, in order to assess affective treatment of performances (LPP).

Pearson correlational analyses were performed between the three apathy subscores and the behavioral and ERP measures in each group, because of an extreme group design. Only significant correlational analyses were reported in the result section.

ANCOVA with sex was calculated due to the difference between the three groups. It showed that differences in sex did not explain any of the results ($p>.05$). See Supplementary Data Table S2 for the detailed results.

Results

1) Descriptive statistics

Table 2 summarizes the demographic and neuropsychological characteristics of the three groups. The executive group was constituted by 63% of subclinical apathy trait and 37% of clinical apathy symptom. In the emotional group, 54% had a subclinical apathy and 46% a clinical apathy.

Table 2: Demographic and neuropsychological characteristics of the three groups.
Values are given as the mean (standard deviation) [the DAS, the Dimensional Apathy Scale; the BDI-II, the Beck Depression Inventory II; the TEPS, the Temporal Experience of Pleasure Scale (Gard et al., 2006); the digit span task from the WAIS-III (Wechsler, 1997)].

	Control	Executive	Emotional	Differences
Age (years)	22 (1.73)	21.4 (1.71)	21.4 (2.13)	n.s
Sex (% of males)	41.66	27.27	63.63 *	$X^2(2)=5.99$, $p<0.05$ Cramer's V=.297
Level of education	Freshman: 20.83% Junior: 50% Senior: 29.17%	Freshman: 40.90% Junior: 50% Senior: 9.10%	Freshman: 45.45% Junior: 36.37% Senior: 18.18%	n.s
DAS executive	8.63 (3.79)	19.1 (1.87) *	7.23 (4,89)	$F(2,65)=67.04$, $p<.001$; $\eta^2=.67$
DAS emotional	6.25 (2.59)	6,64 (2.87)	16,3 (3.40) *	$F(2,65)=82.93$, $p<.001$; $\eta^2=.72$
DAS initiative	7.54 (2.95)	9.45 (2,26) *	7.09 (2.91)	$F(2,65)=4.67$, $p<.02$; $\eta^2=.13$
BDI-II	4.21 (4.27)	10.4 (4.31) *	5.68 (5.54)	$F(2,65)=10.60$, $p<.001$; $\eta^2=.25$
TEPS Anticipatory pleasure	45.1 (6.61)	44.9 (4.26)	45.2 (11.9)	n.s
TEPS Consummatory pleasure	37.4 (5.33)	39.6 (4.51) *	35.5 (6.38)	$F(2,65)=3.17$, $p<.05$; $\eta^2=.09$
Digit span task forward	6.25 (1.15)	6.32 (1.04)	6.18 (0.85)	n.s
Digit span task backward	4.96 (1.12)	4.45 (1.10)	5.23 (1.38)	n.s

In addition to a higher DAS executive score, the executive group presents a higher DAS initiative score, higher BDI score and higher TEPS consummatory score (all $p<.05$). However, these three higher scores are not (sub)clinically significant (Beck et al., 1996; Lafond-Brina & Bonnefond, 2022; Leaune et al., 2022).

In addition to a higher DAS emotional score, the emotional group presents a higher prevalence of male. In the general young adult population, emotional apathy is also more prevalent in men than in women (Lafond-Brina & Bonnefond, 2022).

2) DPX task

a- Behavioral results

The ART-ANOVA performed on RT revealed a main effect of trial ($F(2,128)=120.17$, $p<.001$; $\eta^2=.68$), with RT slower for AY than AX and BX ($p<.001$), and slower for AX than BX ($p<.005$). No effect of group ($p>.91$) nor trial x group interaction ($p>.46$) existed.

Regarding the FA rate, the ART-ANOVA revealed a main effect of trial ($F(2,128)=27.95$, $p<.001$; $\eta^2=.28$), with higher FA rate for AX and AY than for BX ($p<.001$). No effect of group ($p>.78$) nor trial x group interaction ($p>.41$) existed.

The ART-ANOVA performed on the BSI for RT and FA revealed no effect of group (respectively, $p>.83$ and $p>42$).

The ANOVA performed on the goal-maintenance comparison revealed a trial x group interaction ($F(2,64)=3.25$, $p<.04$; $\eta^2=.09$). Executive group had higher FA z-transforms for AX and BX trials compared to those for AY trials ($p<.05$), while the control and emotional groups showed no difference between the two conditions ($p>.12$) (Figure 3).

The ART-ANOVA performed on the total number of omissions revealed a main effect of group ($F(2,64)=4.52$, $p<.05$; $\eta^2=.12$). Executive group made more omissions than the control and emotional groups (respectively, $p<.02$ and $p<.06$), while the control and emotional groups showed a similar profile ($p>.99$).

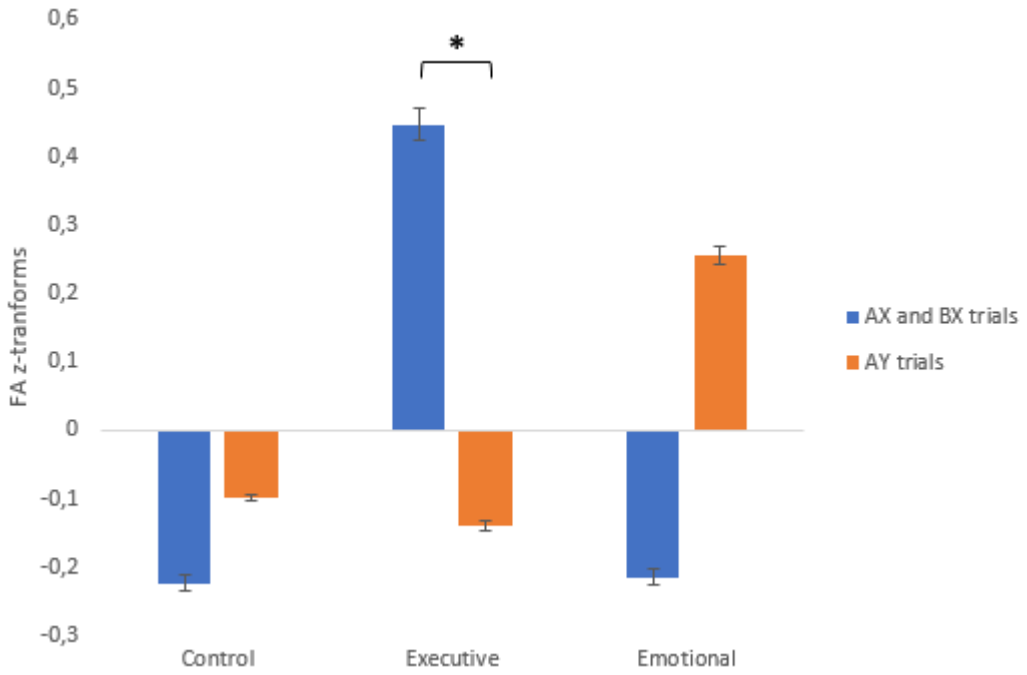

Figure 3: Goal-maintenance comparison

The FA z-transform in AX and BX trials was compared to the FA z-transform in AY trials in the three groups. The executive group was the only one to have higher FA z-transforms for AX and BX trials than for AY trials ($p<.05$). This finding reflected a poor goal maintenance for the executive group.

b- Electrophysiological results

b1- Cue-locked ERP

The ART-ANOVA performed on the P2-N2 difference revealed the classic main effect of cue ($F(1,65)=3.97$, $p<.05$; $\eta^2=.07$); with larger P2-N2 difference after the B cue than the A cue. No effect of group ($p>.47$) nor cue x group interaction ($p>.66$) existed.

The ANOVA performed on the P3b revealed the classic main effect of cue ($F(1,65)=184.19$, $p<.001$; $\eta^2=.74$), with a larger P3b after the B cue than the A cue. No effect of group ($p>.90$) nor cue x group interaction ($p>.68$) existed.

The ANOVA performed on the CNV revealed the classic main effect of cue ($F(1,65)=123.26$, $p<.05$; $\eta^2=.06$), with larger CNV after the A cue than the B cue. No effect of group ($p>.95$) nor cue x group interaction ($p>.79$) exist.

b2- Probe-locked ERP

The ANOVA performed on the N2 revealed a significant trial x group interaction ($F(4,130)=2.69$, $p<.03$; $\eta^2=.11$). The executive group was the only one to present similar N2 amplitudes for AX and AY trials ($p>.47$), whereas N2 was larger in AY trials than in AX trials for the control and emotional groups ($p<.02$) (Figure 4).

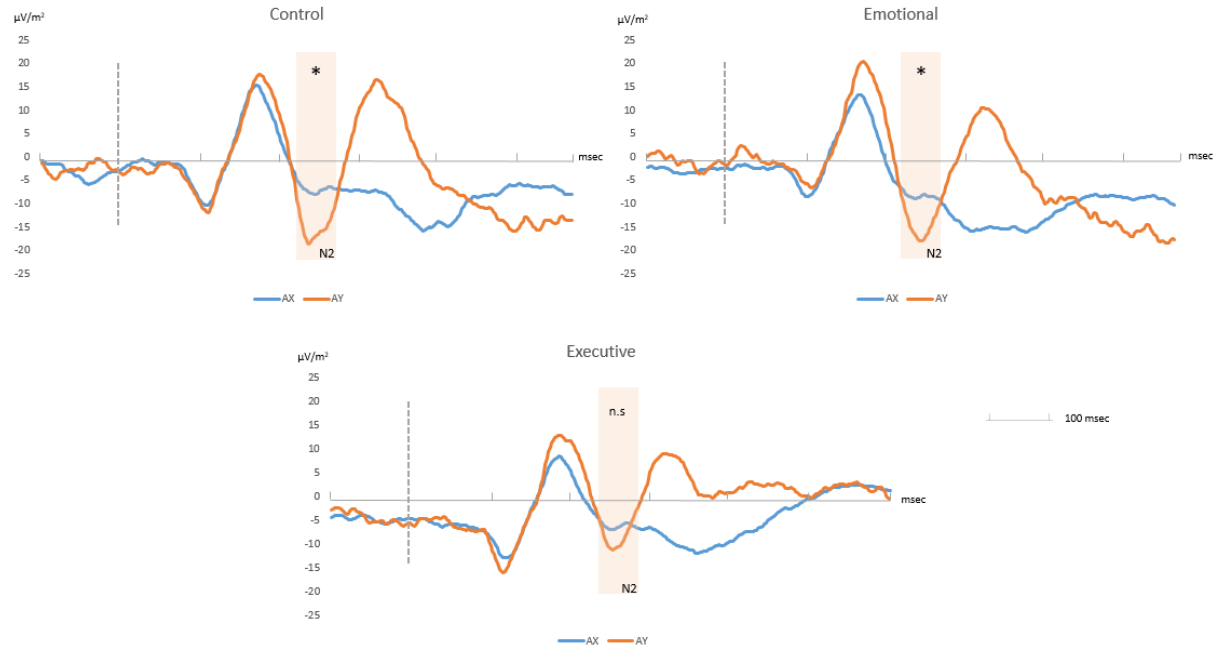

Figure 4: N2 amplitude at FCz in the three groups: * p<.05; n.s: non-significant.
The analyzed time window is represented in orange. The probe appears at 0msec (represented by a vertical dotted line).

The ANOVA performed on the P3a revealed a main effect of trial ($F(2,130)=42.66$, $p<.001$; $\eta^2=.40$), with larger P3a in AY trials than in AX and BX trials ($p<.001$). No effect of group ($p>.22$) nor trial x group interaction ($p>.46$) existed.

3) MID task

a- Behavioral results

The ART-ANOVA performed on RT revealed the classic main effect of cue ($F(2,130)=65.27$, $p<.001$; $\eta^2=.38$), with RT faster for win than loss and neutral cues, and for loss than neutral cues (all $p<.001$). No effect of group ($p>.75$) nor cue x group interaction ($p>.44$) existed.

The ART-ANOVA performed on the rate of anticipations revealed a main effect of cue ($F(2,130)=17.55$, $p<.001$; $\eta^2=.22$), with more anticipations after a win than loss and neutral cues ($p<.001$) and more anticipations after loss than neutral cues ($p<.04$). No effect of group ($p>.37$) nor cue x group interaction ($p>.92$) was found.
The ART-ANOVA performed on omissions revealed there was no effect of cue ($p>.14$), group ($p>.12$), nor cue x group interaction ($p>.41$).

b- Electrophysiological results

b1- Cue-locked ERP

The ART-ANOVA performed on the P3b revealed a main effect of cue ($F(2,130)=3.84$, $p<.03$; $\eta^2=.05$), with larger P3b after a win than a loss cue ($p<.01$). No effect of group ($p>.93$) nor cue x group interaction ($p>.33$) existed.

The ANOVA performed on the CNV revealed a main effect of group ($F(2,65)=4.30$, $p<.02$; $\eta^2=.11$), with less negative CNV amplitude for the control group compared to the executive group ($p<.02$). No effect of cue ($p>.63$) nor cue x group interaction ($p>.22$) was found.

b2- Feedback-locked ERP

Regarding the RewP, the sensitivity for rewards was examined for actual win and loss, so ANOVA was performed including the within-subject factor Feedback (actual win, actual loss) and the between-subject factor Group. The ANOVA performed on the RewP revealed a trend for a main effect of cue ($F(1,64)=3.65$, $p<.06$; $\eta^2=.05$), with larger RewP after an actual win than an actual loss feedback ($p<.05$). No effect of group ($p>.14$) nor cue x group interaction ($p>.77$) existed.

The P3a was examined to shed light on how rewards may modulate attention. The effects of incentive and neutral cues on one feedback were examined to do this. Therefore, two ANOVAs were performed, including the within-subject factor Feedback (for positive feedback: actual win, neutral trial; for negative feedback: actual loss, neutral trial) and the between-subject factor Group.

The ANOVA performed on the P3a between actual win trials and neutral trials with positive feedback revealed a main effect of trial ($F(1,65)=12.53$, $p<.001$; $\eta^2=.16$), with larger P3a after an actual win than a positive neutral feedback ($p<.001$). No effect of group ($p>.58$) nor trial x group interaction ($p>.17$) existed.

The ANOVA performed on the P3a between actual loss trials and neutral trials with negative feedback revealed a main effect of trial ($F(1,64)=20.64$, $p<.001$; $\eta^2=.21$), with larger P3a after an actual win than a positive neutral feedback ($p<.001$), as well as a main effect of group ($F(2,64)=3.72$, $p<.03$; $\eta^2=.10$), with larger P3a for the executive group than the control and emotional group ($p<.05$). No trial x group interaction ($p>.41$) existed.

For the LPP, the affective treatment of a reward was analyzed by examining the emotional effect of receiving or not receiving a potential incentive. Three ANOVAs were performed, including the within-subject factor Feedback (after a win cue: actual win, absence of win; after a loss cue: actual loss, absence of loss; after a neutral cue: positive neutral, negative neutral) and the between-subject factor Group.

The ANOVA performed on the LPP between actual win trials and the absence of win trials revealed there was no effect of trial ($p>.47$), group ($p>.28$), nor trial x group interaction ($p>.16$).

The ANOVA performed on the LPP amplitude between actual loss trials and the absence of loss trials revealed a trial x group interaction ($F(2,64)=3.43$, $p<.04$; $\eta^2=.10$). The emotional group had a reduced LPP amplitude for actual loss than the control and the executive groups (respectively, $p<.04$ and $p<.01$). The executive group was the only one to have a larger LPP for actual loss than for the absence of loss ($p<.02$) (Figure 5).

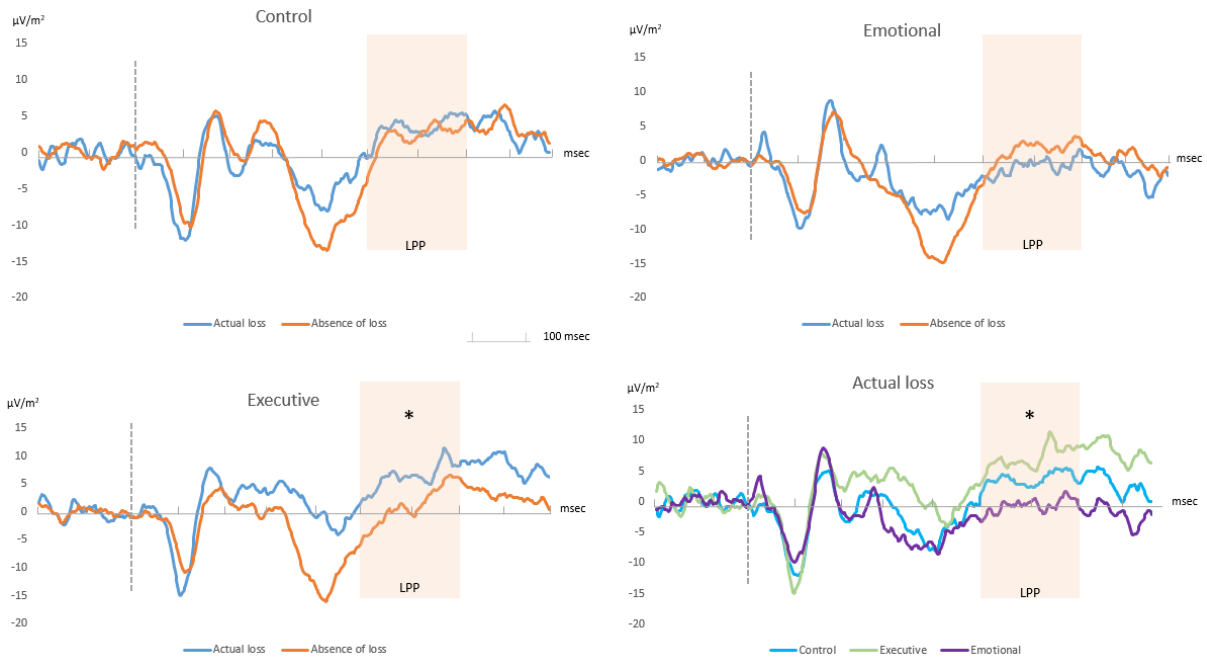

Figure 5: LPP amplitude at CPz in each group for actual loss and absence of loss and LPP amplitude at CPz for actual loss in the three groups: * $p<.05$. The analyzed time window is represented in orange. The feedback appears at 0 msec (represented by the vertical dotted line).

The ANOVA performed on the LPP amplitude between neutral trials with positive and negative feedback revealed a trial x group interaction ($F(2,65)=3.32$, $p<.04$; $\eta^2=.09$). The executive group was the only one to have a larger LPP for neutral trials with negative feedback than for neutral trials with positive feedback ($p<.01$). The executive group presents a larger LPP for neutral trials with negative feedback than the emotional group ($p<.01$).

Table 3: Synthesis of the significant electrophysiological results at the DPX and the MID. Values of ERP amplitudes are given as the mean (standard deviation). The group in bold is significantly different than the two other groups.

	Control	Executive	Emotional	Differences
DPX				
Probe-N2 (AY trials)	-22.3 (2.1)	**-12.4 (4.3)**	-20.3 (3.6)	p<.03; η2=.11
MID				
CNV (all trials)	**-3.02 (3.69)**	-6.66 (2.55)	-5.37 (2.85)	p<.02; η2=.11
P3a (actual loss trials)	5.9 (2.79)	**17.42 (3.33)**	7.41 (3.67)	p<.03; η2=.10
P3a (neutral trials with negative feedback)	2.01 (2.71)	**9.76 (2.82)**	-0.73 (3.11)	
LPP (actual loss trials)	4.24 (2.76)	6.35 (2.5)	**-2.35 (3.37)**	p<.04; η2=.10
LPP (absence of loss trials)	2.27 (1.63)	1.06 (1.51)	0.86 (1.46)	
LPP (neutral trials with positive feedback)	2.36 (1.60)	-0.26 (1.66)	-0.87 (1.18)	p<.04; η2=.09
LPP (neutral trials with negative feedback)	1.89 (1.22)	**4.34 (2.51)**	-1.77 (1.92)	

4) Correlational analyses

In the DPX, Pearson correlational analyses revealed a negative correlation between the N2 amplitude after the AX, AY and BX trials and DAS executive score in the emotional group (respectively, r=-.62, r=.57, r=.60, all p<.05). In people with emotional apathy, the more severe the executive apathy trait, the smaller the N2 amplitude for all the trials.

In the MID, Pearson correlational analyses revealed a positive correlation between LPP amplitude after an actual win and TEPS consummatory score in the control group (r=.42, p<.05). In the control group, the better individuals' capacity for consummatory pleasure, the larger the LPP amplitude for trials with an actual win.

Discussion

This study's main aim was to investigate the cognitive and neuronal mechanisms of multidimensional apathy, specifically executive and emotional apathy. It relied on an EEG study conducted in two groups of healthy young people with executive or emotional phenotypes of subclinical and clinical apathy as well as one group with no apathy. Our results, which were consistent with neuropsychological and fMRI data, showed that distinct mechanisms underlie each form of apathy. In the DPX, the executive group was the only group to present higher errors for AX and BX trials than for AY trials, as well as a reduced probe-N2 amplitude after AY trials. At the MID, only the executive group presented higher amplitudes for P3a and LPP after negative feedback than positive feedback, whatever the cue. On the contrary, in the MID, the emotional group was the only group to present a reduced LPP amplitude for actual loss, compared to the two other groups. These findings allow us to specify these types of apathy for the first time. There is a cognitive control deficit (specifically of the proactive control mode) in the executive form, whereas there is a particular motivational profile in the emotional form, specifically concerning the hedonic impact of reward, that is the liking motivation. Improved knowledge of these mechanisms should help the development of more targeted therapeutic interventions necessary for reducing the debilitating consequences of apathy.

Executive apathy

In accordance with our hypothesis, our behavioral and electrophysiological results found that the executive form of apathy - and solely this form - is underpinned by a deficit of proactive control. Proactive control, which strongly relies on the dorsolateral prefrontal cortex (DLPFC), is conceptualized as the maintenance of goal-relevant information to bias attention, perception, and response preparation in a top-down fashion (Braver, 2012; Braver et al., 2007). In the DPX, this poor goal maintenance corresponded to a deficit in using contextual cue information to guide behavior, as demonstrated in the greater proportion of errors for AX and BX trials compared to AY trials. This behavioral profile, which was observed only in the executive group, was accompanied by a deficit of proactive task goal reconfiguration. Indeed, subjects with executive apathy were not prepared to give a response target to the X probe after an A cue and, therefore, could not detect conflict if the A cue was followed by a Y. This was revealed by the absence of a higher probe-locked N2 in AY trials. This failure of healthy subjects with an executive apathy to recruit proactive control is consistent with impairments in DLPFC and cognitive territory of the basal ganglia, previously revealed in fMRI studies conducted on executive apathy patients (R. Levy & Dubois, 2006; Pagonabarraga et al., 2015;

Radakovic & Abrahams, 2018). The use of a paradigm designed to explore the engagement of two modes of cognitive control, each with a specific temporal dynamic, allowed us to specify the executive processes impaired in executive apathy and thus go even further than the neuropsychological approach classically used to explore apathy (Perri et al., 2018; Raffard et al., 2016). The impairment of the proactive control mode highlighted in executive apathy aligns with clinical observations of the daily functioning of executive apathy patients. These patients are described as having strong difficulties planning and organizing actions and maintaining goals. In the executive group, the deficit to actively maintain, in a sustained manner, the task-relevant information, may also be at the origin of their attentional failures, as revealed by a higher number of omissions in the DPX task (Sagaspe et al., 2012). Finally, our results shed light on the link between the severity of executive apathy and the lack of proactive control (in people with emotional apathy, the higher the associated executive apathy trait, the lower the N2 amplitude for AY trials). Therefore, we could hypothesize that whatever the main form of apathy presented by a subject, people with high executive apathy trait do not anticipate their goal-relevant information according to a context. This result could explain the results of several studies, which have found a correlation between executive deficits and executive apathy as well as unidimensional apathy in patients suffering from psychiatric (Faerden et al., 2009; Konstantakopoulos et al., 2011; Raffard et al., 2016) or neurological disorders (Lohner et al., 2017; Meyer et al., 2014).

Interestingly, our results also revealed that, even in the case of an incentive cue, subjects with executive apathy showed a deficit of proactive control. Indeed, in the MID task, subjects with executive apathy do not consider the context (the reward information given by the cue in the MID task). Exclusively for the executive group, the amplitude of the LPP, a component reflecting affective processing, was larger for neutral trials with negative feedback than for neutral trials with positive feedback. Thus, unlike the other groups, the executive apathy group did not actively maintain the relevant information given by the cue. The deficit of proactive control underlying executive apathy is not modulated by motivation since, in these subjects, the affective processing (liking component) was only modulated by the performance feedback information, regardless of the cue.

Therefore, our results suggest that motivational therapies, based on the activation of efficient motivational strategies, could be useless for treating executive apathy. Instead, cognitive remediation based on executive functions seems to be the most appropriate therapy for reducing the negative impact of executive apathy. Conforming to this, a recent fMRI study on depressive patients showed the benefits of a video game intervention designed to improve cognitive control on activation and functional connectivity of the cognitive control network as well as on self-reported apathy (Gunning et al., 2021). Furthermore, when considering pharmacological treatments, dopaminergic treatments had already been tested for

unidimensional apathy, with very heterogeneous effects along the subjects and the pathologies (Herrmann et al., 2008; Mintzer et al., 2021; Padala et al., 2017; Rosenberg et al., 2013; Ruthirakuhan et al., 2018). However, results from some studies in which participants' profile of multidimensional apathy has been assessed a posteriori, showed that participants with executive apathy benefited the most from the dopaminergic treatments (Herrmann et al., 2008; Padala et al., 2017). Our results are in accordance with these studies, since only executive apathy is underlied by a deficit of proactive control supported by the dopaminergic system. On the contrary, dopaminergic drugs could not be useful in emotional apathy, since the liking deficits are underlied by the opioid and cannabinoid systems. Therefore, for the next pharmacological studies, wisely choose the participants with a profile of apathy could change the effect response of a treatment in a pathological population.

Emotional apathy

Regarding the emotional form of apathy, our results, in line with our hypothesis, reveal that this form of apathy is underpinned by a specific motivational profile. This result agree with previous fMRI studies, performed on patients suffering from emotional apathy, which showed these patients had dysfunctions of the orbital and ventromedial prefrontal cortex and the limbic territories of the basal ganglia, especially the ventral striatum (Casey et al., 2018; Knutson et al., 2005). However, the structures highlighted in the fMRI studies could not distinguish between wanting and/or liking deficits in emotional apathy. Our electrophysiological results specified an impaired liking process but a preserved wanting process in healthy subjects with emotional apathy. Indeed, the emotional group could anticipate based on motivational cues to the same extent as the control group: they did not show any alteration of wanting components, as revealed by the P3b and CNV components (Demidenko et al., 2021; B. K. Novak et al., 2016; K. D. Novak & Foti, 2015). Concerning the liking motivation, the first step of reward responsiveness was preserved in emotional apathy. Indeed, like the control group, people with emotional apathy modulated their RewP, with a larger RewP for gain than loss of rewards, which is assumed to reflect early processes that will lead to positive affects (Gable et al., 2021). However, the last stage process of the liking component was impaired in emotional apathy, as revealed by the absence of modulation by incentive punishments of the ERP component (LPP), assumed to reflect the affective processing of feedback information (Broyd et al., 2012). The LPP could reflect a lack of sensitivity to punishment, that could prevent subsequent behavioral adjustments (Glazer et al., 2018). This lack of sensitivity to punishment has already been linked to emotional apathy as a one-year predictor in patients with schizophrenia, through self-reported questionnaires (Raffard et al., 2019). This specific motivational pattern could explain the emotional indifference and lack of emotional responsiveness in daily life that

patients with emotional apathy are often described as having. Reduced sensitivity to punishments and danger could result in lower behavioral responsiveness to negative or stressful events. Indeed, a recent review on clinical and rodents studies confirms that the negative valence system allows to differentiate depression and apathy: the punitions induced exaggerated emotional responses in depression, but blunted responses in apathy (Jackson & Robinson, 2022). This blunt anxiety and stress response generates a lack of reaction to the environment, producing a reduction of goal-directed behavior. Moreover, the hedonic interface theory posits that positive and negative affective experiences act as motivation for goal-directed behaviors by adding value to voluntary actions (Dickinson & Balleine, 2010). However, this theory also states that once values or desires are assigned to goal-directed behaviors, the cognitive processes converting these values in pursuit of the goals can function in the absence of affect. As we hypothesized, subjects with emotional apathy present preserved cognitive control processes as seen in the fact that their behavioral and electrophysiological patterns are similar to the control group in the DPX task.

Moreover, despite an anatomical overlap between emotional apathy and anhedonia, our electrophysiological results at the MID could help to clarify the distinction between these two symptoms. Indeed, anhedonia, clinically defined as the inability to experience and/or anticipate pleasure, is underpinned by the same structures as emotional apathy (Gard et al., 2006; Husain & Roiser, 2018; Pagonabarraga et al., 2015; Treadway & Zald, 2011). However, while our results shed the light on emotional blunting for loss in emotional apathy, anhedonia had been linked to an emotional blunting for gain, reflecting by a reduced LPP when obtaining a positive reward (Dell'Acqua et al., 2022; Garland et al., 2023; Klawohn et al., 2021). Moreover, depressed patients present an emotional blunting for positive events (i.e., anhedonia) but an attentional bias to negative events (i.e., hypersensitivity to loss, the contrary to the deficit we highlighted in emotional apathy) (Epstein et al., 2006; Leppänen, 2006; Ma, 2015; Xie et al., 2021). Therefore, depression could be linked only to anhedonia, but not to emotional apathy. A first but tenuous argument in favor of this hypothesis could be that emotional apathy is the only form of apathy that is never correlated with depression, in healthy population for different cultures (Kawagoe et al., 2020; Lafond-Brina & Bonnefond, 2022; Santangelo, Raimo, et al., 2017), as well as in various neurogenerative and psychiatric pathologies (Barek et al., 2021; Radakovic et al., 2017, 2018; Raimo et al., 2020; Santangelo, Siciliano, et al., 2017). This hypothesis needs to be explored because it could help to improve the understanding of emotional apathy and anhedonia, in order to help creating new therapies in depression.

Moreover, the representation of genre could be a specific pattern of emotional apathy linked to the specific liking motivational impairment. Indeed, in our epidemiological study, we show that the masculine gender was specifically associated with emotional apathy,

whereas the feminine gender was more prevalent in executive and initiative apathy (Lafond-Brina & Bonnefond, 2022). Several studies in young adults showed that adherence to masculine norms is associated with less fear of failure and punishment, a lack of emotional expression, reduced motivation, and a lack of perseverance and engagements in actions (Streck et al., 2022; Yu et al., 2021). These associations are coherent with our results and the clinical descriptions of emotional apathy. Thus, we wonder if social masculinity norm favors the emotional apathy trait, and thus the trait being a product of gender stereotypes, and/or if the emotional apathy trait is biologically more prevalent in the male sex, underlying the emergence of traditional masculinity in society. Our data do not allow us to answer these questions. Nevertheless, several studies in the Orsini lab with rodents could tend not to dismiss the biological hypothesis over the normative one by showing that sexual hormones could be linked to motivation and goal-directed behaviors. For example, estrogen may play a major role in increasing the sensitivity to rewards and punishments and goal-directed behaviors, inducing less apathy in female rats with higher estrogen rates compared to females not in estrus and males (Orsini et al., 2022). Further studies at the intersection of biology, psychology, and sociology could answer this timely question.

Finally, by highlighting the hedonic mechanism underlying emotional apathy, our results should inform more targeted treatments. Indeed, contrary to executive apathy, motivational therapies seem quite suitable to address emotional apathy by relying on their excellent proactive capacities. Moreover, one study already showed that emotional cognitive behavioral therapy could modulate neural structures underlying emotional processing in depressive patients; however, the study did not test the impact of the therapy on apathy (Ritchey et al., 2011). For pharmacological treatments, our results, in accordance with the literature, could suggest the importance of testing opioids or cannabinoids treatments specifically for people with emotional apathy. Indeed, the liking, specifically impaired in emotional apathy, is modulated by opioid or endocannabinoid neurotransmitters in the limbic prefrontal cortex, the orbitofrontal, the insula regions, and the ventral pallidum, but not by dopaminergic neurotransmitters (Berridge & Robinson, 2016; Smith & Berridge, 2007). One study showed that endocannabinoid lipids and opioid peptides enhance socioemotional behaviors in rodents (Manduca et al., 2016). Thus, enhancing cannabinoid and opioid signaling could help facilitate incentive motivational goal-directed behavior. However, future studies will need to be cautious about the dosage to ensure emotionally apathetic people do not go from emotional indifference and apathy to addiction and compulsive drug seeking (Mitchell et al., 2018).

Limitations

Despite some subclinical and clinical symptoms of apathy, all participants in the current study were free of any lifetime neurological, metabolic, or psychiatric diagnoses and were all university students with high education. This could have resulted in a high functioning sample. In addition, in a previous study with university students, about 20% presented a specific executive or emotional apathy, whereas 7% had an initiative form, 14% more than one form of apathy and 70% no apathetic trait (Lafond-Brina & Bonnefond, 2022). Thus, our apathetic samples were chosen for having a specific form of apathy, whereas in the general population and in neurodegenerative pathologies, people often present several forms of apathy at once (Radakovic & Abrahams, 2018). Therefore, the choice of our specific sample may reduce generalizability to the general population. Replication of our results in more general, neurological, and psychiatric samples could build on these results toward a more general cognitive and neural substrate of multidimensional apathy. Moreover, following the RDoC perspective, investigating the substrate of apathy in different healthy and patient samples could reveal similarities and dissimilarities between different groups, and increase the understanding of apathy as a transdiagnostic symptom (Klaasen et al., 2017; Nusslock & Alloy, 2017).

Conclusion and perspectives

Our study provides a more thorough understanding of the mechanisms underlying multidimensional apathy, which can inform novel non-pharmacological or pharmacological treatment strategies in the treatment of apathy. Indeed, by using a phenotyping (or extreme groups) approach, which is more powerful than correlations in the case of a reduced sample size, we specified, for the first time, the specific mechanisms underlying executive and emotional apathy. Only in neurodegenerative disorders, several studies shed the light on dominant form of apathy, like executive apathy in Parkinson disease (Radakovic et al., 2018). However, in psychiatric, even if almost all the disorders are associated with apathy (Strauss & Cohen, 2017), a multidimensional approach of apathy is rarely used, and the difference between each form of apathy and anhedonia or avolition are still unknown. Further research should focus on multidimensional apathy in psychiatry and explore the dominant form of apathy in distinct psychiatric disorders, to help developing new, personalized efficient treatments for reducing the debilitating consequences of this symptom.

Acknowledgements

We thank the staff of the Unit 1114 of the French Institute of Health and Medical Research and of the Strasbourg University Hospital, and especially Julien Krieg for his assistance with the tasks.

Funding

This research was supported by the French Ministry of Higher Education and Research grant (to G. L-B).

Authors Contributions

G. L-B: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Visualization; Writing - original draft; Writing - review & editing.

B. P: Data curation; Investigation; Writing - review & editing.

A. B: Conceptualization; Data curation; Funding acquisition; Methodology; Project administration; Resources; Supervision; Validation; Writing - review & editing.

Competing Interests Statement: None

The authors declare no competing interests to report.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation (Research ethics committee of the University of Strasbourg - UNISTRA/CER/2020-13) and with the Helsinki Declaration of 1975, as revised in 2008.

Research data

Research data is available on request to G.L-B.

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Résumé des principaux résultats et objectifs des analyses complémentaires

L'analyse des données comportementales et électrophysiologiques aux deux tâches cognitives (DPX et MID) a permis de mettre en évidence des dysfonctionnements distincts associés aux formes exécutive et émotionnelle.

L'apathie exécutive est associée à un dysfonctionnement du mode de contrôle proactif, se traduisant par une non prise en compte des informations contextuelles fournies par l'indice, que cette information soit motivationnelle (MID) ou non (DPX). L'apathie émotionnelle est quant à elle associée à un déficit de *liking*, se traduisant par une indifférence affective aux feedbacks négatifs.

Les analyses complémentaires ont pour objectif de :

(1) tester dans quelle mesure les dysfonctionnements de ces mécanismes sont bien spécifiques aux formes exécutive et émotionnelle ou s'ils sont également présents dans l'apathie d'initiation ;

(2) tester l'hypothèse d'une forme mixe pour l'apathie d'initiation, c'est-à-dire une forme rassemblant les dysfonctionnements associés aux formes exécutive et émotionnelle.

Pour cela, les mesures comportementales et électrophysiologiques issues de la DPX des sujets avec une apathie d'initiation ont été comparées à celles des sujets contrôles et des sujets avec une apathie exécutive. Les données issues de la MID des sujets avec une apathie d'initiation ont, quant à elles, été comparées à celles des sujets contrôles et des sujets avec une apathie émotionnelle.

Analyses complémentaires

Analyses complémentaires

Results

Objective 1: Specificity of cognitive and emotional dysfunctions in executive and emotional forms of apathy

1) Executive apathy

Behavioral results

The ANOVA performed on the goal-maintenance comparison revealed a trend for a trial x group interaction ($F(2,64)=2.42$, $p<.07$; $\eta^2=.08$). Executive group had higher FA z-transforms for AX and BX trials compared to those for AY trials ($p<.05$), while the control and initiative groups showed no difference between the two conditions ($p>.36$).

Probe-locked ERP

The ANOVA performed on the N2 revealed a significant trial x group interaction ($F(4,132)=3.27$, $p<.01$; $\eta^2=.09$). The executive group was the only one to present similar N2 amplitudes for AX and AY trials ($p>.60$), whereas N2 was larger in AY trials than in AX trials for the control and initiative groups ($p<.03$).

2) Emotional apathy

One subject with initiative apathy was excluded from analyses because he anticipated more than 15% of the trials per block.

Feedback-locked ERP

The ANOVA performed on the RewP revealed a main effect of group ($F(1,64)=3.01$, $p<.05$; $\eta^2=.08$), with larger RewP for the control and initiative groups than the emotional group (both $p<.04$). No effect of feedback ($p>.27$) nor feedback x group interaction ($p>.36$) existed.

The ANOVA performed on the LPP amplitude between actual loss trials and the absence of loss trials revealed a trend for a trial x group interaction ($F(2,64)=2.58$, $p<.08$; $\eta^2=.07$). The emotional group had a reduced LPP amplitude for actual loss than the control and the initiative groups (respectively, $p<.02$ and $p<.05$).

Objective 2: Mixed form in initiative apathy

The analyses revealed that the initiative group is not impaired at any behavioral or electrophysiological results. Participants with initiative apathy show even a larger amplitude for the CNV and the P3a than the control and emotional groups, reflecting good capacities of wanting (CNV) and liking (P3a).
Annexe 5 presents the detailed results of the analyses.

Résumé des principaux résultats

S'agissant du caractère spécifique des mécanismes cognitifs et motivationnels associés aux formes exécutive et émotionnelle, les analyses complémentaires ont permis de montrer que l'apathie exécutive est la seule forme d'apathie multidimensionnelle spécifiquement sous-tendue par un déficit de contrôle proactif et que l'apathie émotionnelle est la seule forme d'apathie spécifiquement sous-tendue par un déficit de *liking*.

Elles permettent également de préciser les déficits de *liking* dans l'apathie émotionnelle. En plus d'une insensibilité à la punition (LPP) (mise en évidence dans l'étude 2), l'apathie émotionnelle est associée à un trouble précoce du *liking* (RewP), indiquant une perte de sensibilité à la récompense. Une réduction d'amplitude de la RewP pour des essais récompensés financièrement a déjà été associée à une hypoactivation du striatum ventral chez des sujets sains ainsi que corrélée à la sévérité du score d'anhédonie chez des sujets en rémission de dépression (Carlson et al., 2011; Weinberg & Shankman, 2017). Ces résultats confirment l'indifférence émotionnelle, pour le négatif et le positif, observée en clinique, spécifique aux personnes souffrant d'apathie émotionnelle.

S'agissant de l'hypothèse de l'apathie d'initiation comme forme mixte, les résultats complémentaires indiquent que l'apathie d'initiation n'est pas associée aux mêmes dysfonctionnements que ceux mis en évidence pour les formes exécutive et émotionnelle. Ce résultat conforte l'hypothèse à explorer d'un mécanisme différent impliqué : la prise de décision basée sur l'intégration des informations cognitives et motivationnelles.

Étude 3

Lafond-Brina, G., Pham, B. T., & Bonnefond, A. (2023). Initiative apathy trait underlies individual differences in the ability to anticipate and expend cognitive effort in cost-benefit decision-making tasks. *Cerebral Cortex*, 33(12), 7714-7726.

L’annexe 6 présente le matériel supplémentaire de l’étude 3.

Cerebral Cortex, 2023, 1–13
https://doi.org/10.1093/cercor/bhad074
Original Article

Initiative apathy trait underlies individual differences in the ability to anticipate and expend cognitive effort in cost-benefit decision-making tasks

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Initiative apathy is the most disabling form of apathy, prevalent both in neuropsychiatric pathologies and in the healthy population. This apathy has been specifically associated with functional abnormalities of the anterior cingulate cortex, a key structure underlying Effort-based Decision-Making (EDM). The main aim of the present study was to explore, for the first time, the cognitive and neural effort mechanisms of initiative apathy, by distinguishing the steps of effort anticipation and effort expenditure and the potential modulating effect of motivation. We conducted an EEG study in 23 subjects with specific subclinical initiative apathy and 24 healthy subjects with no apathy. The subjects had to complete two effort tasks. The analysis of behavioral choices, CNV, and mPFC theta power highlighted that initiative apathy is associated with effort avoidance and impairments of effort anticipation and effort expenditure that suggest EDM deficits. Better knowledge of these impairments should aid the development of new, more targeted therapeutic interventions necessary for reducing the debilitating consequences of initiative apathy.

Key words: avolition; EEG; executive control; motivation; self-esteem.

Introduction

Effort-based Decision-Making (EDM) is a vast field of research in neuroscience that tries to understand people's willingness to work for rewards and achieve a goal-directed behavior. A goal-directed behavior is one that will only be completed if the action is motivating (the goal reward is valuable enough) and does not require too much effort (the goal seems possible to achieve) (Shenhav et al. 2017). The effort needed to reach a goal can also be rewarding in itself (Inzlicht et al. 2018). EDM can be broken down into two main steps: (i) anticipating the effort exertion, including effort- and reward-based evaluation and decision-making, and (ii) expending the effort (Zhang and Zheng 2022). Effort anticipation is translated by a proactive allocation, whose most consistent electrophysiological correlate is the contingent negative variation (CNV), a negative-going slow wave with a central distribution. The CNV amplitude is higher when completing effortful and rewarding tasks, and the amplitude is positively correlated with better accuracy and faster responses to the task (Frömer et al. 2021). Frontal-midline theta activity reflects the second step of cognitive effort mobilization, as there is a higher theta power in tasks requiring higher mental effort (Smit et al. 2005; Domic et al. 2021; McFerren et al. 2021).

A deficit in goal-directed behavior characterizes initiative apathy, a disabling symptom (Robert et al. 2018). Clinically, this form of apathy, with the most disabling behavioral consequences, is often described as mental emptiness and an inability to think of new things or be spontaneous, which results in behavioral inertia (Laplane et al. 1982; Levy and Dubois 2006). Initiative apathy is prevalent in many neurological, neurodegenerative, and psychiatric pathologies (Radakovic et al. 2016; Raffard et al. 2019; Quang et al. 2022) but also present in 2.5% of the healthy population (Lafond-Brina and Bonnefond 2022). At a subclinical level, i.e. at mild degrees of dysfunction, initiative apathy has even been reported to be present in about 6% of the general population and associated with difficulties tied to daily life (Ang et al. 2017; Lafond-Brina and Bonnefond 2022). Interestingly, fMRI studies have highlighted that initiative apathy is specifically associated with functional abnormalities of the anterior cingulate cortex (ACC; Pagonabarraga et al. 2015; Le Heron et al. 2018). The ACC is a key structure notably underlying EDM, and it has been suggested that effort-based decision making is likely to be altered in initiative apathy (Cléry-Melin et al. 2011). Indeed, ACC is involved in effort anticipation, with a higher BOLD signal in the ACC before a high compared to a low effort in a rewarded task (Kurniawan et al. 2013). It has been reported that many apathetic patients suffering either from depression or neurological or neurodegenerative diseases had ACC dysfunctions (Touroutoglou et al. 2019, for a review). In accordance with this hypothesis, one fMRI study with healthy subjects suffering from initiative apathy showed a specific link between initiative apathy and increased effort sensitivity in an EDM task. It also demonstrated a correlation between the severity of initiative apathy and decreased structural and functional connectivity in the ACC (Bonnelle et al. 2016).

The main aim of the present study is to better understand the mechanisms underlying initiative apathy. To do that, we explored neural correlates of effort anticipation and effort expenditure during the realization of two effort tasks in two groups of healthy young people: one with a specific subclinical initiative apathy

Received: December 13, 2022. **Revised:** February 19, 2023. **Accepted:** February 22, 2023

and one group with no apathy. The combined use of these two effort-related decision-making tasks allowed us to investigate the potential modulating effects of motivation on these two steps and how effort- and reward-related information are accounted for when making a choice.

Materials and methods

Subjects

In a previous, non-experimental study, an online survey on the prevalence and consequences of multidimensional apathy was conducted among the student population of a French university (see Lafond-Brina and Bonnefond 2022, for more details). This exploratory survey, conducted on about 4000 young adults, allows us to define the cut-off for each form of subclinical apathy in the healthy young population. Indeed, subjects completed the three subscores of the Dimensional Apathy Scale (DAS; Radakovic and Abrahams 2014). The DAS is a 24-item scale assessing the severity of executive, emotional, and initiative apathy. Items are scored on a 4-point Likert scale based on the frequency of the occurrence of apathy symptoms in the previous month (1 = "hardly ever," 4 = "almost always"). Three cut-offs of subclinical apathy were defined based on these subscores: initiative score above the cut-off of 14, executive score above 16, and emotional score above 12. Interestingly, the stability of the DAS subscores measured at one-year intervals suggested that the subclinical apathy measurement was not state-dependent but rather a trait measurement.

In the present study, 47 right-handed subjects participated. They were selected based on their responses to the online survey using the DAS. The initiative apathy group was composed of 23 participants presenting the initiative form of subclinical apathy (initiative score above the cut-off of 14), and having scores for the two other forms below the cut-offs for the general population (executive and emotional scores below the respective cut-offs of 16 and 12). The 24 participants composing the control group did not present any form of apathy (subscores below the cut-offs for the general population).

Participants with a history of neurological, metabolic, sensorial, psychiatric disorders, or psychiatric disorders in first-degree relatives, who consumed psychoactive drugs and/or cannabis in the last 3 months, and/or had general anesthesia in the past three months were excluded. Moreover, subjects with mild or severe depressive symptoms as determined by the Beck Depression Inventory II (BDI-II; score $\geq$16) were excluded (Beck et al. 1996). Table 1 summarizes the demographic and neuropsychological characteristics of the two groups. In the sample, to reflect the specificities of the general young adult population, initiative apathy is associated with higher scores on executive apathy and depressive symptoms (Lafond-Brina and Bonnefond 2022).

The study protocol was approved by the local ethics committee (University review board: UNISTRA/CER/2020-13), and the selected subjects were paid for their participation.

Tasks and behavioral measures

The participants completed the Induced Effort (IE) task and the EDM task in a counterbalanced order. These tasks were adapted from the Demand Selection Task (McGuire and Botvinick 2010) and the Deck Choice Effort task (Reddy et al. 2015). Both tasks lasted about 30 min and were divided into three blocks of, respectively, 40 and 60 trials each, separated by short breaks. A training of a few minutes preceded the completion of each task, in which the participants had to achieve success in six consecutive trials.

In the IE task, the cognitive effort is manipulated by changing the difficulty level (Fig. 1). Concretely, subjects first see a cue indicating the level of difficulty of the following sequence (two different levels: easy, difficult). This cue has the shape of a thermometer, sparsely filled in the case of the easy level and almost full in the difficult one. For each block, the two types of cues are presented in a random order and in similar proportions (50% each). Then, a sequence of five numbers is presented. For each sequence, subjects had to say if the number presented is odd/even (press left for odd, right for even) if the background color was dark gray, or higher/lower than the number 5 (press left for lower, right for higher) if the background was light gray. The easy level corresponds to a sequence in which the background color is the same for the five numbers (same cognitive activity), whereas the difficult level requires a switch between the two activities. At the end of each sequence, positive feedback (symbolized by a white disc) appeared on the screen in case of one or no error, and negative feedback (a gray disc) was given if more than one error has been made.

The efficiency, i.e. the ratio between the mean number of accurate responses per sequence and the mean of reaction time per sequence, was calculated.

The EDM task is a decision-making task that manipulates both cognitive effort and motivation (Fig. 2). At the beginning of a trial, participants are presented with two options. Each option proposes two cues indicating the level of difficulty (similar to the IE task) and the possible reward (two different levels: low, high). The reward cue is represented with a Euro symbol: one Euro sign in the case of the low reward, and three Euro signs for the high reward. In each block, all choice combinations are presented in a random order and in similar proportions. First, subjects must choose between the two options presented (press left for the left option, right for the right one). Then, a sequence of five numbers is presented with the same design as in the IE task. At the end of each sequence, feedback based on the performance (similar to that of the IE task) and the reward earned (one Euro sign for a low reward, three Euro signs for a high reward) is presented.

The subject was randomly presented with all possible combinations of choices (Fig. 3). Four types of choices were studied: choices for effort (with constant reward), choices for reward (with constant effort), choices for optimality (where optimal choices propose a higher reward for the easiest effort), and choices for preference (work harder for more reward or milder for less reward).

The percentages of each type of choice, time taken to choose, and efficiency were calculated.

Participants told they would receive a financial bonus based on performance but were given a standard bonus amount, corresponding to the maximal bonus they could have earned during the task.

Electrophysiology

Electrophysiological preprocessing. Electroencephalograms (EEGs) were recorded using 64 Ag/AgCl BioSemi ActiveTwo System electrodes mounted on an elastic cap according to the standard 10-10 system and with a 0.01–500 Hz band-pass filter. Brain-Vision Analyzer 2.1 software was used to analyze the data sampled at 512 Hz. A 0.5-Hz offline high-pass filter, a 40-Hz off-line low-pass filter, and a 50-Hz notch filter were applied. EEGs were re-referenced to the average of the two earlobes. Blinks and horizontal eye movements were removed using a regression algorithm (Gratton et al. 1983). The noisy scalp channel was defined as having an amplitude exceeding $\pm$100 μV throughout

Table 1. Demographic and neuropsychological characteristics of the two groups. Values are given as the mean (standard deviation in parentheses) [DAS: Dimensional Apathy Scale; BDI-II: Beck Depression Inventory II; SES: Rosenberg Self-Esteem Scale (Rosenberg 1965); TEPS: Temporal Experience of Pleasure Scale (Gard et al. 2006); digit span task from the WAIS-III (Wechsler, 1997); DPX: Dot Pattern Expectancy task; MacDonald et al. 2005)].

	Control group	Initiative apathy group	P-value
Age (years)	21.95 (1.73)	20.74 (2.22)	$P < 0.04$
Sex (M/F)	10/14	7/16	$P < 0.45$
DAS executive cut-off: 16	8.63 (3.79)	11.61 (3.47)	$P < 0.01$
DAS emotional cut-off: 12	6.25 (2.59)	6,13 (2.98)	$P < 0.90$
DAS initiative cut-off: 14	7.45 (2.95)	15.04 (1.36)	$P < 0.001$
BDI-II	4.21 (4.27)	8.48 (4.53)	$P < 0.002$
Rosenberg SES	29.38 (4.92)	26.43 (2.87)	$P < 0.02$
TEPS anticipatory pleasure	45.08 (6.60)	41.57 (6.04)	$P < 0.07$
TEPS consummatory pleasure	37.38 (5.33)	36.96 (4.66)	$P < 0.80$
Digit span task forward	6.25 (1.15)	6.52 (1.41)	$P < 0.50$
Digit span task backward	4.96 (1.12)	5.17 (1.37)	$P < 0.60$
DPX task: reaction times of AY trials (ms)	642.79 (163.81)	692.78 (197.21)	$P < 0.35$
DPX task: reaction times of BX trials (ms)	478.79 (244.14)	534.20 (245.47)	$P < 0.45$
DPX task: rate of false alarms of AY trials	34.33 (25.88)	39.94 (22.80)	$P < 0.45$
DPX task: rate of false alarms of BX trials	15.46 (24.73)	15.06 (16.97)	$P < 0.95$

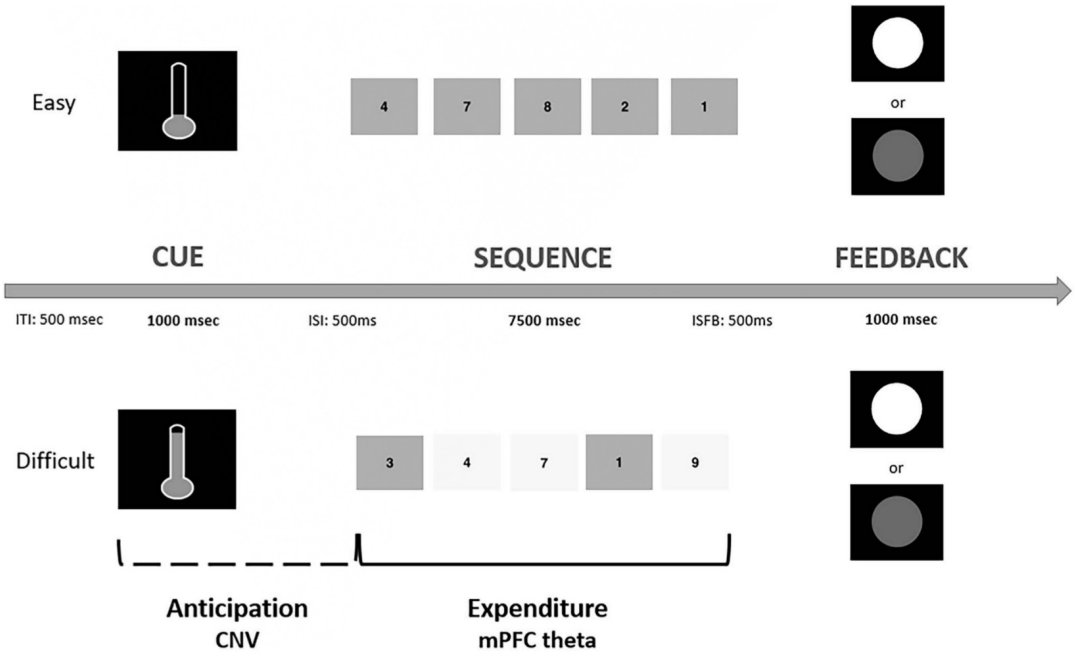

Fig. 1. The IE task. Presentation of an easy (on top) and a difficult trial (at the bottom). The CNV is the electrophysiological correlate of effort anticipation, observed before the sequence begins. The mPFC theta power spectrum calculated during the sequence reflects the effort expenditure.

the recording and was interpolated by the average of the four nearest spatial electrodes (one interpolated electrode in four subjects in the IE task, as well as in three subjects in the EDM task).

For the IE task, the EEG was segmented from −250 to 11,000 ms relative to the onset of the effort cue. For the EDM task, the EEG was segmented from −250 to 11,500 ms relative to the onset of the choice cue. All EEG data were visually inspected for artifacts using a semi-automatic procedure. The EEG segments were rejected based on the following criteria: a maximum voltage difference of less than 0.5 μV within 100 ms intervals, a voltage step of more than 50 μV between sample points, a maximum of 100 μV, a minimum of −100 μV, and a voltage difference of 100 μV within a given trial. Additional artifacts were identified visually.

Event-related potential analysis: the CNV. In both tasks, the event-related potential (ERP) were averaged separately for each trial and were baselined to a pre-stimulus interval of −200 to 0 ms. The EEG data were then transformed using current-source density analysis. The CNV parameters chosen for the analyses were determined by referencing the literature and the study data, as this negative slow wave is known to begin approximately 1000 ms prior to target onset and to be maximal immediately prior to target

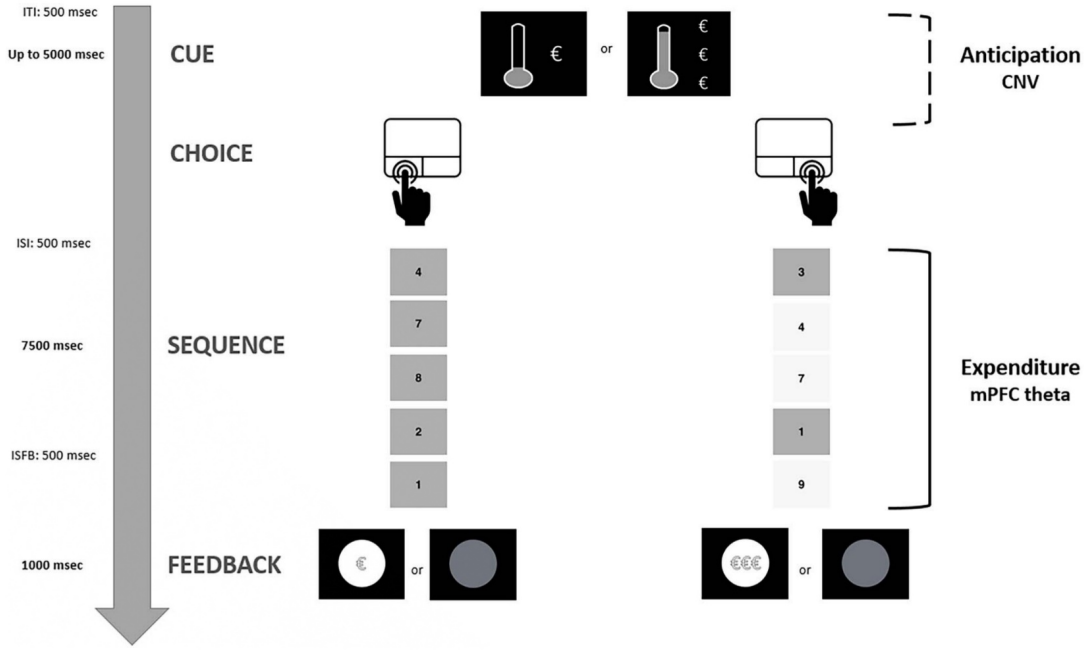

Fig. 2. The EDM task. Presentation of a choice for preference, with the sequence induced by choosing the easy low-reward option (on the left) and the difficult high-reward option (on the right). The CNV is the electrophysiological correlate of effort choice anticipation, observed before the choice response. The mPFC theta power spectrum calculated during the sequence reflects the effort expenditure.

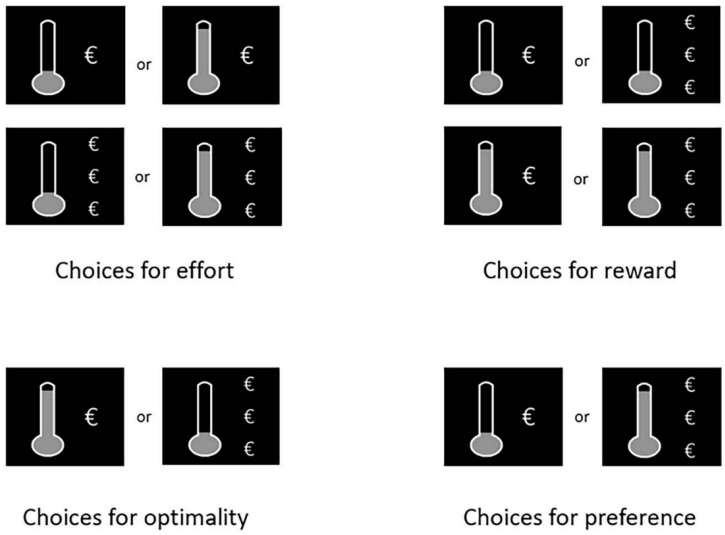

Fig. 3. The possible choices in the EDM task. The four types of choices were presented to participants in similar proportions (25% each). For each choice, the options were randomly presented on the right and on the left. The choices for effort (easy, difficult) had a constant reward. The choice for reward (low, high reward) required constant effort. For the choices for optimality, optimal choices proposed a higher reward for the easiest sequence, whereas non-optimal choices offered a lower reward for a more difficult sequence. For choices for preference, one option was to work harder for a higher reward (high reward difficult), whereas the other option was to work less for a lower reward (low reward easy).

onset at central sites (Novak and Foti 2015; Schevernels et al. 2015; Zhang and Zheng 2022). The CNV was extracted at the electrode with the maximum amplitude and was scored using time-window averages. In the IE task, since the effort cue and the stimulus are delay fixed at 1500 ms, the CNV was computed at Cz, in the time range between 1100 and 1350 ms after the effort cue. In the EDM task, where the delay between the cue and the stimulus is unknown, because of the variable time to make a choice in each trial, the CNV was computed at Cz, in the time range between −100 and 0 ms before the choice response.

Power spectrum analysis. The theta power spectrum (4–8 Hz theta band) was extracted from 7.5 s of the sequence of five numbers. The theta power spectrum was computed in the medial prefrontal cortex (mPFC) electrodes, with a cluster of the four electrodes where the maximum amplitude was observed for each subject.

The beta power spectrum (13–21 and 22–30 Hz beta band) was extracted from 7.5 s of the sequence of five numbers. The beta power spectrum was computed in the central and medial frontal cortex electrodes, with a cluster of eight electrodes (Fz, FCz, Cz, CPz, C1, C2, C3, C4) for each subject.

Statistical analysis

A two-tailed significance level of 0.05 and a trend level of 0.10 were used for all tests. Effect sizes were calculated using a partial eta square (η_p^2).

In the IE task, ANOVAs were performed for behavioral data, the CNV amplitude, and the mPFC theta power, including the within-subject factor Effort cue (easy, difficult) and the between-subject factor Group (control, initiative apathy).

In the EDM task, for behavioral data, four types of choices were dissociated: Choice for reward (low, high), Choice for effort (easy, difficult), Choice for optimality (optimal, not optimal), and Choice of preference (high reward difficult, low reward easy). First, the percentage of choices was subjected to a one-sample Student's *t*-test with a reference of 0.50 to test the randomness of the choices. Then, the percentage of choices per type was subjected to one-way ANOVA's, with the between-subject factor Group (control, initiative apathy). Finally, behavioral data (efficiency and time to choose) were subjected to ANOVA's, including one of the within-subject factor Type of choices and the between-subject factor Group (control, initiative apathy). ANOVAs were performed for the CNV amplitude, the mPFC theta power, and the centro-median beta power, including the within-subject factor Effort (easy, difficult), the within-subject factor Reward (low, high) and the between-subject factor Group (control, initiative apathy).

Pearson correlational analyses were performed between the DAS initiative apathy subscore, the DAS executive and emotional subscores, the validated scales (BDI-II, SES, TEPS), and the behavioral and ERP measures when data were normally distributed (Shapiro–Wilk $P > 0.05$). Kendall correlational analyses were performed when data were not normally distributed (Shapiro–Wilk $P < 0.05$).

ANCOVAs with age, depressive symptoms, and executive apathy as covariates were conducted due to the difference between the two groups. We found that no difference could explain any of the results ($P > 0.05$). See Supplementary Data Table S1 for the detailed results.

Results

IE task

Behavioral results. The ANOVA performed on efficiency revealed a main effect of effort cue ($F(1,45) = 196.68$, $P < 0.001$; $\eta^2 = 0.81$) and a trend for a main effect of group ($F(1,45) = 3.73$, $P < 0.06$; $\eta^2 = 0.08$). Efficiency was lower for difficult than easy cues ($P < 0.001$, $d = 2.07$) and tended to be lower in the initiative than in the control group ($P < 0.06$, $d = 0.54$) (Fig. 4). No effort cue × group interaction was observed ($P > 0.88$).

Effort anticipation. The ANOVA performed on CNV amplitude revealed an effort cue × group interaction ($F(1,45) = 8.56$, $P < 0.005$; $\eta^2 = 0.16$). Bonferroni post-hoc comparisons revealed that the CNV amplitude after a difficult cue was less negative in the initiative than the control group ($P < 0.02$, $d = 0.71$). In the initiative group, the CNV was less negative after a difficult cue than after an easy cue ($P < 0.02$, $d = 0.66$), whereas there was no difference in the control group ($P < 0.20$) (Fig. 5).

Pearson correlational analyses revealed a positive correlation between CNV amplitude after a difficult cue and DAS initiative score ($r = 0.29$, $P < 0.05$) in the sample (both groups). The more severe the initiative apathy trait, the more positive (i.e. the less negative) the CNV amplitude for difficult cues (Fig. 6). Pearson correlational analyses also revealed a positive correlation between CNV amplitude after an easy cue and TEPS anticipatory score ($r = 0.20$, $P < 0.05$) in the sample.

Effort expenditure. The ANOVA performed on mPFC theta power revealed an effort cue × group interaction ($F(1,45) = 11.59$, $P < 0.001$; $\eta^2 = 0.20$) (Fig. 7). Bonferroni post-hoc comparisons revealed a higher mPFC theta power after a difficult cue than an easy cue only in the control group ($P < 0.003$, $d = 0.86$), whereas no such difference was observed in the initiative group ($P > 0.90$). Moreover, after an easy cue, the initiative group had a trend of a higher mPFC theta power than the control group ($P < 0.06$, $d = 0.77$).

Pearson correlational analyses revealed that in the sample (both control and initiative groups), there was a positive correlation between mPFC theta after an easy cue and DAS initiative score ($r = 0.40$, $P < 0.05$), and a negative correlation between mPFC theta after an easy cue and self-esteem score ($r = -0.35$, $P < 0.05$). The more severe the initiative apathy trait and the lower the self-esteem, the higher the mPFC theta power in the easy cue (Fig. 8).

EDM task

Behavioral results. For both groups, all types of choices were different from random, except for the choices for rewards (all $P < 0.05$, except choices for reward $P > 0.20$).

The ANOVA performed on the percentage of difficult choices revealed a main effect of group ($F(1,45) = 4.10$, $P < 0.05$, $\eta^2 = 0.08$). The initiative group made less difficult choices than the control group (15% vs 35%, respectively). The ANOVA performed on the percentage of high reward choices revealed no effect of group ($F(1,45) = 1.36$, $P < 0.25$, $\eta^2 = 0.03$). The ANOVA performed on the percentage of optimal choices revealed a main effect of group ($F(1,45) = 4.23$, $P < 0.05$, $\eta^2 = 0.09$). The initiative group made fewer optimal choices than the control group (1% vs 16%, respectively). Kendall correlational analyses revealed that in the sample (both groups), there was a negative correlation between the percentage of optimal choices and the DAS initiative score ($\tau = -0.43$, $P < 0.05$) (Fig. 9). The ANOVA performed on the percentage of high reward difficult choices revealed no effect of group ($F(1,45) = 0.85$, $P < 0.35$, $\eta^2 = 0.02$).

The ANOVA performed on the time taken to make a choice revealed a main effect of reward ($F(1,44) = 8.30$, $P < 0.01$; $\eta^2 = 0.16$), with more time taken for high reward than low reward. The ANOVA performed on the time taken to make a choice revealed a main effect of optimality ($F(1,12) = 4.60$, $P < 0.05$; $\eta^2 = 0.28$), with more time taken for optimal than non-optimal choices. There was no effect of group ($P < 0.25$) and no reward × group interaction ($P < 0.20$).

The ANOVA performed on efficiency revealed an effort × group interaction ($F(1,41) = 5.07$, $P < 0.03$; $\eta^2 = 0.11$) but no motivation × group interaction ($F(1,44) = 0.53$, $P < 0.55$; $\eta^2 < 0.01$). Bonferroni post-hoc comparisons revealed that the initiative group was less efficient after a difficult choice than the control group ($P < 0.05$, $d = 0.59$). The initiative group was also less efficient after a difficult than an easy choice ($P < 0.001$, $d = 1.11$).

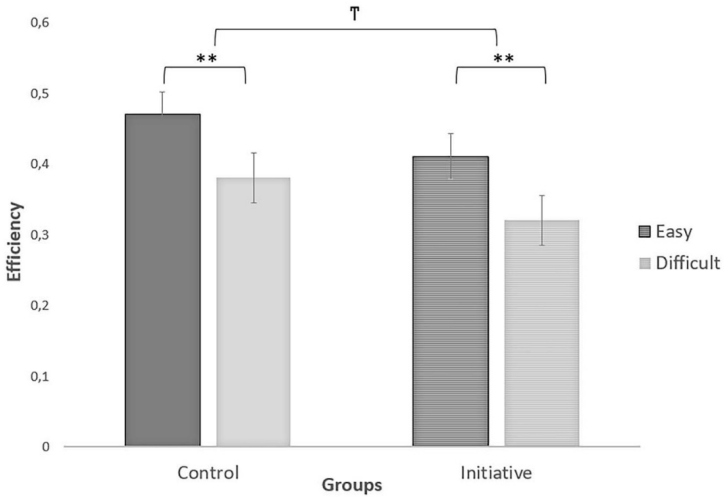

Fig. 4. Mean and standard deviation of efficiency for control and initiative groups during easy (in dark gray) and difficult (in light gray) trials in the IE task: $^{**}P < 0.01$; T $P < 0.06$. The control group is represented in solid colors and the initiative group in striped colors.

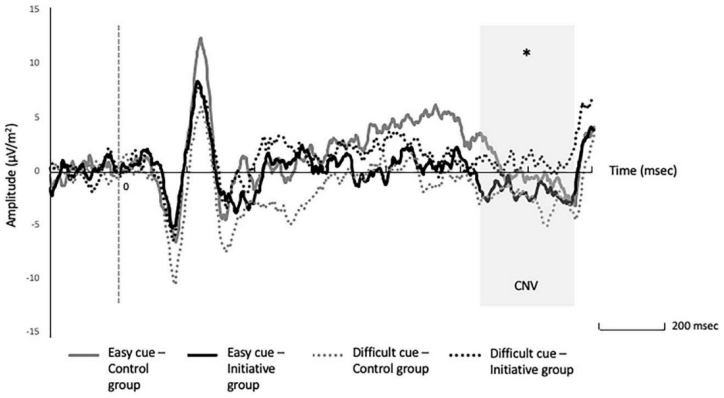

Fig. 5. CNV amplitude at Cz after an easy and a difficult cue in the control and initiative groups during the IE task: $^{*}P < 0.05$. The analyzed time window is represented in gray. The effort cue appears at 0 ms.

Effort choice anticipation. The ANOVA performed on CNV amplitude revealed a trend for a main effect of effort ($F(1,44) = 3.20$, $P < 0.08$; $\eta^2 = 0.07$), with a more negative CNV amplitude after a difficult than an easy cue. No other effect was observed. Pearson correlational analyses revealed that in the sample (both groups), there was a positive correlation between CNV amplitude after a difficult low reward cue and TEPS consummatory score ($r = 0.44$, $P < 0.05$).

Effort expenditure. The ANOVA performed on mPFC theta power revealed an effort × reward × group interaction ($F(1,39) = 8.19$, $P < 0.01$; $\eta^2 = 0.17$). Bonferroni post-hoc comparisons revealed a higher mPFC theta power after a difficult high reward choice than all the other choices in the control group (difficult low reward $P < 0.03$, $d = 0.56$; easy high reward $P < 0.02$, $d = 0.49$; easy low reward $P < 0.06$, $d = 0.40$). The initiative group had a lower mPFC theta power after a difficult high reward choice than an easy high reward choice ($P < 0.01$, $d = 0.61$) and a trend for a lower mPFC theta power after a difficult high reward choice than after a difficult low reward choice ($P < 0.07$, $d = 0.43$). The control group also had a trend for a higher mPFC theta power after a difficult high reward choice than the initiative group ($P < 0.06$, $d = 0.81$) (Fig. 10).

Pearson correlational analyses revealed that in the control group, there was a negative correlation between mPFC theta after an easy low reward choice and DAS initiative score ($r = -0.49$, $P < 0.05$). Instead, in the initiative group, the analyses revealed a positive correlation between mPFC theta after an easy low reward and after a difficult low reward choice and DAS initiative score (respectively, $r = 0.42$ and 0.51, $P < 0.05$). The more severe the initiative apathy trait, the higher the mPFC theta power in the easy low reward choices. In the initiative group, the more severe the initiative apathy, the higher the mPFC theta power in the difficult low reward choices. Moreover, Pearson correlational analyses revealed that in the sample (both groups), there was a negative correlation between mPFC theta after a difficult high reward choice and DAS initiative score ($r = -0.35$, $P < 0.05$). The more severe the initiative apathy trait, the lower the mPFC theta power in the difficult high reward choices (Fig. 11).

Following the mPFC theta results obtained, we analyzed the beta power spectrum by distinguishing two frequency bands: the

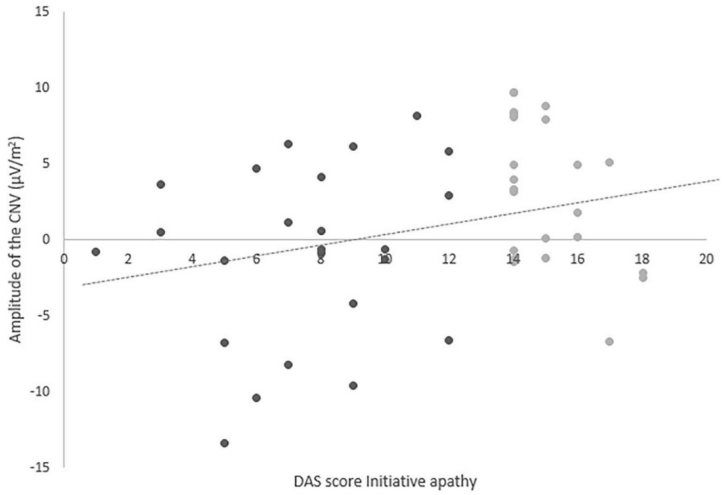

Fig. 6. Correlation between CNV amplitude for difficult trials in the IE task and DAS score of initiative apathy ($r = 0.29$, $P < 0.05$). The control group is represented in dark gray and the initiative group in light gray.

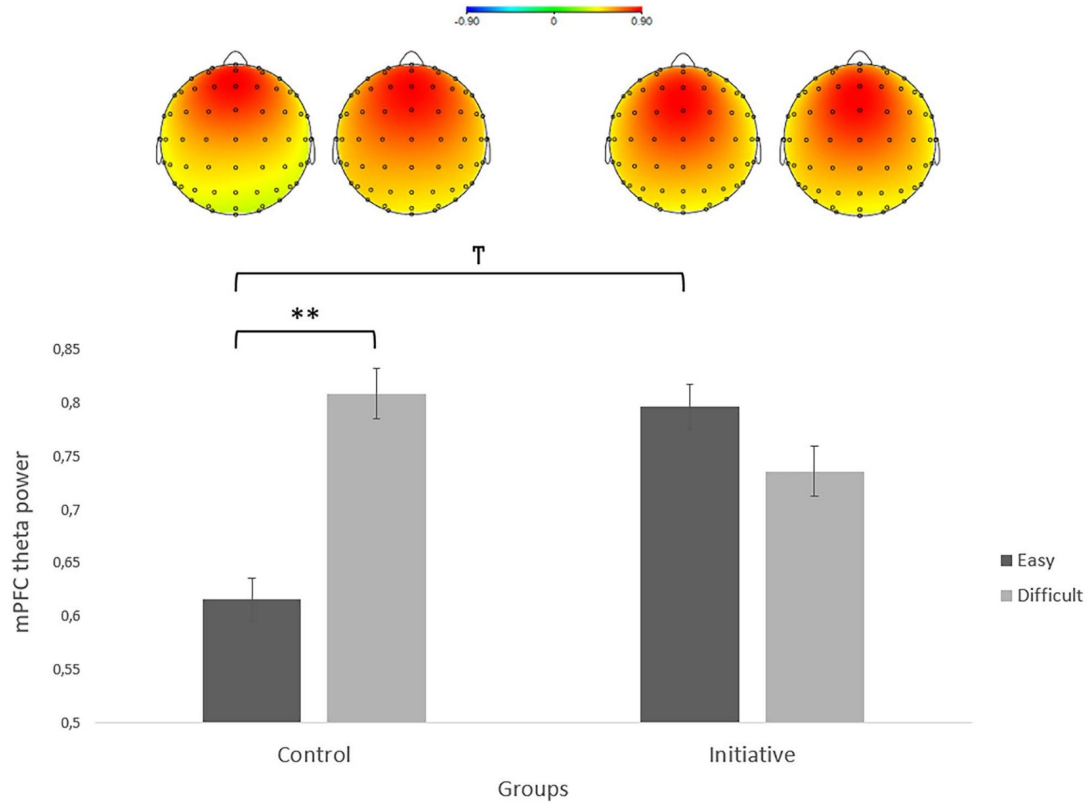

Fig. 7. Mean and standard deviation of mPFC theta power after an easy and a difficult cue in the control and initiative groups during the IE task: ** $P < 0.01$; T $P < 0.06$.

13–21 Hz low beta band, reflecting the normal activating network, and the 22–30 Hz high beta band, reflecting the over-stimulation network (Demerdzieva 2011; Díaz et al. 2019).

The ANOVA performed on low beta power revealed a trend of a main effect of effort ($F(1,38) = 2.55$, $P < 0.10$; $\eta^2 = 0.06$) on the power, with a higher low-beta-band power after a difficult than an easy high reward choice. No other effect was observed. Bonferroni post-hoc comparisons revealed a lower low-beta-band power after a difficult high reward choice than an easy high reward choice in the initiative group ($P < 0.04$, $d = 0.40$), but not in

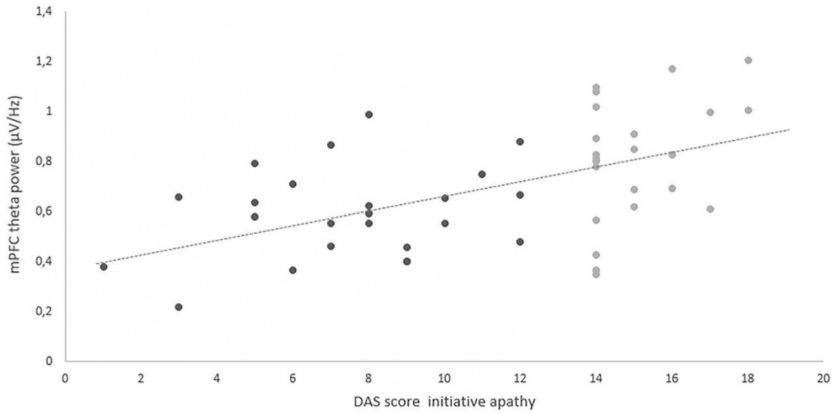

Fig. 8. Positive correlation between mPFC theta after an easy cue in the IE task and DAS score of initiative apathy ($r = 0.40$ $P < 0.05$). The control group is represented in dark gray and the initiative group in light gray.

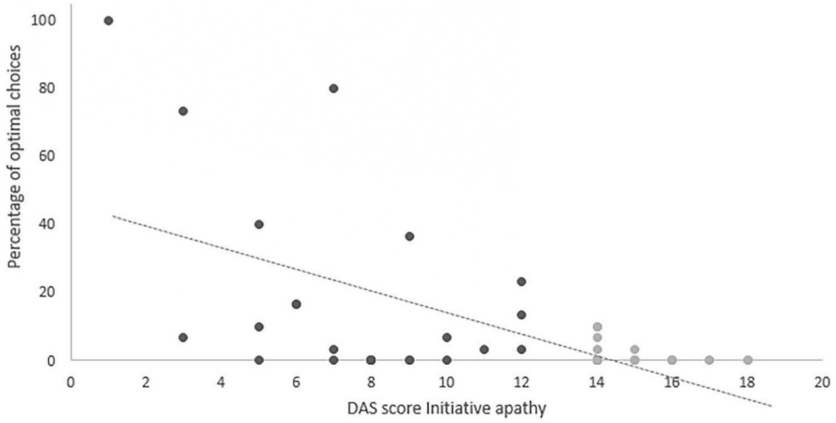

Fig. 9. Distribution of the percentage of optimal choices in the EDM task according to the severity of the DAS score of initiative apathy ($\tau = -0.43$, $P < 0.05$). The control group is represented in dark gray and the initiative group in light gray.

the control group ($P < 0.75$). The ANOVA performed on high beta power revealed no effect of effort ($P < 0.36$) and no effect of group ($P < 0.40$) on the power. Furthermore, there was no interaction ($P < 0.60$).

Discussion

The main aim of the present study was to further the understanding of the cognitive and neural effort-based mechanisms underlying initiative apathy. Using two tasks—an imposed effort task and a free choice EDM task—and an EEG recording, we explored electrophysiological correlates of effort anticipation and effort expenditure and their potential modulation by motivation in healthy subjects with a subclinical level of initiative apathy. Our results, highlighted both by contrasting the initiative and healthy control groups (extreme-group approach) and by linking the results more directly to the level of initiative apathy (individual differences approach), showed effort avoidance and effort expenditure impairments that suggest that subjects with initiative apathy have EDM deficits.

First, our behavioral results suggest that people with a subclinical level of initiative apathy are more sensitive to cognitive effort. Indeed, in the EDM task, subjects with initiative apathy are less willing to choose trials that require greater effort, with this group making 50% fewer difficult choices than healthy control subjects. The avoidance of cognitive effort aligns with Bonnelle et al.'s (2016) findings that a group with a similar trait of initiative apathy avoids physical effort (Bonnelle et al. 2016). Both illustrate well the significant decrease in effort and productivity that characterizes the initiative form of apathy described in various neurological and psychiatric pathologies (Marin and Wilkosz 2005). Interestingly, the analysis of electrophysiological data in the IE task, which imposes the level of trial difficulty, revealed that subjects with initiative apathy do not even prepare themselves for difficult trials. Indeed, subjects with initiative apathy not only show a smaller CNV amplitude in difficult trials compared to easy trials but also a smaller CNV amplitude in difficult trials compared with control subjects. Subjects with initiative apathy do not anticipate that they will need to expend mental effort. They do not proactively modulate attentional resources as a function of the expected effort, a specificity which could be directly related to the reduced activation in the dorsal ACC and supplementary motor area (SMA), the two main regions altered in initiative apathy (Pagonabarraga et al. 2015). Indeed,

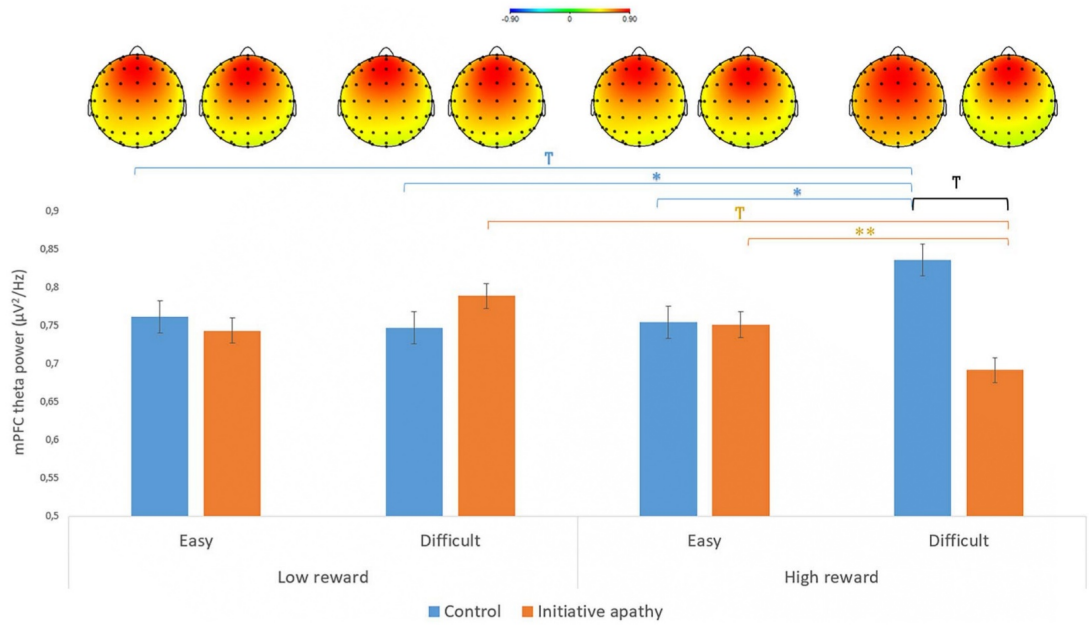

Fig. 10. Mean and standard deviation of mPFC theta power for the four types of choices in the control and initiative groups during the EDM task: $^{**}P < 0.01$; $^{*}P < 0.05$, T $P < 0.07$.

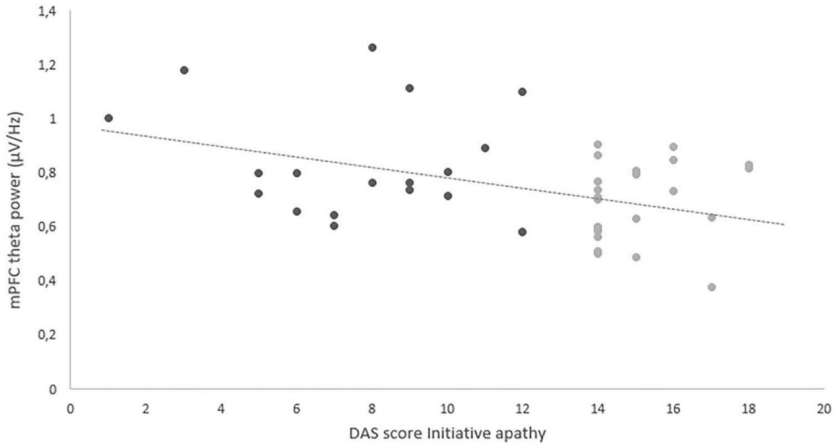

Fig. 11. Negative correlation between mPFC theta after a difficult high reward choice in the EDM task and DAS score of initiative apathy ($r = -0.35$, $P < 0.05$). The control group is represented in dark gray and the initiative group in light gray.

previous studies conducted on healthy subjects showed that reduced activity in the ACC and SMA was linked to impaired ability to anticipate, evidenced by a smaller CNV (Gómez et al. 2003; Nagai et al. 2004). A decreased structural and functional connectivity between the ACC and SMA has been correlated with increased initiative apathy and the lower willingness to engage in an effort (Bonnelle et al. 2016). Moreover, by highlighting the link between the severity of subclinical initiative apathy and effort anticipation (whereby the higher the initiative apathy trait, the lesser the effort anticipation), the study results allow us to further the understanding of individual differences in the ability to anticipate effort. It must be underlined that motivation, manipulated in the present study through low and high rewards, did not show any effect on the effort anticipation, both for subjects with and without initiative apathy. It may be the case that incentives were not rewarding enough to lead subjects to modulate their preparation according to the value of the reward (Bonnelle et al. 2015; Green et al. 2015).

Interestingly, cognitive effort avoidance and effort anticipation impairments have been related to inefficient cognitive effort expenditure in depressed people (Berwian et al. 2020; Tran et al. 2021). In relation to these findings, our results concerning the effort expenditure provide some explanations for previous specificities highlighted in subjects with initiative apathy. Indeed, while completing the trials in the IE task, subjects with initiative apathy have the same mPFC theta power in easy and difficult trials, and

this power is equivalent to that of control subjects in difficult trials. Thus, in contrast to healthy subjects whose mPFC theta power increases as a function of difficulty, as previously shown (Smit et al. 2005; Mussel et al. 2016), subjects with initiative apathy do not display evidence of such effort expenditure modulation. This result suggests that subjects with initiative apathy have an impaired effort expenditure, possibly due to the alterations evidenced in the ACC (Domic et al. 2021; McFerren et al. 2021). Moreover, as for the results on anticipation, our results shed light on the link between the severity of subclinical initiative apathy and the allocation of effort expenditure (the higher the initiative apathy trait, the higher the effort expenditure on easy trials). Therefore, people with high initiative apathy trait do not modulate their effort expenditure according to a context only defined by effort. It is still unknown how these subjects modulate effort expenditure in a task that combines effort and motivation.

In the EDM task, if mPFC theta power is modulated by motivation, as previously shown in healthy people (Cohen et al. 2007; Gruber et al. 2013), in the sense that the highest mPFC theta occurs in a difficult sequence with high reward, such modulation does not exist in subjects with initiative apathy. Subjects with initiative apathy seem unable to strategically modulate their effort expenditure since they stop investing effort only when the potential reward is higher. Therefore, contrary to healthy subjects, subjects with initiative apathy seem unable to compute effort costs and motivational benefits, i.e. calculate when they need to work harder to obtain a reward that justifies investing the effort (Kurzban 2016; Shenhav et al. 2017). Moreover, correlations between the severity of initiative apathy and the lack of modulation of effort expenditure for difficult trials with low and high rewards confirm that individual differences in initiative apathy trait could modulate the capacity to compute effort and reward information during periods of effort expenditure.

It is difficult to interpret our effort expenditure results because EDM paradigms in the literature only compare low-reward low-effort conditions with high-reward high-effort ones. Studies usually conclude by finding an effort discounting, where high-demand effort can discount reward to obtain it (Westbrook and Braver 2015; Chong et al. 2017; Bogdanov et al. 2022). In the present study, the same amount of effort is valuated differently according to the reward: the effort is willingly exerted only for a small reward but not a large reward. Instead of effort discounting, these abnormal effort expenditure results might be explained by a deficit of incentive motivation secondary to a distortion of performance judgments (Cléry-Melin et al. 2011; Green et al. 2015). Following this hypothesis, people with initiative apathy may guess that they should perform better for difficult high-reward trials but feel unable to fulfill this expectation. These defeatist beliefs could prevent them from engaging more effortfully in effortful trials with potentially high rewards. However, our study did not ask participants about their anxiety or defeatist beliefs. A first but tenuous argument in favor of this hypothesis could be that subjects with initiative apathy present a modulation of beta power activity assumed to reflect a hypo-arousal that has been linked to lower cognitive resources and anxiety (Díaz et al. 2019; Micoulaud-Franchi et al. 2021). Indeed, people with initiative apathy tend to present a lower beta power only after being presented with a difficult choice with a potential high reward compared with other choices, whereas healthy subjects present no modulation of beta power when presented with all choices. Moreover, this beta result could be linked to the fact that the higher the severity of initiative apathy, the lower the self-esteem and the higher the allocation of the effort expenditure for imposed easy trials in the IE task. Lastly, healthy people usually will undertake effortful behaviors when the consequences of their behaviors are under their direct control (i.e. when they choose the consequence), relative to when they follow someone else's decision (i.e. the consequence was imposed on them) (Chambon et al. 2020). Studies have already shown that people with subclinical anxiety, defeatist beliefs, and aberrations in decision-making have a diminished preference for free choices compared to imposed choices (Zorowitz et al. 2020; Zorowitz et al. 2021). Therefore, a distortion of performance judgments, maybe underlined by lower self-esteem and/or higher anxiety, could lead to abnormal effort expenditure in initiative apathy.

Finally, our results all point toward abnormal effort anticipation and expenditure when situations are experienced more difficult, suggesting specific effort impairments in initiative apathy. This finding aligns with what is usually observed in clinical descriptions: mental emptiness in daily life with difficulties in engaging in complex goal-directed behaviors. In effort-cost theories, people who are effort-avoidant and unable to anticipate and strategically modulate their effort expenditure could present abnormal cost-benefit computations. Indeed, healthy cost-benefit decision-making weighs the potential rewards conferred by effort expenditure against its effort costs. A healthy subject will be motivated to expend effort to obtain a high reward and be unwilling to exert a higher effort for a low reward (Westbrook and Braver 2015; Kool and Botvinick 2018; Bogdanov et al. 2022). In contrast, abnormal cost-benefit decision-making implies an inability to optimize the effort choice in response to the reward information in the environment. Indeed, in the EDM task, apathetic participants made fewer than 1% of optimal choices, in terms of maximizing rewards for less effort, suggesting that the few times they chose effortful options, they did not make strategic choices but did so for choices with lower rewards. Their non-optimal decision-making does not seem to be explained by a comprehension difficulty since any participant randomly chooses their effort options. Furthermore, in all the sample, the fewer optimal choices the participants make, the higher their initiative apathy trait is, suggesting that the initiative apathy trait might govern someone's efficacy in combining effort and reward information to make a free choice. In practical terms, this link between the severity of initiative apathy and non-optimal EDM could explain some clinical behaviors seen in patients with initiative apathy. Indeed, whether they have a neurological, neurodegenerative, or psychiatric disorder, these patients are often described as finding it difficult to initiate an action but being able to complete this action when someone helps them start (Levy and Dubois 2006). Therefore, any therapy that aims to alleviate their apathetic symptoms needs to start with external guidance that naturally overrides the decision-making stage of the action process. Further studies need to explore these psychological difficulties that initiative apathy subjects face and its consequences for EDM in daily life.

To conclude, this study sheds light on the specificities of EDM in initiative apathy, which induces a cognitive effort avoidance similar to the clinical descriptions of these patients. These specificities could be explained by an abnormal modulation of the effort expenditure. Indeed, people with a high initiative apathy trait do not seem "less able" than healthy subjects with a low initiative apathy trait to produce an overall effort. However, they seem unable to optimize the anticipation and expenditure of effort

in response to the reward information in the environment. This inability could be underpinned by abnormal cost-benefits computations. Moreover, these abnormal effort mechanisms could be specific to this form of apathy since only the initiative apathy trait in the normal population is related to individual differences in the ability to anticipate and expend effort according to the context. Since initiative apathy is the most disabling form of apathy and is prevalent in the population, but patients are often left without any support, it seems crucial to conduct additional studies that further the understanding of the mechanisms underlying this symptom and can help propose new and efficient targeting treatments.

Acknowledgments

We thank the staff of the Unit 1114 of the French Institute of Health and Medical Research and of the Strasbourg University Hospital, and especially Julien Krieg for his assistance with the tasks.

Data availability

Data can be available on request.

Supplementary material

Supplementary material is available at *Cerebral Cortex* online.

Funding

This research was supported by the French Ministry of Higher Education and Research grant (to G.L.-B.).

Conflict of interest statement: None declared.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation (Research ethics committee of the University of Strasbourg—UNISTRA/CER/2020-13) and with the Helsinki Declaration of 1975, as revised in 2008.

Authors' contributions

Giulia Lafond-Brina (Conceptualization, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing—original draft, Writing—review and editing), Bich-Thuy Pham (Investigation, Writing—review and editing), Anne Bonnefond (Conceptualization, Data curation, Methodology, Project administration, Supervision, Validation, Writing—review and editing).

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Résumé des principaux résultats

L'étude 3 a permis de mettre en évidence, à l'aide de deux tâches cognitives (effort imposé ou choix libre), l'altération des processus d'effort et de prise de décision chez des sujets avec un phénotype pur d'apathie d'initiation.

Plus précisément, les sujets avec une apathie d'initiation ont des difficultés pour anticiper et déployer de l'effort cognitif en fonction des indices du contexte. De façon intéressante, les résultats révèlent également que plus un individu présente un trait d'apathie d'initiation sévère, plus il présente des difficultés à anticiper l'effort cognitif et à adapter le déploiement de l'effort aux indices contextuels cognitifs et motivationnels. Par ailleurs, nos résultats mettent également en évidence un évitement de l'effort cognitif et une incapacité à effectuer des choix optimaux pour les personnes avec un trait d'apathie d'initiation. En révélant une corrélation négative entre le pourcentage de choix optimaux et la sévérité de l'apathie d'initiation, nos résultats suggèrent que l'apathie d'initiation pourrait être associée à une difficulté à combiner/intégrer des informations de nature différente pour prendre une décision. Enfin, ces déficits d'effort et de prise de décision semblent être spécifiques à l'apathie d'initiation puisque seul le trait d'apathie d'initiation dans la population jeune est lié aux différences individuelles dans la capacité d'anticiper et de déployer des efforts selon le contexte.

Méta-analyse

Lafond-Brina, G., Dormegny-Jeanjean, L. & Bonnefond, A. (en préparation). A systematic review and ALE meta-analysis of cognitive control and motivation in schizophrenia and mood disorders: implications for multidimensional apathy.

A systematic review and ALE meta-analysis of cognitive control and motivation in schizophrenia and mood disorders: implications for multidimensional apathy

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Abstract

Apathy is present in more than 50% of patients suffering from schizophrenia (SZ) and mood disorders (MD). Even though these two disorders are very different, in psychiatry, apathy is typically assumed to be the same unidimensional clinical entity, sharing the same pathophysiological processes and symptoms, regardless of the underlying diagnosis. The field of neurology proposes another perspective: three forms of apathy —emotional, executive, and initiative— are related, respectively, to a disturbance in motivational processing, cognitive control, or both. In this study, we explored whether this latter model can be applied in psychiatry by identifying differences between SZ and MD through a PRISMA meta-analysis of imaging studies on motivational and cognitive control networks. We searched in the Sleuth BrainMap database for studies with SZ, MD, and/or healthy controls using the Monetary Incentive Delay Task or the AX-Continuous Performance Task, which explore motivation and cognitive control, respectively. We then conducted a coordinate-based activation likelihood estimation analysis. Twenty functional MRI studies were identified and included in the analysis. The results highlight that emotional apathy could be dominant in SZ, as evidenced by a hypoactivity in the motivational structures and a specific hyperactivity in the right cerebellar vermis that has previously been linked to emotional blunting and apathy. Initiative apathy could be dominant in MD, as evidenced by hypoactivity in both cognitive control and motivational structures, which has previously been linked to the co-occurrence of executive difficulty and amotivation. Despite a small number of studies, our results could help target new individualized treatment strategies in precision psychiatry based on a multidimensional approach to apathy.

Keywords

Proactive control
Wanting
Liking
Avolition
Activation likelihood estimation
Functional MRI

Introduction

Apathy, a behavioral symptom that often appears during the prodromal phase of psychiatric disorders, is prevalent in patients suffering from both psychotic disorders (including schizophrenia [SZ]) and mood disorders (MD) (Cannon et al., 2016; Faerden et al., 2009; Galderisi et al., 2021; Ishizaki & Mimura, 2011; Mulin et al., 2011). Paradoxically, apathy, which is extremely burdensome for these patients, has been poorly studied in psychiatry, and dedicated treatment options remain scarce (Galderisi et al., 2018; Ma et al., 2021).

Why does psychiatry need to reconsider its common approach to apathy? Historically, psychiatry of the early 20th century described a precise semiology of apathy and motivational disorders with a multitude of symptom-specific terms: “avolition” for lack of initiative, “apragmatism” for inability to conduct daily basis actions, and “athymhormie” (i.e. the loss of psychic self-activation conceptualized by the French psychiatrists Dide and Guiraud) (see review by Dollfus, 2018). This detailed semiology carried certain hypotheses, including that the various apathetic symptoms may be supported by specific pathophysiological processes that may interact with each other. By extension, these symptoms and the pathophysiological processes associated with them may be transnosographic for some, and specific to MD or SZ for others (e.g., according to Delay’s concept of “hypothymie”, SZ patients seem indifferent to their emotional blunting, whereas MD patients suffer from it and demonstrate guilt, sadness, or moral pain; Delay, 1946).

However, the atheoretical conception of modern psychiatric classifications (i.e., the DSM and the ICD) has replaced these systems-based neurology approaches (Foucher & Bennouna Greene, 2010). In this context, semiological terms used for apathy-related symptoms in various disorders are now considered almost synonymous and even sometimes used without distinctions, while, paradoxically, the possibility that they may involve transdiagnostic pathophysiological pathways or equifinality has been bypassed (review in Strauss & Cohen, 2017). As apathy is still underdiagnosed and underrecognized as the outcome of specific pathophysiological processes, psychiatry lacks specific therapeutic strategies (Galderisi et al., 2018). Some treatments may even worsen these processes (e.g. selective monoamine reuptake inhibitor in MD; see Ma et al., 2021; McCabe et al., 2010; Padala et al., 2020), which can result in apathy as a chronic residual symptom. Recent neuroscience-based approaches (e.g. the Research Domain Criteria [RDoCs] initiative) propose modeling the link between pathology, behavior, and neurobiology using transdiagnostic constructs (see review in Barch et al., 2016). However, the RDoCs initiative is still seeking a model for practical application in the clinical setting.

Levy and Dubois’s (2006) neurological model of apathy may be a good compromise to overcome these limits while retaining operationalized and practical model. Indeed, based on

clinical observations of neurological patients with brain lesions affecting the prefrontal cortex (PFC) and the basal ganglia, three forms of apathy —emotional, executive, initiative— related to a disruption of “emotional–affective”, “cognitive” or “auto-activation” processing, respectively, have been identified (Levy & Dubois, 2006; Pagonabarraga et al., 2015; Radakovic & Abrahams, 2018). As such, the existence of a dominant form of apathy is assumed to be related to a neurological system dysfunction, irrespective of the overall diagnosis. For example, emotional apathy would suggest a specific impairment of the motivational network (orbital and ventromedial PFC, as well as the limbic territories of the basal ganglia, especially the ventral striatum; Kringelbach, 2005; Kringelbach & Rolls, 2004; Zald, 2007), while executive apathy suggests an impairment of the cognitive control network (dorso/ventrolateral PFC, as well as the cognitive territory of the basal ganglia; Miller & Cohen, 2001; Nejati et al., 2018). Therefore, the neurological model of apathy links symptomatology and pathophysiological impairment more readily than the DSM's atheoretical model. This approach is also more practical and easily applicable to clinical medicine than the RDoCs initiative’s, insofar as it remains compatible with the categorical biomedical paradigm and with the development of operationalized diagnostic and treatment guidelines.

fMRI studies in SZ and MD have already explored the potential links between functional impairments of cognitive processes and apathy without a physiopathological hypothesis. In this sense, concerning motivational processing, a body of evidence exists in favor of preserving ability to experience immediate pleasure (i.e. liking related processes) in SZ, but impaired ability to hedonic processes that involve a time delay (e.g. in wanting related processes) (see a review in Moran et al., 2022). However, more mixed evidence exists in MD, with clinical studies pointing toward impaired wanting-related processes (Hallford et al., 2020), whereas fMRI studies identify both wanting and liking deficits (Barch et al., 2016; Borsini et al., 2020; Rizvi et al., 2018). Concerning cognitive control processing in SZ, several studies have shown an inability to anticipate and actively represent goal information needed to guide behavior (i.e. the deficit of proactive cognitive control process; see a review in Barch & Sheffield, 2017), whereas in MD, the evidence is more heterogeneous and points to cognitive control deficits that can be more proactive or reactive depending on the context and the emotional and motivational state of the subjects (Grahek et al., 2018, 2019; Paulus, 2015).

Highlighting the dominant form of apathy in SZ and MD could be a first step to providing some more precise hypotheses in terms of the impaired mechanisms behind apathy in these two disorders. To do this, the development of meta-analysis methods for neuroimaging data provides a valuable tool for combining data across diverse studies and building consensus in the identification of neuroanatomical correlates of specific processes. Activation likelihood estimation (ALE) metanalysis, one of the most promising and reliable statistical meta-analysis approaches, weights the foci by the number of participants in each study, identifies common

activations across different studies, and uses random-effects inference (Eickhoff et al., 2009, 2012; Laird, Lancaster, et al., 2005). An ALE meta-analysis of neuroimaging studies of motivational and cognitive control processes in SZ and MD, discussed in regard to the known neural substrates of multidimensional apathy, thus seems like a promising approach to investigating the existence of dominant forms of apathy in psychiatric disorders. The objective of the present meta-analysis is to determine the extent to which the observed functional activations of motivational and cognitive control networks in SZ and MD could suggest the existence of dominant forms of apathy specific to each of these psychiatric disorders.

Method

Literature selection

A search of the Sleuth BrainMap database (Laird, Lancaster, et al., 2005) was performed to identify all English-language, peer-reviewed studies that reported fMRI activations related to motivation or cognitive control in healthy controls (HC) and patients suffering from SZ and/or MD, using fMRI or positron emission tomography (PET). The online research was conducted using the diagnosis keywords 'Schizophrenia' or 'Major depressive disorder' or 'Bipolar disorder' or 'Healthy controls' and the paradigm keywords 'Reward' or 'Go/no go' or 'n-back' or 'button press'. No other research filter was used. In addition, all the references of retrieved studies and pertinent review articles were manually checked.

To investigate motivational processes, we only examined studies that used the MID task (Knutson et al., 2000). The MID task is a simple detection task that allows the exploration of the two motivational components, the wanting, *i.e.* the anticipation of a reward, and liking, *i.e.* the feeling of pleasure when obtaining that reward (Berridge et al., 2009; Gard et al., 2006; Knutson et al., 2000) (Figure 1a). During the MID, the wanting is investigated by the reward or loss cue vs neutral cue during the anticipation phase; the liking during the receipt phase.

To investigate cognitive control, we only examined studies that used the AX-Continuous Performance Test (AX-CPT) task (Servan-Schreiber et al., 1996). The AX-CPT is a cue-probe detection task that is the most used paradigm to explore proactive and reactive cognitive control processes (Servan-Schreiber et al., 1996), corresponding respectively to a control mode engaged before *versus* at the moment of target appearance (Braver, 2012; Braver et al., 2009) (Figure 1b). During the AX-CPT, the A vs B cues reflect the proactive cognitive control, whereas the reactive cognitive control is based on AX vs AY vs BX trials.

Figure 1

For the current meta-analysis, the following inclusion criteria for fMRI studies were utilized:
(1) subjects were healthy controls or patients diagnosed with either MD or SZ;
(2) MD or SZ were diagnosed according to DSM-III, DSM-IV(−TR) or DSM-5;
(3) studies reporting imaging results of activations and deactivations using blood oxygen level-dependent (BOLD) fMRI (1.5 or 3T) with whole brain analysis;

(4) studies using the MID (wanting and liking) and/or the CPT-AX (cognitive control) as experimental fMRI paradigms and reporting first-level analysis results (i.e. paradigm-related within group contrasts);
(5) studies contrasted directly two active conditions (e.g., monetary gain or loss vs neutral cue, B vs A cues);
(6) coordinates were reported in either standard Talairach space or Montreal Neurologic Institute (MNI) space.

Studies were excluded if:
(1) the subject pool overlapped with other published studies on smaller subsets of the same sample (in that case, the subject included was the one with the larger sample size).
(2) there was no whole-brain analyses;
(3) coordinates could not be retrieved;
(4) comparisons included a resting state condition.
No age, gender or treatment restrictions were applied.

ALE meta-analysis procedure

Coordinates from motivation and cognitive control studies were analyzed separately following the Activation Likelihood Estimation (ALE) technique implemented in GingerALE 3.0.2 (http://brainmap.org/ale/, RRID: SCR_014921). This version uses a random effect model and weighting for sample size of the original studies (Eickhoff et al., 2009; Laird, Fox, et al., 2005). Coordinates of the foci of activation reported in the original studies were transformed into Talairach space using the Lancaster transform (icbm2tal tool) in GingerALE (Laird et al., 2010). In ALE, activation foci reported in original studies are treated as 3D Gaussian distributions centered at the reported coordinates. Activation probabilities are then calculated for each standard-space voxel to construct ALE maps for contrasts of interest. To determine the reliability of the ALE map, null-distributions are generated by analyzing the distribution of ALE values across independent studies, which is conceptually similar to using permutation tests of individual voxels across experiments. The observed values in the ALE distribution are then compared to the null distribution in order to assign probability estimates to the experimental data.
Three ALE analysis sets, based on paradigm related within-group contrasts maps for each group (MD, SZ and HC) were realized. Then, for comparisons, the ALE maps for SZ and MD for each experimental design were contrasted using subtraction meta-analysis procedure implemented in GingerALE (Laird, Fox, et al., 2005). For all analyses, only clusters exceeding the $p = 0.05$ FWE-corrected significance threshold were considered.

For visualization, whole-brain maps of ALE maps were imported into multi-image analysis GUI (MANGO; http://ric.uthscsa.edu/mango, RRID: SCR_009603) and overlaid onto a standardized anatomical template in Talairach space (Colin 1x1x1, available in www.brainmap.org/ale).

Results

1598 records were identified in the Sleuth database and 20 studies were included in the meta-analysis (see the flow diagram of studies selection process in Figure 2).

Figure 2

Identification details of included studies, within each domain, are reported in Table 1a. The sample characteristics for each study are summarized in Table 1b.

Table 1

The detailed information about cluster size and peak ALE maxima and locations are show in Table 2

Table 2

1. Motivational task

1.1. Wanting (reward/loss > neutral cues)

A total of 15 experiments with 289 HC reporting 170 foci, 4 experiments with 99 MD patients reporting 75 foci, and 11 experiments with 227 SZ patients reporting 94 foci were included in the analyses for wanting.

1.1.1. Within-group analyses

For wanting, ALE analysis revealed, in MD, that no brain regions are consistently found to present a modulation of likelihood of activation after a reward (or loss) cue compared to a neutral cue.

ALE analysis revealed that SZ patients have several regions that present increased activity after a reward (or loss) cue than a neutral cue in right frontal lobe, such as inferior and middle frontal gyrus and insula, as well as in anterior and posterior lobe of the cerebellum, including culmen, declive and uvula.

ALE analysis revealed that HC have increased activity after a reward (or loss) cue compared to a neutral cue that is more frequently reported in a set of subcortical areas, including bilateral putamen, bilateral lateral globus pallidus, bilateral caudate body, precentral gyrus, insula, as well as occipital lobe and right precuneus.

1.1.2. Mood disorders vs. healthy controls

Impossible to do because of the lack of activation in the MD group.

1.1.3. Schizophrenia vs. healthy controls

During reward (or loss) anticipation compared to neutral cue, ALE analysis revealed that, compared to SZ, HC showed increased activity in a set of subcortical areas, including bilateral putamen, left lateral globus pallidus, bilateral caudate body, left ventral anterior and lateral nucleus, right amygdala, right precentral gyrus, as well as left occipital lobe. Conversely, SZ patients present greater activation HC on the right anterior lobe of the cerebellum, including culmen, declive and uvula, as well as the right insula (see Figure 3.a).

1.2. Liking (reward/loss > neutral feedback)

A total of 11 experiments with 230 HC reporting 120 foci, 4 experiments with 99 MD patients reporting 10 foci, and 7 experiments with 170 SZ patients reporting 9 foci were included in the analyses for liking.

1.2.1. Within-group analyses

For liking, ALE analysis revealed, after reward (or loss) feedback compared to neutral feedback, that MD patients present increased activity of a broad cortical-subcortical network, including left posterior cingulate, left culmen and precuneus, bilateral caudate body, left putamen and bilateral ventral lateral nucleus.

ALE analysis revealed, after reward (or loss) feedback compared to neutral feedback, that SZ patients present increased activity in bilateral frontotemporal gyrus, such as insula, superior temporal gyrus, inferior frontal gyrus, (anterior) cingulate gyrus, as well as in the right posterior-anterior lobe, including uvula, declive and culmen.

ALE analysis revealed, in HC, increased activity after reward (or loss) feedback compared to neutral feedback are consistently found in a bilateral cortical-subcortical network, including putamen, caudate (head and body), lateral globus pallidus, amygdala.

1.2.2. Mood disorders vs. healthy controls

During the reward (or loss) > neutral feedback contrast, HC compared to MD showed greater activation in the cortical-subcortical network, including bilateral putamen, bilateral lateral globus pallidus, left caudate (head and body), left amygdala (see Figure 3.b).

1.2.3. Schizophrenia vs. healthy controls

During the reward (or loss) > neutral feedback contrast, ALE analysis revealed that activations are common to SZ patients and HC (see Figure 3.b).

Figure 3

2. Cognitive control tasks (B > A cues)

Because of the lack of articles studying the reactive mode, we focus on the proactive cognitive control, with the anticipation of contextual cues (B vs A cues).
A total of 5 experiments with 122 HC reporting 24 foci, 2 experiments with 34 MD patients reporting 5 foci, and 5 experiments with 128 SZ patients reporting 27 foci were included in the analyses.

2.1. Within-group analyses

ALE analysis revealed that MD patients present an increased activity after a B cue than an A cue that is more frequently reported in several regions in bilateral frontal gyrus, such as right inferior frontal gyrus, left middle / medial frontal gyrus, and anterior cingulate, as well as in the left parietal lobe, including precuneus.

ALE analysis revealed that SZ patients have more consistently an increased activity after a B cue than an A cue in several regions in bilateral frontal lobe, such as middle and inferior frontal gyrus.

ALE analysis revealed that HC present increased activity after a B cue than an A cue in several regions in right frontal lobe, such as middle and inferior frontal gyrus.

2.2. Mood disorders vs. healthy controls

During the B cue > A cue contrast, ALE analysis revealed that HC showed present a greater activation in right middle frontal gyrus compared to MD (see Figure 4).

2.3. Schizophrenia vs. healthy controls

During the B cue > A cue contrast, ALE analysis revealed that SZ patients compared to HC showed increased activation in left inferior and middle frontal gyrus (see Figure 4).

Figure 4

Discussion

This ALE meta-analysis of neuroimaging studies of motivational and cognitive control networks in SZ and MD has highlighted that patients suffering from psychiatric disorders, in comparison to HC, present specific patterns of activation. Moreover, these patterns are distinct for SZ and MD and thus could suggest, based on the multidimensional neurological model of apathy, the existence of different dominant forms of apathy.

Concerning SZ, during the MID, SZ patients present the same activation as HC during the feedback phase, in accordance with the literature about a preserved liking in SZ (Da Silva et al., 2017; Gard et al., 2007). However, during the cue phase, compared to HC, SZ patients present more frequent hypoactivation of the motivational network (bilateral putamen, left lateral globus pallidus, bilateral caudate body, left ventral anterior and lateral nucleus, right amygdala). This result suggests impaired wanting in SZ (Frost & Strauss, 2016). However, interestingly, during the cue phase, SZ patients also present more consistent hyperactivation than HC of the right cerebellar vermis (culmen, declive and uvula). The cerebellar vermis in the cerebellum is a well-known structure for the regulation of emotions and affects (Glickstein, 2007; Yucel et al., 2013). Theta burst stimulation of this structure in SZ has previously been shown to offer the potential to modulate emotions and affects in SZ patients (Demirtas-Tatlidede et al., 2010). Since the cerebellum is highly connected to the motivational network and to the dorsolateral and ventral PFC (Alalade et al., 2011; Krienen & Buckner, 2009; Salamon et al., 2007), the hyperactivation of the cerebellar vermis in SZ could thus be a sort of compensation for the hypofunctionality of the wanting network. The hyperactivation of the cerebellar vermis highlighted specifically in SZ in the present study, and which has previously been correlated to the severity of apathy and emotional blunting in this pathology (Mothersill et al., 2016), could therefore suggest a dominant emotional-affective form of apathy in SZ. Results obtained with AX-CPT strengthen this hypothesis in a way that excludes the cognitive one. Indeed, in comparison to HC, SZ patients present a more frequent hyperactivation of the frontal cognitive structures, especially the bilateral frontal gyrus, known to support the execution of attentional and cognitive control (Brass et al., 2005; Li et al., 2013). This hyperfrontality in some regions of the PFC in SZ had previously been highlighted to reflect a shift in strategy in an attempt to compensate for the proactive difficulty often shown by SZ patients (Callicott et al., 2003; Holmes et al., 2005; Kwashie et al., 2023; Lesh et al., 2013; Manoach, 2003). Accordingly, an ALE meta-analysis of executive functioning in SZ confirmed the hyperactivation of the midline areas as a compensatory response for the executive difficulties and/or as an alternate attentional strategy to support task performance (Minzenberg et al., 2009). Using such strategies do not fit with the hypothesis of a dominant cognitive form of apathy in SZ, with cognitive apathy being precisely associated with a reduced functioning of

the executive and attentional networks (Levy & Dubois, 2006; Pagonabarraga et al., 2015; Sultzer et al., 2013). As suggested in the only study that has investigated the three forms of apathy in SZ, via a survey and neuropsychological tests, SZ patients with emotional apathy could actually be even more prone to using this compensatory strategy by allocating more attentional resources to non-emotional stimuli (Raffard et al., 2016).

By highlighting impaired functioning of wanting and liking (MID), as well as cognitive control (AX-CPT), the results of the two tasks in the MD patients suggest further a mixed form of apathy in MD (i.e., initiative apathy). Indeed, firstly, in the MID, MD patients show a total lack of activation during the cue phase. At the feedback reception, in comparison to HC, they present more frequent hypoactivation, even if they recruit larger structures of the motivational network (bilateral putamen, bilateral lateral globus pallidus, left caudate, left amygdala). Then, regarding the results highlighted in the present meta-analysis with the AX-CT, compared to HC, MD patients present more consistent hypoactivation of the PFC, as well as the right middle frontal gyrus and left inferior frontal gyrus, two structures supporting cognitive control. In the literature, the reduced connectivity of these PFC regions has previously been shown in MD and correlated to the severity of the MD (Murrough et al., 2016). Such cognitive disruptions in MD have been previously related to inhibition and shifting impairments (Grahek et al., 2019; Snyder, 2013). Interestingly, and despite the vast heterogeneity in MD, the reduced activation of the PFC during cognitive control tasks has been correlated to a specific anhedonic phenotype of depression, confirming the combination of mixed impairments, both in the cognitive control and motivation domains (Pizzagalli & Roberts, 2022).

Does this mean that these results correspond to pathophysiological or etiological mechanisms common to MD and SZ, insofar as they are marked by apathy? We believe that we can make no such claim, for several reasons. Firstly, because these observations come from heterogeneous populations, it is now well accepted that there are subtypes of SZ, as well as in MD, and that many of them are accompanied by apathetic symptoms. This heterogeneity implies substantial inter-individual variability in functional imaging studies (Feder et al., 2017; Santo-Angles et al., 2021). Secondly, while experimental conditions may have reduced this heterogeneity, they also focused on certain neurological systems more involved in the tasks, thus underestimating lesser-involved dysfunctions further up the etiological causal chain. It is quite possible that we have identified downstream activity modifications in the processes affected by the various forms of apathy and that these modifications are common to the different pathologies by the equifinality effect (Strauss & Cohen, 2017). A new analysis considering the differences between clinical phenotypes within each diagnosis and exploring the different networks that may influence the regions we have identified, including under ecological conditions, would complete our description of the pathophysiology of apathy during psychiatric diseases.

This study has some limitations, the main one being the relatively small number of studies included and their own small population sizes. Some limits are inherent to the literature to date, with a lack of results for some contrasts and paradigms and poor control on the treatment, age, and severity of the disorders. Moreover, psychiatric diagnoses are based on DSM classification: if populations are assumed to be comparable, they are also likely to be heterogeneous within the groups themselves and according to their pathophysiological processes. Finally, this study is a coordinate-based meta-analysis of studies that lack power, which can create some false negatives, especially in the case of heterogeneous groups (Müller et al., 2018). However, the realization of image-based meta-analyses required unavailable, highly detailed data. If they were available, their analysis could also offer possibilities for phenotyping according to this three-dimensional model of apathy.

Relying on an ALE meta-analysis of neuroimaging studies that have investigated motivational or cognitive control processing via the MID or the CPT-AX in SZ or MD, we highlighted specific impairments in each of these two pathologies. The discussion of these specificities, in regard to the known neural substrates of multidimensional apathy, allowed us to suggest a dominant emotional-affective form of apathy in SZ and a dominant initiative form in MD that could support the development of new therapeutic strategies in precision psychiatry.

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Tables

Table 1a: Study information for all papers included in the meta-analysis.

Study	Imaging modalities	N, SZ	N, MD	N, HC	Task	Experimental conditions	Contrasts
(Esslinger et al., 2012)	3T MRI MNI	27	-	27	MID	Cue (reward or loss vs neutral)	SZ, HC
(Mucci et al., 2015)	3T MRI MNI	28	-	22	MID	Cue (reward or loss vs neutral) Feedback (reward or loss vs neutral)	SZ, HC
(Nielsen et al., 2012)	1.5T MRI Talairach	31	-	31	MID	Cue (reward or loss vs neutral) Feedback (reward or loss vs neutral)	SZ, HC
(da Silva Alves et al., 2013)	3T MRI MNI	10	-	12	MID	Cue (reward or loss vs neutral)	SZ, HC
(Juckel, et al., 2006)	1.5T MRI MNI	10	-	10	MID	Cue (reward or loss vs neutral)	SZ, HC
(Schlagenhauf et al., 2008)	1.5T MRI MNI	10	-	10	MID	Cue (reward vs neutral)	SZ, HC
(Juckel et al., 2012)	1.5T MRI MNI	13	-	13	MID	Cue (reward or loss vs neutral) Feedback (reward or loss vs neutral)	SZ, HC
(Kirschner et al., 2016)	3T MRI MNI	27	-	25	MID	Cue (reward vs neutral) Feedback (reward vs neutral)	SZ, HC
(Subramaniam et al., 2015)	3T MRI MNI	37	-	20	MID	Cue (reward or loss vs neutral) Feedback (reward or loss vs neutral)	SZ, HC
(Knutson et al., 2008)	1.5T MRI Talairach	-	14	12	MID	Cue (reward or loss vs neutral) Feedback (reward or loss vs neutral)	MD, HC
(Pizzagalli et al., 2009)	1.5T MRI MNI	-	30	31	MID	Cue (reward or loss vs neutral) Feedback (reward or loss vs neutral)	MD, HC
(Caseras et al., 2013)	3T MRI MNI	-	31	19	MID like	Cue (reward or loss vs neutral) Feedback (reward or loss vs neutral)	MD, HC
(Arrondo et al., 2015)	3T MRI MNI	22	24	21	MID	Cue (reward vs neutral) Feedback (reward vs neutral) in HC	SZ, MD, HC
(Bjork et al., 2004)	3T MRI Talairach	-	-	24	MID	Cue (reward or loss vs neutral) Feedback (reward or loss vs neutral)	HC
(Abler et al., 2008)	3T MRI MNI	12	-	12	MID	Cue (Reward vs. neutral) Feedback (Reward vs. neutral)	SZ, HC
(MacDonald et al., 2005)	1.5T MRI Talairach	18	-	28	AX-CPT	Cue type (A vs B)	SZ, HC
(MacDonald III & Carter, 2003)	1.5T MRI Talairach	17	-	17	AX-CPT	Cue type (A vs B)	SZ, HC
(Holmes et al., 2005)	1.5T MRI Talairach	7	10	9	AX-CPT	Cue type (A vs B)	SZ, MD, HC
(Smucny et al., 2018)	1.5T MRI MNI	70	24	53	AX-CPT	Cue type (A vs B)	SZ, MD, HC
(Perlstein et al., 2003)	1.5T MRI Talairach	16	-	15	AX-CPT	Cue type (A vs B)	SZ, HC

Table 1b: Participants information for all papers included in the meta-analysis.

Study	N			Age			Gender (M/F)			Treatments (mg of CLPZ equivalents)	
	SZ	MD	HC	SZ	MD	HC	SZ	MD	HC	SZ	MD
(Esslinger et al., 2012)	27	-	27	27.8 (7.4)	-	27.1 (5.9)	20/7	-	20/7	0	-
(Mucci et al., 2015)	28	-	22	33.1 (6.7)	-	31.9 (8.5)	18/10	-	10/12	?	-
(Nielsen et al., 2012)	31	-	31	25.9 (6.4)	-	25.7 (5.8)	22/9	-	22/9	0	-
(da Silva Alves et al., 2013)	10	-	12	22.7 (3.2)	-	34.6 (11.2)	10/0	-	12/0	?	-
(Juckel, et al., 2006)	10	-	10	26.8 (7.8)	-	31.7 (8.4)	10/ 0	-	10/ 0	0	-
(Schlagenhauf et al., 2008)	10	-	10	30.5 (10.6)	-	31.8 (8.7)	9/1	-	9/1	189 (8)	-
(Juckel et al., 2012)	13	-	13	25.5 (4.6)	-	25.7 (4.8)	11/2	-	11/2	?	-
(Kirschner et al., 2016)	27	-	25	31.9 (7.1)	-	33.0 (9.7)	18/9	-	16/9	491 (349)	-
(Subramaniam et al., 2015)	37	-	20	45.1 (9.9)	-	43.7 (13.3)	25/12	-	14/6	375 (555)	-
(Knutson et al., 2008)	-	14	12	-	30.7 (8.8)	28.7 (4.3)	-	5/11	4/8	-	0
(Pizzagalli et al., 2009)	-	30	31	-	43.2 (12.9)	38.8 (14.5)	-	15/15	18/13	-	0
(Caseras et al., 2013)	-	31	19	-	40.5 (8.1)	42.3 (6.0)	-	11/20	7/13	-	428
(Arrondo et al., 2015)	22	24	21	32.7 (7.6)	33.1 (9.2)	34.3 (10.1)	19/3	17/7	17/4	401 (91)	401 (91)
(Bjork et al., 2004)	-	-	24	-	-	23.8 (2.0)	-	-	6/6	-	-
(Abler et al., 2008)	12	-	12	36.7 (7.8)	33.9 (11.2)	36.2 (11.2)	5/7	7/5	7/5	595 (357)	375 (397)
(MacDonald et al., 2005)	18	-	28	27.5 (10.2)	-	25.4 (7.5)	13/5	-	18/10	0	-
(MacDonald III & Carter, 2003)	17	-	17	34.2 (7.7)	-	33.5 (5.8)	12/5	-	12/5	?	-
(Holmes et al., 2005)	7	10	9	39.0 (6.9)	32.0 (9.9)	34.3 (8.1)	6/1	7/3	5/4	?	?
(Smucny et al., 2018)	70	24	53	21.0 (3.0)	22.6 (2.9)	21.1 (2.8)	59/11	15/9	31/22	258 (214)	202 (109)
(Perlstein et al., 2003)	16	-	15	36.8 (1.9)	-	36.4 (1.8)	11/5	-	9/6	175.3 (30)	-

Table 2: Imaging results. Talairach coordinates x, y, z in mm; BA: Brodmann area.

a. Specific effects of one group compared to another group. b. Shared effects of two groups.

a. Specific effects									
	Cluster Level			Peak Level					
	n°	K (cm^3)	P_{FWE}	Z	P_{FWE}	x	y	z	Peak location (BA)
Wanting									
HC > SZ	1	628	<.05	2.82	.002	-24	-90	3	L Middle Occipital Gyrus (18)
				2.56	.005	-19	-101	0	L Cuneus (18)
				2.32	.01	-27	-96	-5	L Lingual gyrus (18)
	2	458	<.05	2.56	.005	-20	-6	16	L Putamen
				2.48	.006	-18	-2	12	L Putamen
				2.45	.007	-15	0	15	L Caudate body
				2.29	.009	-16	-10	14	L Ventral lateral nucleus
				2.28	.01	-29	-10	26	L Insula
				2.23	.01	-18	-4	6	L Lateral globus pallidus
	3	144	<.05	2.15	.01	20	6	12	R Putamen
				2.02	.02	18	10	12	R Caudate body
				1.97	.02	12	14	10	R Caudate body
				1.95	.02	18	10	6	R Putamen
	4	129	<.05	1.78	0.3	56	2	22	R Precentral gyrus (6)
				1.78	0.3	55	6	16	R Inferior frontal gyrus (44)
SZ > HC	1	392	<.05	1.99	.02	28	-57	-24	R Culmen
				1.78	.03	26	-67	-22	R Declive
				1.76	.03	36	-50	-27	R Culmen
	2	237	<.05	2.53	.006	30	26	0	R Insula (13)
				2.26	.01	36	26	0	R Inferior frontal gyrus (47)
Liking									
HC > SZ	0								
SZ > HC	0								
HC > MD	1	1297	<.05	2.48	.006	-26	-22	-2	L Putamen
				2.28	.01	-25	-27	-1	L Thalamus
				2.27	.01	-19	-2	0	L Lateral globus pallidus
				2.05	.02	-8	6	0	L Caudate body
	2	137	<.05	2.27	.01	28	6	-2	R Putamen
				2.07	.01	17	1	10	R Putamen
				1.97	.02	24	-8	0	R Lateral globus pallidus
MD > HC	0								
Cognitive control									
HC > SZ	0								
SZ > HC	1	78	<.05	2.06	.01	-34	24	18	L Insula (13)
				2.03	.02	-39	28	18	L Middle frontal gyrus (46)
				1.99	.02	-44	26	14	L Inferior frontal gyrus (46)
HC > MD	1	30	<.05	1.76	.03	50	24	31	R Middle fontal gyrus (9)
MD > HC	0								
SZ > MD	1	220	<.05	2.03	.02	52	25	0	R Middle frontal gyrus (45)
				1.83	.03	48	30	26	R Middle fontal gyrus (9)
	2	153	<.05	1.65	.04	-43	21	14	L Inferior frontal gyrus (45)
MD > SZ	0								

a. Shared effects									
	Cluster Level			Peak Level					
	n°	K (cm^3)	P_{FWE}	Z	P_{FWE}	x	y	z	Peak location (BA)
Wanting									
SZ = HC	1	4	<.05		.004	46	0	6	R Precentral gyrus (44)
					.003	44	-2	6	R Insula (13)
Liking									
SZ = HC	1	1284	<.05		.007	39	16	-4	R Inferior frontal gyrus (47)
					.003	53	11	-9	R Superior temporal gyrus (38)
	2	953	<.05		.004	0	16	32	L Cingulate gyrus (32)
					.003	0	12	32	L Cingulate gyrus (24)
					.001	-4	2	34	L Cingulate gyrus (24)
	3	576	<.05		.006	62	-17	18	R Postcentral gyrus (40)
	4	251	<.05		$6.4*10^{-4}$	10	-56	-32	R Cerebellar tonsil
MD = HC	1	273	<.05		.003	-16	-13	24	L Caudate body
					$8.1*10^{-4}$	-26	-4	20	L Putamen
	2	128	<.05		.005	16	-8	24	R Caudate body
Cognitive control									
SZ = HC	1	1564	<.05		.001	40	28	6	R Inferior frontal gyrus (13)
					.005	40	10	32	R Middle frontal gyrus (9)
					.006	32	50	28	R Superior frontal gyrus (9)
MD = HC	1	810	<.05		$6.4*10^{-6}$	34	38	20	R Middle frontal gyrus (10)
					.001	34	22	14	R Insula (13)
					.003	52	16	10	R Inferior frontal gyrus (44)
SZ = MD	1	637	<.05		$3.2*10^{-5}$	40	30	14	R Middle frontal gyrus (46)
					$8.3*10^{-5}$	36	14	26	R Middle frontal gyrus (9)
					.004	51	16	9	R Precentral gyrus (44)

Figures

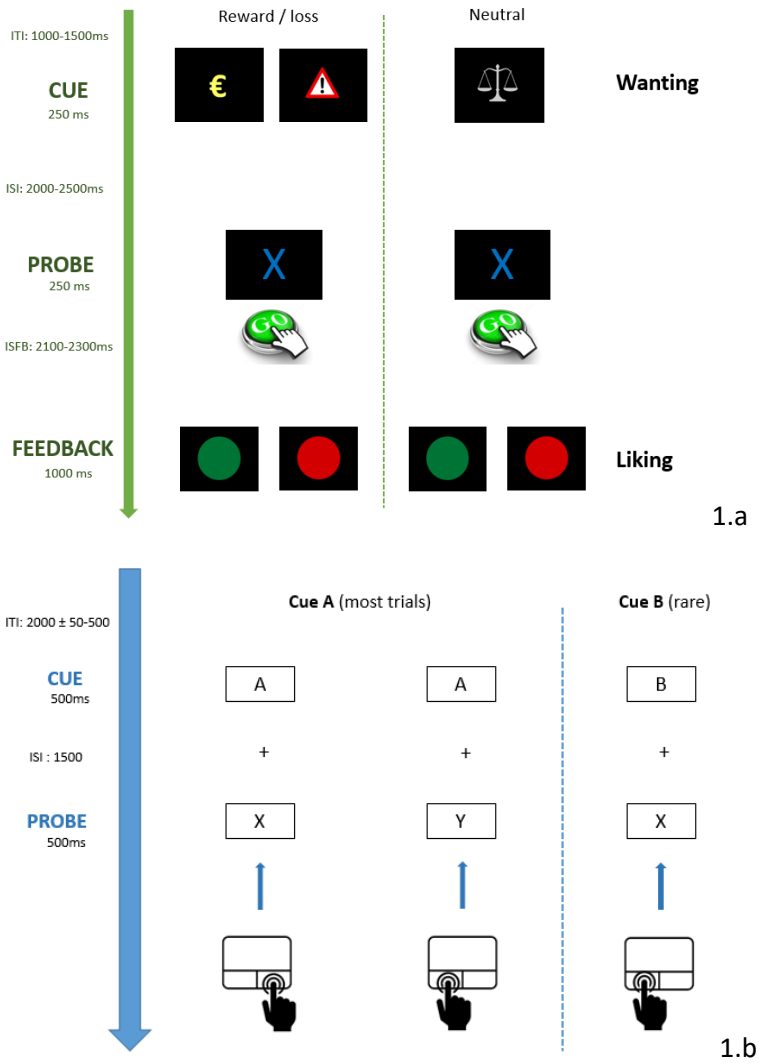

Figure 1: The MID and the AX-CPT tasks

1.a: The MID is a visual detection task in which subjects are required to respond as quickly as possible by pressing a response button at the presentation of the probe (a cross generally). An incentive (reward or loss) or neutral cue (no reward and no loss) is presented before the probe. Either positive or negative (a green or red disc generally) feedback (FB) is given after the response. The FB informs the participant if his or her response was completed with enough speed, and in case of incentive cues about the obtained reward or loss. After a reward cue, positive FB indicates an actual monetary reward, whereas negative FB indicates the absence of a monetary reward. After a loss cue, positive FB indicates the absence of monetary loss, whereas negative FB indicates an actual monetary loss. After a neutral cue, positive and negative FB indicates no monetary variation.

1.b: The AX-CPT is a cue-probe detection task in which letters are presented one by one on the screen: A or B cues alternated with combinations of X or Y probes. The subjects had to respond after the probes by pressing the right button in cases presenting the target sequence (“A cue – X probe” trials). In all other cases, they had to press the left button. Thus, four types of trials were differentiated: AX, AY (where Y is any other combination apart from X), BX (where B is any other combination apart from A), and BY trials. The target sequence (AX) was more frequent (about 70% of trials) than the other sequences (AY, BX and BY), leading participants to develop a strong expectation of making a “match” in response to probes following ‘A’ cues compared to ‘B’ cues generally.

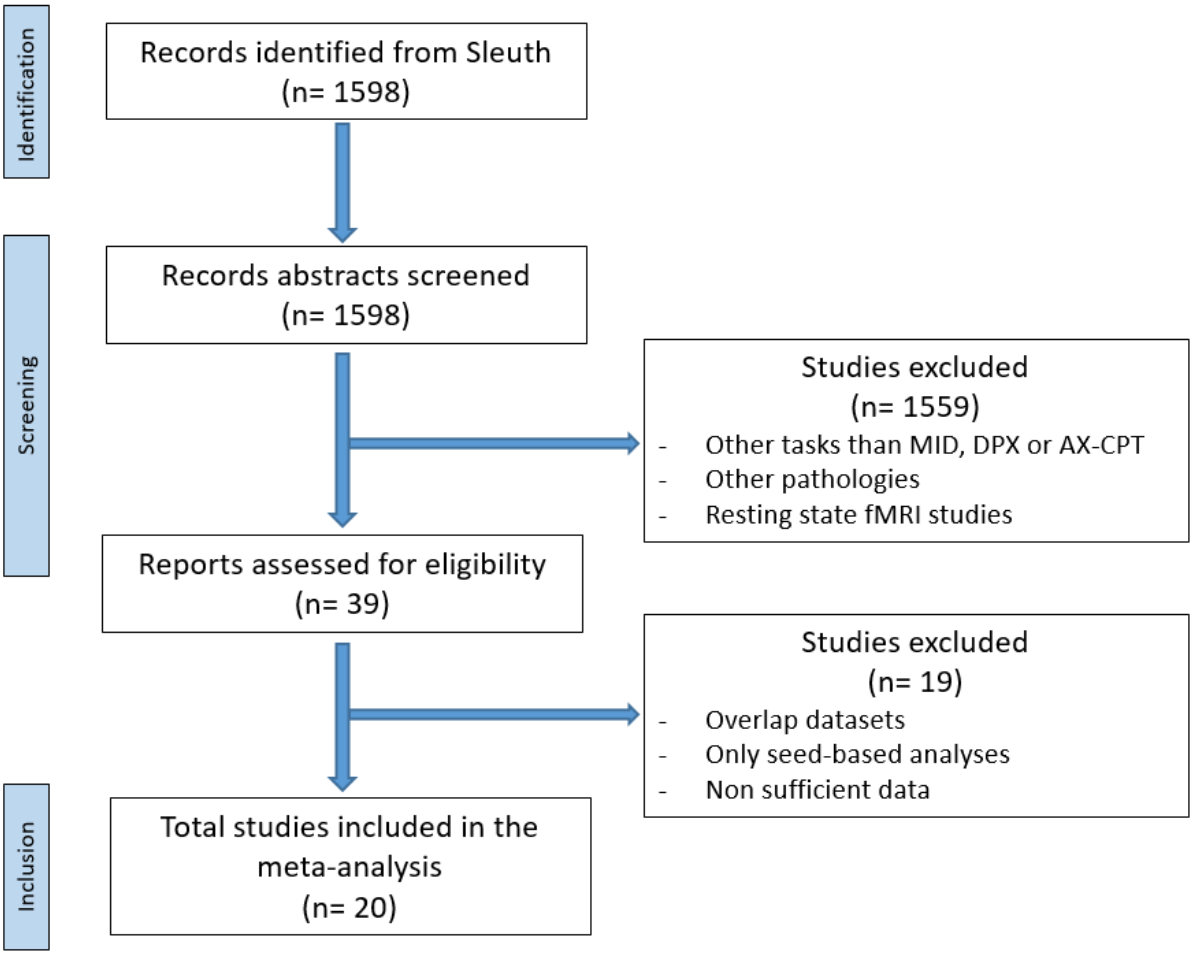

Figure 2: PRISMA flow diagram of the identification of articles

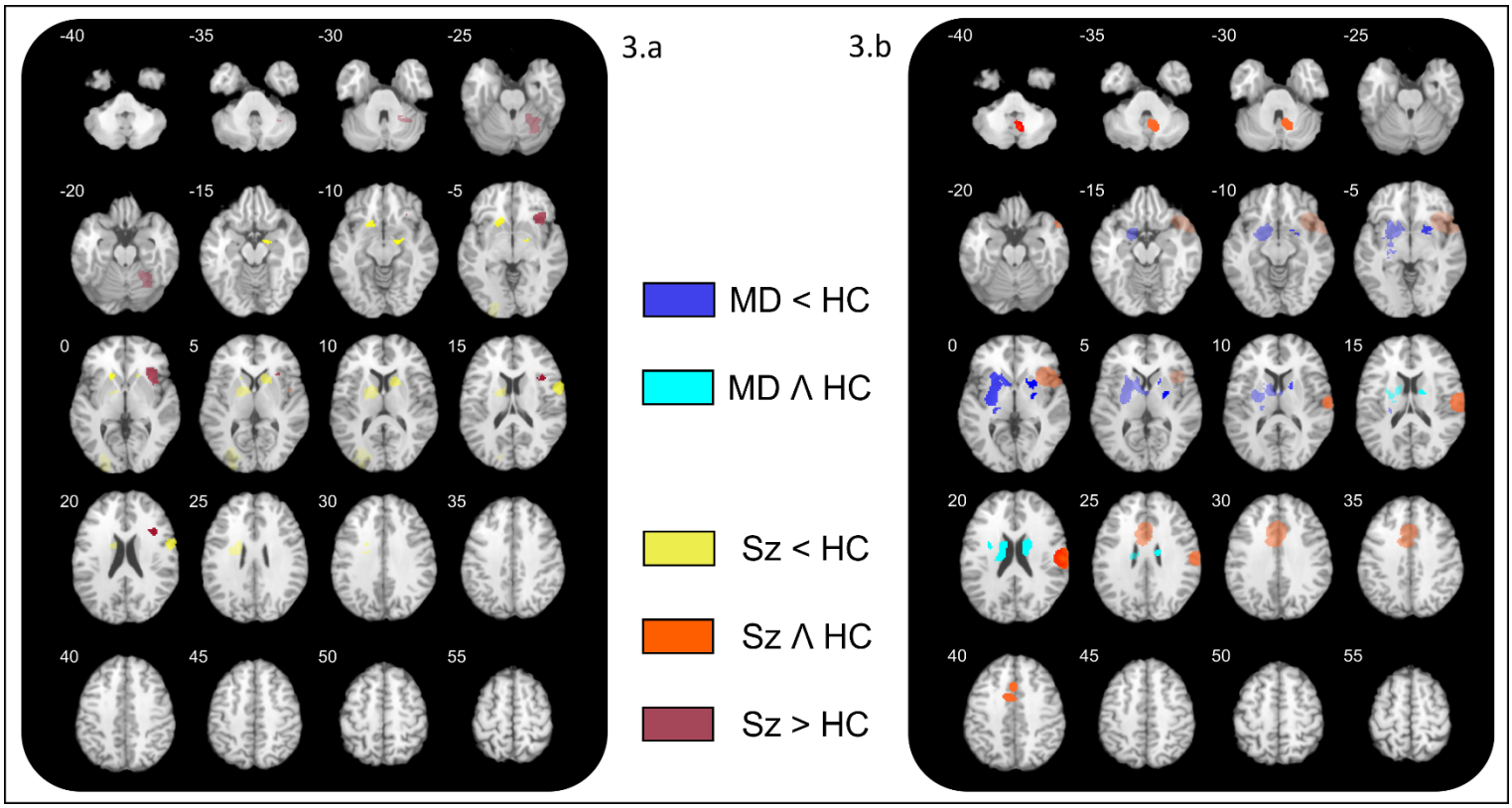

Figure 3: Contrasts maps representing face to face comparison and co-activations (conjunctions [Λ]) **between patients** (i.e. schizophrenia [Sz] and mood disorders [MD]) **and healthy controls** (HC) **of hyperactivations observed with the Monetary Incentive Delay task.**

Numbers correspond to the positioning of the slice in the Z-axis, in mm. ALE meta-analysis (subtraction analysis), p<.05 FWE at the cluster level.

3.a: in “wanting” paradigm;
3.b: in “liking” paradigm.

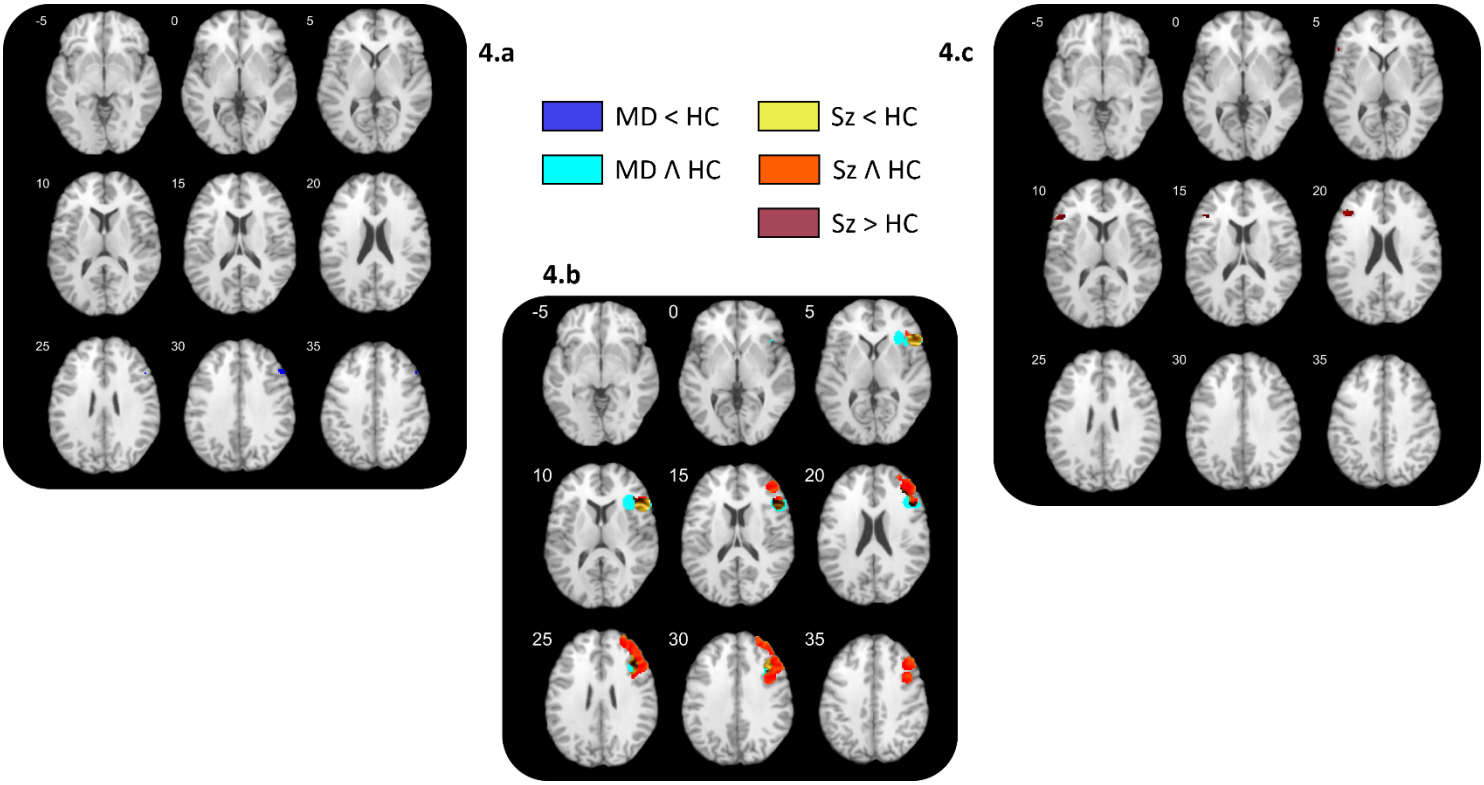

Figure 4: Contrasts maps representing face to face comparison and co-activations (conjunctions [Λ]) **between patients** (i.e. schizophrenia [Sz] and mood disorders [MD]) **and healthy controls** (HC) **of hyperactivations observed with the AX-Continuous Performance Task (proactive control).**

Numbers correspond to the positioning of the slice in the Z-axis, in mm. ALE meta-analysis (subtraction analysis), p<.05 FWE at the cluster level.

4.a: when activation in HC are superior to those in other conditions
4.b: common activations between HC and patients
4.c: when activation in HC are inferior to those in other conditions

Résumé des principaux résultats de la méta-analyse et objectifs de l'étude 4

En mettant en évidence des dysfonctionnements différents dans la schizophrénie et la dépression, grâce à une méta-analyse par estimation de la probabilité d'activation (ALE) en IRMf des réseaux motivationnels et de contrôle cognitif, nous faisons l'hypothèse d'une forme émotionnelle dominante dans la schizophrénie (sous-tendue par l'hypoactivité des structures motivationnelles et l'hyperactivité du vermis cérébelleux droit), et d'une forme d'initiation dominante dans la dépression (sous-tendue par l'hypoactivité observée à la fois au niveau des structures motivationnelles et de contrôle cognitif).

Sur cette base, l'étude 4 (en cours, les données présentées ici ne sont que préliminaires) a pour objectif de :

(1) tester l'hypothèse de formes dominantes d'apathie dans deux pathologies psychiatriques. A la lumière des résultats obtenus à la méta-analyse, nos hypothèses se sont affinées : l'apathie émotionnelle pourrait être dominante dans la schizophrénie, l'apathie d'initiation dans les troubles dépressifs ;

(2) étudier le caractère transnosographique des mécanismes cognitifs et motivationnels associés aux formes émotionnelle et exécutive, mis en évidence dans des formes isolées chez les sujets sains (étude 2).

Étude 4

Étude 4 : Mécanismes de l'apathie multidimensionnelle dans la schizophrénie et les troubles dépressifs

Methods

Subjects

31 subjects have so far been recruited: 14 healthy controls, 10 patients with unipolar or bipolar depressive disorder, and 7 patients with schizophrenia. The psychiatric patients were diagnosed apathetic by an experienced psychiatrist using a quantitative structured interview of apathy: the Lille Apathy Rating Scale (LARS) (Sockeel et al., 2006). The LARS cut-off for an apathy in psychiatry was already defined in the literature, with a score equal or above a cut-off of -23 at the LARS (Sockeel et al., 2006; Yazbek, Norton, et al., 2014). The participants of the control group were chosen for not having any form of apathy, based on the DAS cut-offs obtained in Study 1. Table 1 summarizes the apathetic characteristics of the three groups.

Table 1: Demographic and neuropsychological characteristics of the three groups.
Values are given as the mean (standard deviation in parentheses) (LARS: Lille Apathy Rating Scale; DAS: Dimensional Apathy Scale).

	Control group N= 14	Schizophrenia group N= 7	Depressive group N= 10
LARS Cut-off: ≥-23		-12.66 (8.50)	-1.8 (13.36)
DAS emotional Cut-off: ≥12	7.36 (2.90)	13.43 (2.51)	10.70 (3.83)
DAS executive Cut-off: ≥16	5.36 (2.73)	12.57 (4.35)	16.40 (4.06)
DAS initiative Cut-off: ≥14	7.43 (3.03)	12.71 (2.81)	17.00 (4.11)

Statistical analysis

A two-tailed significance level of 0.05 and a trend level of 0.10 were used for all tests. Effect sizes were calculated using a partial eta square (η_p^2). Even if the sample size is small, the three DAS subscores were normally distributed (Shapiro-Wilk p>.05), with the presence of a homogeneity of variances (Levene's p>.05). One-way ANOVAs were performed for each DAS subscore, including the between-subject factor Group (control, schizophrenia, depression). Multiple regression analyses, aided by LASSO variables selection, were performed to identify the best multivariable model for each DAS subscore. In the multiple regression analysis, regression coefficients were made commensurate by standardizing each variable. Independent variables were ranked in order of entry into the LASSO regression. LASSO overcomes various limitations of classic variable selection procedures such as multicollinearity to enable reliable selection of independent variables (T. Chen et al., 2016). Independent variables selected by LASSO were entered into the linear model for additional backward elimination trimming, as univariate analysis may also miss significant predictors, and such models may be biased (H. Wang et al., 2017). Then, ANCOVAs were used to compare the effects of the three DAS scores and the effect of the groups on the subscales identified though the regression analyses. In the case of statistically significant interactions with ANOVAs or ANCOVAs, respectively Tukey or Bonferroni correction for multiple comparisons was conducted.

Results

1) Profile of apathy scores in schizophrenia and depression

The one-way ANOVA performed on DAS emotional scores revealed a main effect of group ($F(2,28)=9.22$, $p<.001$; $\eta^2=.38$). Tukey post-hoc comparisons revealed that the DAS emotional score was higher in schizophrenia and depression than in control group (respectively p<.001 and p<0.04), and tended to be higher in schizophrenia than in depression group (p<.08) (Figure 1-A).

The one-way ANOVA performed on DAS executive scores revealed a main effect of group ($F(2,28)=196.68$, $p<.001$; $\eta^2=.68$). Tukey post-hoc comparisons revealed that the DAS executive score was higher in depression and schizophrenia groups than in control group (p<.001), and higher in depression than in schizophrenia group (p<.05) (Figure 1-B).

The one-way ANOVA performed on DAS initiative scores revealed a main effect of group ($F(2,28)=23.9$, $p<.001$; $\eta^2=.63$). Tukey post-hoc comparisons revealed that the DAS initiative score was higher in depression and schizophrenia groups than in control group ($p<.005$), and higher in depression than in schizophrenia group ($p<.03$) (Figure 1-C).

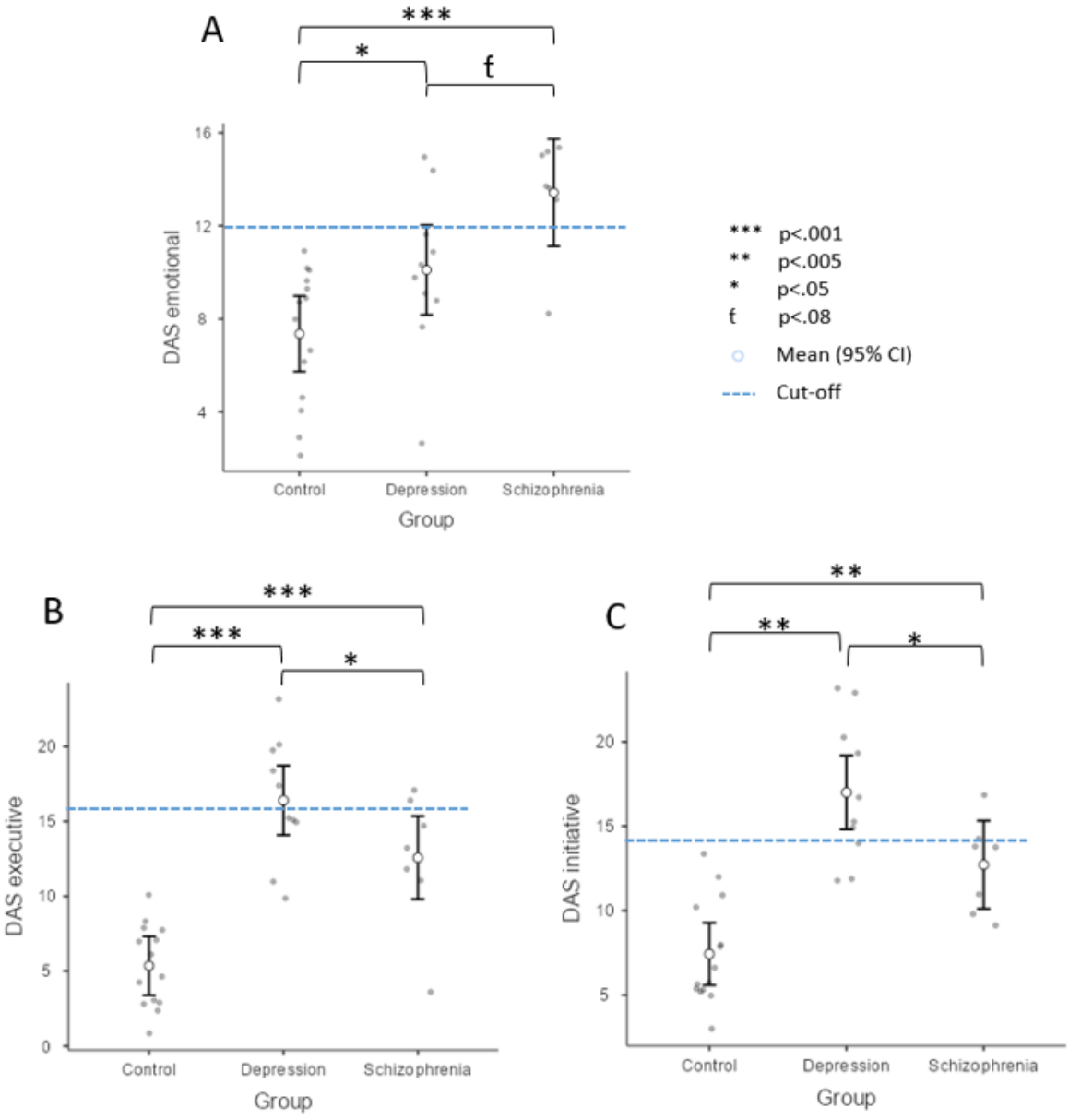

Figure 1: Distribution of the DAS emotional, executive and initiative scores for healthy controls, and patients suffering from schizophrenia or depression.
Mean and standard deviation for each group, as well as the cut-off for each DAS subscore are indicated.

2) Mechanisms underlying multidimensional apathy in psychiatric disorders

The regression model best fitted to the DAS emotional score showed the following factors to be significantly associated with higher DAS emotional score: less negative CNV after B cues at the DPX and after reward cues at the MID (Table 2).

Table 2: Best-fit general linear models of emotional apathy in all the sample (N=31)

Variable	Estimate (B)	Standard Error	t value	p
DPX CNV after B cues	0.23	0.08	3.03	<0.006
MID CNV after reward cues	0.24	0.08	2.91	<0.008

The ANCOVA performed on the amplitude of the CNV after B cues in the DPX revealed that the DAS emotional score had a main effect ($F(1,24)=5.86$, $p<.03$, $\eta^2=.20$). Neither the factor group, nor the other DAS scores had a significant main effect (all $p>.50$). The interaction between DAS emotional score and the group was not significant ($p>.40$).
The ANCOVA performed on the amplitude of the CNV after reward cues in the MID revealed that the group had a main effect ($F(2,25)=4.32$, $p<.03$, $\eta^2=.26$). Bonferroni post-hoc comparisons revealed that the CNV amplitude after a reward cue was less negative for the schizophrenia group than the depressed group ($p<.02$). Neither DAS emotional score, nor the other DAS scores had a significant main effect (all $p>.40$). None of the interactions between group and the other variables were significant (all $p>.45$).

The regression model best fitted to the DAS executive score showed the following factors to be significantly associated with higher DAS executive score: more positive P3a for AX trials at the DPX, and less positive P3a for neutral trials with positive feedback at the MID (Table 3).

Table 3: Best-fit general linear models of executive apathy in all the sample (N=31)

Variable	Estimate (B)	Standard Error	t value	p
DPX P3a for AX trials	0.30	0.14	2.04	0.05
MID P3a for neutral trials with positive feedback	-0.36	0.15	-2.35	<0.03

The ANCOVA performed on the amplitude of the P3a for AX trials in the DPX revealed that the group had a trend for a main effect ($F(2,24)=3.23$, $p<.06$, $\eta^2=.21$). Bonferroni post-hoc comparisons revealed that the P3a amplitude for AX cue was similar in the three groups (all $p>.10$). Neither DAS executive score, nor the other DAS scores had a significant main effect (all $p>.30$). None of the interactions between group and the DAS scores were significant (all $p>.50$).

The ANCOVA performed on the amplitude of the P3a for neutral trials with positive feedback in the MID revealed no group effect ($p>.51$), nor DAS scores effects (all $p>.40$).

Any significant factor emerged from the regression model for DAS initiative.

Résumé des principaux résultats

Ces premiers résultats, bien qu'obtenus auprès d'un petit échantillon de sujets, confirment l'intérêt d'une évaluation multidimensionnelle de l'apathie pour tenter de mieux caractériser un profil apathique. En effet, ces deux groupes de patients présentent une sévérité d'apathie comparable avec le score unidimensionnel à la LARS, mais des profils différents d'apathie multidimensionnelle avec la DAS.

S'agissant de la question de l'existence de formes dominantes d'apathie dans chacune de ces deux pathologies psychiatriques, notre échantillon est à ce jour encore trop faible pour pouvoir y répondre avec certitude. Toutefois, et en accord avec nos hypothèses, nos premières analyses révèlent que, pour les patients souffrant de schizophrénie, non seulement le score d'apathie émotionnelle est le plus élevé des trois formes d'apathie, mais aussi qu'il est significativement plus élevé que dans les deux autres groupes. A contrario, chez les patients souffrant de dépression, ce sont les scores d'apathie exécutive et d'initiation qui sont les plus élevés, des scores eux aussi significativement plus élevés que dans les deux autres groupes.

S'agissant du caractère potentiellement transnosographique des dysfonctionnements des mécanismes motivationnels et cognitifs associés aux formes émotionnelle et exécutive, nos premiers résultats mettent en évidence des mécanismes distincts pour chaque forme d'apathie en psychiatrie, dans la continuité de ceux précédemment identifiés chez les sujets sains (études 2 et 3).

(1) L'apathie émotionnelle est prédite par l'amplitude de la CNV (dans les deux tâches cognitives), un potentiel évoqué reflétant l'anticipation d'un stimulus à venir. Dans la DPX, plus le score d'apathie émotionnelle est élevé, moins l'amplitude de la CNV est négative pour les indices B non cibles. Ainsi, l'anticipation de ces essais rares est d'autant moins importante que l'apathie émotionnelle est sévère. Ce résultat pourrait suggérer que le contrôle cognitif est préservé en cas d'apathie émotionnelle puisque ces personnes apathiques prennent bien en considération le contexte (i.e. l'indice) pour répondre, ce qui est cohérent avec les résultats obtenus, dans l'étude 2, avec des sujets sains présentant un phénotype d'apathie émotionnelle (étude 2). En revanche, à la MID, plus le score d'apathie émotionnelle est élevé, moins l'amplitude de la CNV est négative pour les indices récompensant. Ainsi, l'anticipation d'un gain monétaire est d'autant moins importante que l'apathie émotionnelle est sévère. Ce résultat pourrait donc suggérer que chez les patients présentant une apathie émotionnelle le dysfonctionnement des mécanismes motivationnels soit davantage lié au *wanting.* Soulignons également que ce résultat est modulé par la pathologie, les patients schizophrènes ayant un score plus élevé d'apathie émotionnelle présenteraient davantage ce trouble du *wanting*.

(2) L’apathie exécutive est prédite par l’amplitude de la P3a, un potentiel évoqué reflétant l'inhibition d'une réponse motrice préparée (ou la résolution d’un conflit entre la réponse préparée et celle qui doit être donnée). Dans la DPX, plus le score d’apathie exécutive est élevé, plus l’amplitude de la P3a est positive pour les essais AX, des essais qui ne devraient pas induire de conflit de réponse. Ce résultat, cohérent avec ceux obtenus, dans l’étude 2, avec des sujets sains présentant un phénotype d’apathie exécutive, pourrait suggérer une mauvaise préparation du schéma de réponse dominant à la présentation de l’indice chez ces sujets, et donc, un mode de fonctionnement moins proactif.

(3) Parmi les indicateurs issus de la DPX et de la MID, aucun n’a permis de prédire l’apathie d’initiation, renforçant encore l’hypothèse que l’apathie d’initiation soit une forme à part entière associée à des dysfonctionnements spécifiques.

Discussion

L'objectif principal de cette thèse était de mieux caractériser les mécanismes associés à chaque forme d'apathie : l'apathie émotionnelle, exécutive et d'initiation, avec une approche phénotypique (études 1 à 3) et transnosographique (méta-analyse et étude 4). L'approche phénotypique a permis d'identifier la prévalence des phénotypes de chaque forme d'apathie dans la population normale, ainsi que les processus spécifiquement associés à chacune d'elles. L'approche transnosographique, en s'appuyant sur une méta-analyse et l'analyse des données préliminaires de l'étude expérimentale menée dans la schizophrénie et les troubles dépressifs, a permis de tester le caractère transnosographique de ces processus et d'étudier les profils d'apathie multidimensionnelle existant dans ces deux pathologies.

Après un bref rappel des principaux résultats obtenus pour chacune des trois formes d'apathie dans la population normale et pathologique, nous les mettrons en perspective avec le modèle multidimensionnel de l'apathie de Levy et Dubois (2006), et discuterons de chaque phénotype apathique chez le sujet sain comme potentiel facteur de risque au développement d'un trouble psychiatrique. Pour finir, notre discussion abordera l'intérêt clinique de l'évaluation multidimensionnelle de l'apathie en psychiatrie, en développant plus spécifiquement les pistes thérapeutiques des formes émotionnelle et exécutive d'apathie.

1. L'identification de mécanismes associés à chaque sous-forme d'apathie

1.1. L'apathie émotionnelle

Les études menées dans le cadre de cette thèse ont permis de progresser dans la compréhension de l'apathie émotionnelle, caractérisée cliniquement par un émoussement affectif et une perte d'intérêt au quotidien (R. Levy & Dubois, 2006). Grâce à une approche dimensionnelle normativiste de l'apathie, nous avons isolé le phénotype d'apathie émotionnelle comme l'extrémité du continuum. L'enquête menée auprès de la population étudiante strasbourgeoise (étude 1) a permis de révéler qu'environ 10 % des jeunes adultes présentaient un trait ou un symptôme d'apathie émotionnelle et que les prédicteurs spécifiques de cette forme d'apathie sont les processus motivationnels de *liking* et de *wanting*, ainsi que le sexe masculin. L'étude expérimentale menée à la suite de cette enquête, a mis en évidence, chez des sujets sains présentant un phénotype d'apathie émotionnelle, un déficit de *liking* se manifestant, dans la MID, par une insensibilité à la perte (étude 2). L'approche transnosographique qui a suivi a mis en évidence, grâce à une méta-analyse tout d'abord, des dysfonctionnements au niveau du *wanting*, révélés par une hypoactivation des structures motivationnelles, dans la dépression et la schizophrénie. Tandis que les patients dépressifs présentaient des hypoactivations de structures motivationnelles et cognitives, les patients schizophrènes présentaient uniquement une hypoactivation des structures motivationnelles, nous permettant de faire l'hypothèse d'une forme dominante d'apathie émotionnelle dans la schizophrénie. Les résultats issus de l'étude 4, bien qu'encore préliminaires, sont cohérents avec cette hypothèse. En effet, c'est dans le groupe de patients schizophrènes que le score d'apathie émotionnelle est le plus élevé (comparativement aux deux autres groupes), et c'est ce groupe uniquement qui modère la corrélation entre le déficit de *wanting* (qui serait le prédicteur spécifique de l'apathie émotionnelle) et la sévérité de l'apathie émotionnelle.

Pris ensemble, les résultats de ces trois études révèlent tout d'abord le caractère dimensionnel de cette sous-forme d'apathie, présente sur le continuum entre la population normale et les patients en psychiatrie. Le trait d'apathie émotionnelle présent chez les sujets sains jeunes pourrait même être un des traits de vulnérabilité pour le développement d'une schizophrénie, voire constituer un endophénotype de la schizophrénie, comme suggéré par quelques études s'appuyant sur des approches électrophysiologiques (Strauss et al., 2018), interindividuelles plus qualitatives (Luther et al., 2016; Meehl, 2001; Rector et al., 2005; Velthorst et al., 2009) ou fonctionnelles (Yan et al., 2016). En effet, il a non seulement été montré que les troubles du *liking* (révélés par une LPP d'amplitude similaire entre les essais récompensants, punitifs et neutres) sont présents chez les sujets jeunes en phase prodromale

de psychose, sans traitement psychotique (Strauss et al., 2018) mais aussi que ces troubles (évalués subjectivement) sont plus élevés chez les jeunes à risque de développer une schizophrénie ou présentant une personnalité schizotypique. L'insensibilité émotionnelle que traduisent ces mesures subjectives pourrait donc être une vulnérabilité latente au développement de troubles du spectre de la schizophrénie (Luther et al., 2016; Meehl, 2001; Rector et al., 2005; Velthorst et al., 2009). Yan et collaborateurs (2016), en montrant que seules les personnes schizotypiques avec un trait apathique partagent ces dysfonctions fonctionnelles du *liking* (hypoactivation du striatum ventral) avec les personnes à risque de développer une schizophrénie et les personnes schizophrènes, suggèrent donc que c'est l'apathie qui pourrait être un des potentiels biomarqueurs de diagnostic et de prévention de la schizophrénie (Yan et al., 2016).

En mettant en évidence les dysfonctionnements motivationnels des personnes souffrant d'apathie émotionnelle (études 1 à 4), nos résultats confirment l'hypothèse émise dans le modèle multidimensionnel d'apathie de Levy et Dubois (2006). Grâce à l'exploration distincte des processus motivationnels de *liking* et de *wanting*, ils permettent même de la préciser. De façon intéressante, les premiers résultats obtenus chez les patients pourraient, à ce stade, suggérer l'implication de processus motivationnels distincts de ceux mis en évidence dans la population normale. L'absence potentielle d'un mécanisme transnosographique fait écho à des études antérieures qui ont révélé, dans la schizophrénie, un glissement d'un déficit de *liking* mis en évidence pendant les phases prodromales (Strauss et al., 2018; Yan et al., 2016) vers des troubles de wanting une fois la schizophrénie installée (Arrondo et al., 2015; Burrer et al., 2020; Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006; Juckel, Schlagenhauf, Koslowski, Wüstenberg, et al., 2006; Kirschner et al., 2016, 2019; Kluge et al., 2018; Simon et al., 2010, 2015; Stepien et al., 2018; Waltz et al., 2010). Deux hypothèses principales sont avancées dans la littérature pour expliquer ce changement. Tout d'abord, celle suggérant que l'absence prolongée de ressenti émotionnel (déficit de *liking*), en enlevant toute valeur motivationnelle à une récompense obtenue, induirait à long terme une altération de l'envie d'obtenir à nouveau cette récompense (déficit de *wanting)* (Dickinson & Balleine, 2010). Dès lors, certains auteurs suggèrent que les déficits de *liking,* étroitement associés à l'apathie lorsque la psychose se développe pendant la phase prodromale, ne deviendraient qu'une cause secondaire d'apathie à mesure que la maladie s'établit et que les troubles du *wanting* s'intensifient (Heerey & Gold, 2007). Ensuite, à un niveau plus pharmacologique, la prise régulière d'antipsychotiques atypiques et d'autres médicaments psychotropes pourrait avoir des effets normalisants, directs ou indirects, sur les mécanismes du *liking.* En effet, plusieurs études en IRMf ont montré que les antipsychotiques de deuxième génération ont un effet normalisant sur l'activation du striatum ventral lors du *liking* dans la schizophrénie (Mucci et al., 2015; Nielsen et al., 2012; Schlagenhauf et al., 2008).

1.2. L'apathie exécutive

Nos études ont également permis de progresser dans la compréhension de l'apathie exécutive, caractérisée cliniquement par des difficultés cognitives lors de l'organisation de tâches dans la vie quotidienne (R. Levy & Dubois, 2006). Cette forme d'apathie est la plus fréquente dans la population jeune, puisqu'elle est présente chez environ 12 % des jeunes adultes (étude 1) et est prédite par les symptômes dépressifs subcliniques et la fatigue. L'étude expérimentale menée auprès de sujets sains avec un phénotype d'apathie exécutive a montré qu'elle était associée à un déficit de contrôle cognitif proactif, c'est-à-dire une incapacité à s'appuyer sur les informations contextuelles, qu'elles soient ou non motivationnelles, pour anticiper, se préparer à la survenue d'un événement. Grâce à l'approche transnosographique sur laquelle s'appuient la méta-analyse et l'étude 4, nous avons à la fois mis en évidence, dans la dépression uniquement, une hypoactivation des structures du contrôle cognitif et un score d'apathie exécutive plus élevé chez ces patients comparativement aux patients schizophrènes et aux sujets contrôles. Si les résultats de cette dernière étude sont encore à considérer avec précaution, étant donné le petit nombre de patients inclus à ce jour, ils sont cohérents avec ceux mis en évidence chez les sujets sains (étude 2), en identifiant le défaut de contrôle proactif comme prédicteur spécifique de l'apathie exécutive.

En accord avec le modèle multidimensionnel d'apathie de Levy et Dubois (2006), l'ensemble de nos résultats sur l'apathie exécutive confirme l'implication des processus de contrôle cognitif dans les difficultés des personnes souffrant de cette forme d'apathie et permet de les spécifier davantage. En effet, dans ce travail de thèse, nous avons choisi d'étudier les processus de contrôle cognitif en nous appuyant sur le modèle théorique « Dual–Mechanisms of Control » qui regroupe ces processus sur la base de leur dynamique temporelle d'engagement (Braver, 2012; Braver et al., 2007). Selon ce modèle, la dynamique temporelle d'engagement de ces processus (*i.e.* un mode de contrôle engagé de façon proactive *versus* un mode de contrôle engagé de façon réactive) permettrait d'expliquer les variabilités interindividuelle et intergroupe en termes de performances ou d'efficience de ces processus. Les résultats issus des études 2 et 4, précisent, en effet, via deux analyses statistiques différentes, que seul le mode de contrôle proactif est altéré dans l'apathie exécutive. Par ailleurs, en révélant la présence de ce dysfonctionnement à la fois chez les sujets sains présentant un phénotype d'apathie exécutive mais aussi chez les patients schizophrènes et dépressifs, nos résultats suggèrent que le dysfonctionnement du mode de contrôle proactif pourrait être un mécanisme transnosographique. Ce trouble proactif a été mis en évidence à plusieurs reprises dans les troubles dépressifs, subcliniques et cliniques (Hybels et al., 2001; Meeks et al., 2011; Rodríguez et al., 2012; Schultz et al., 2018). Dans nos résultats, dans la

mesure où l'apathie exécutive est fréquemment associée aux symptômes dépressifs (études 1, 2 et 4), nous pouvons nous demander si l'apathie exécutive ne pourrait être qu'un symptôme associé à un trouble dépressif sous-jacent. En montrant un lien spécifique entre déficits de contrôle proactif et apathie exécutive mais aucun lien avec les symptômes dépressifs, nos résultats suggèrent le rôle potentiellement médiateur que pourrait jouer l'apathie exécutive dans la relation entre troubles proactifs et dépression. Une étude antérieure va dans le même sens en montrant que la sévérité des troubles du contrôle cognitif proactif n'est pas corrélée aux symptômes dépressifs, mais serait liée à la sévérité des symptômes apathiques dans la dépression, la bipolarité et la schizophrénie (Zhu et al., 2019). Les liens entre troubles du contrôle cognitif et intensité du trouble dépressif (subclinique à clinique) n'ont en fait été montrés qu'en l'absence d'une mesure d'apathie (Hybels et al., 2001; Meeks et al., 2011; Rodríguez et al., 2012; Schultz et al., 2018). Si l'étude 4 ne nous a pas permis pour le moment de distinguer, au sein du groupe de patients dépressifs, les troubles dépressifs unipolaires et bipolaires, soulignons l'existence d'études montrant une altération plus importante du mode de contrôle proactif dans la bipolarité que dans la dépression (Afshari et al., 2020; M.-H. Chen et al., 2020; Cotrena et al., 2016; M.-H. Huang et al., 2022; Maalouf et al., 2010; Martínez-Arán et al., 2004). Par exemple, dans une étude en IRMf menée par Huang et collaborateurs (2020) auprès de patients souffrant de troubles dépressifs unipolaires et bipolaires, le réseau du contrôle cognitif (préfronto-pariétal) serait altéré dans la bipolarité, alors que le réseau sous-tendant la prise de décision (cortex préfrontal, cortex cingulaire antérieur, pallidum) serait dysfonctionnel dans la dépression (C.-C. Huang et al., 2020). Ces résultats pourraient donc suggérer une forme plus sévère, voire dominante, d'apathie exécutive dans la bipolarité que dans la dépression unipolaire.

Pour finir, si, à première vue, nos résultats peuvent paraître étonnants dans la schizophrénie, les déficits de contrôle proactif ayant été largement démontrés dans cette pathologie (Barch et al., 2001; Holmes et al., 2005; MacDonald III & Carter, 2003; Perlstein et al., 2003; Yoon et al., 2008), ils ne les contredisent en aucun cas, dans la mesure où ils ne permettent pas d'exclure la présence d'une apathie exécutive dans la schizophrénie. En effet, plus les patients schizophrènes ont une apathie exécutive sévère, plus ils ont des troubles du contrôle proactif (étude 4). Les résultats issus de notre méta-analyse montrent, par ailleurs, chez les patients souffrant de schizophrénie, une hyperactivation du cortex préfrontal dorsolatéral dans la CPT-AX. Malheureusement, dans ces études, l'apathie n'a pas été mesurée de façon suffisamment systématique, pour qu'on puisse la mettre en lien avec ce fonctionnement atypique. A notre connaissance, seule l'hypoactivation de cette région, mise en évidence dans les pathologies neurodégénératives, a été associée à l'apathie exécutive (R. Levy & Dubois, 2006; Monchi et al., 2007; Pagonabarraga et al., 2015). L'existence d'une prévalence élevée d'une forme conjuguée d'apathie émotionnelle – exécutive dans la

schizophrénie, une forme extrêmement rare dans la population jeune, avec moins de 2 % des profils d'apathie (étude 1), reste donc tout à fait possible.

1.3. L'apathie d'initiation

Les données acquises dans le cadre de ces différentes études ont, de la même façon, également permis de progresser dans la compréhension de l'apathie d'initiation, une forme caractérisée cliniquement par une perte de spontanéité dans la planification d'actions et les réactions émotionnelles et qui peut se traduire par un vide mental (R. Levy & Dubois, 2006). Le phénotype d'apathie d'initiation est le moins fréquent dans la population jeune, présent chez environ 7 % des jeunes adultes, et est prédit par un manque de dynamisme et de contacts sociaux (étude 1). De façon intéressante, l'apathie d'initiation est la seule forme dans laquelle les formes mixtes (c'est-à-dire la présence combinée d'un phénotype d'apathie d'initiation et d'un autre phénotype) étaient aussi fréquentes que le phénotype seul. Les analyses complémentaires réalisées nous ont toutefois permis de montrer que le phénotype d'apathie d'initiation n'est pas associé aux mêmes dysfonctionnements que ceux mis en évidence pour les formes exécutive et émotionnelle. En effet, cette forme serait spécifiquement associée à des difficultés d'anticipation et de déploiement d'un effort cognitif adapté aux informations contextuelles concernant l'effort et la récompense (étude 3), mais également, à un niveau plus comportemental, à des prises de décision aberrantes. De plus, dans la population jeune, les différences interindividuelles au niveau de ces résultats sont expliquées en partie par l'apathie d'initiation. Grâce à l'approche transnosographique, nous avons à la fois mis en évidence, dans la dépression uniquement, une hypoactivation des structures du contrôle cognitif et de la motivation et, un score d'apathie d'initiation plus élevé chez ces patients comparativement aux patients schizophrènes et aux sujets contrôles (méta-analyse et étude 4). Les résultats de l'étude 4, bien que préliminaires, restent cohérents avec ceux mis en évidence chez les sujets sains (étude complémentaire), dans la mesure où aucun des indicateurs associés à un dysfonctionnement des processus de contrôle cognitif ou motivationnels ne prédit cette forme d'apathie dans les pathologies psychiatriques.

Depuis le modèle de Levy et Dubois (2006), l'apathie d'initiation reste la forme d'apathie dont les mécanismes sous-jacents sont les moins bien définis. Selon les outils utilisés (questionnaires, tests neuropsychologiques et IRMf) et les pathologies étudiées, l'apathie d'initiation est tantôt envisagée comme une forme mixte, (Perri et al., 2018), tantôt comme une forme phénotypique (Radakovic et al., 2016). D'ailleurs, dans la création du questionnaire DAS, l'apathie d'initiation était la seule forme corrélée aux autres formes d'apathie, un résultat retrouvé dans l'étude 1 (Radakovic & Abrahams, 2014). Nos résultats

permettent d'affiner les hypothèses du modèle multidimensionnel d'apathie de Levy et Dubois, qui suggérait la possibilité que l'apathie d'initiation soit sous-tendue par la combinaison des déficits des deux autres formes ou au contraire, sous-tendue par des déficits spécifiques en lien avec l'intégration des processus cognitifs et motivationnels. Nos résultats montrent que ces deux hypothèses peuvent être valides avec à la fois l'existence de formes mixtes (étude 1) et d'un phénotype associé à des mécanismes spécifiques (études complémentaire, 3 et 4). En revanche, les résultats de la méta-analyse ne permettent pas, dans la dépression, de départager ces deux hypothèses.

De manière intéressante, dans la littérature, trois études ont mis en évidence que des troubles de la prise de décision chez des sujets sains pourraient être un précurseur au développement d'une dépression, voire constituer un endophénotype de la dépression (Boeker et al., 2012; M. L. Cléry-Melin & Gorwood, 2016; M.-L. Cléry-Melin et al., 2019). Nos résultats montrent que ces troubles de la prise de décision pourraient être expliqués par des différences interindividuelles de sévérité de cette forme d'apathie suggérant que l'apathie d'initiation, en altérant les capacités de prise de décision, pourrait être un des facteurs de vulnérabilité à l'apparition d'une dépression au cours de la vie. Néanmoins, notre approche électrophysiologique n'a pas permis de véritablement spécifier ces déficits de prise de décision. Une collaboration en cours avec le laboratoire de *Neural computation and cognition* (Université de Brown, Providence, USA) nous permettra, grâce à une approche computationnelle prenant en compte essais par essais les réponses comportementales et électrophysiologiques de l'ensemble des sujets sains recrutés, de mieux comprendre les mécanismes de prise de décision déficitaires dans l'apathie d'initiation en spécifiant les profils de sensibilité à l'effort cognitif et à la récompense.

2. L'intérêt clinique d'une conception multidimensionnelle de l'apathie en psychiatrie

A ce jour, aucun traitement efficace de l'apathie n'existe, l'hétérogénéité des réponses aux traitements testés est très forte d'une pathologie à une autre, d'un patient à un autre, et parfois même d'une forme d'apathie à une autre. L'évaluation multidimensionnelle de l'apathie, qui permet de mieux cibler les dysfonctionnements spécifiques à chaque forme d'apathie, devrait participer au développement d'une psychiatrie de précision, individualisée sur le profil de chaque patient (Gracia-García et al., 2021).

2.1. Perspectives thérapeutiques pour l'apathie émotionnelle

Nos résultats ont mis en évidence le dysfonctionnement du *liking* chez les sujets sains et du *wanting* chez les patients pour la forme émotionnelle, une forme qui pourrait s'avérer plus fréquente dans la schizophrénie. Les systèmes opioïde et endocannabinoïde sous-tendent le processus motivationnel de *liking* (Berridge & Robinson, 2016; Smith & Berridge, 2007). Des études récentes en preuve de concept ont permis de montrer, chez des patients dépressifs avec une apathie, les effets bénéfiques d'antagonistes aux récepteurs opioïdes kappa sur l'apathie et l'activation striatale au moment de l'attribution d'une récompense (Borsini et al., 2020; Krystal et al., 2020). Cette piste thérapeutique reste toutefois pour des raisons éthiques à envisager avec précaution, en raison notamment des risques de mésusages des opioïdes et des effets de dépendance associés (Volkow & Blanco, 2021). Concernant le système endocannabinoïde, des résultats similaires sont obtenus avec l'anandamide (Mitchell et al., 2018). Dans les pathologies psychiatriques, le système dopaminergique sous-tend les difficultés de *wanting* (Berridge & Robinson, 2016; Smith & Berridge, 2007). Parmi les antipsychotiques atypiques, l'amisulpride et l'aripiprazole augmentent la transmission dopaminergique et améliorent l'hypoactivation striatale associée au traitement motivationnel (Admon et al., 2017; Borsini et al., 2020; Reimherr et al., 2010). Enfin, des traitements anti-inflammatoires pourraient être une nouvelle stratégie médicamenteuse de l'apathie émotionnelle, aussi bien chez les sujets sains que chez les patients en psychiatrie (Felger et al., 2016). En effet, des dysfonctionnements fronto-striataux du réseau de la récompense, à la fois pendant le *liking* et le *wanting*, ont été associés à une augmentation des processus inflammatoires ainsi qu'à une augmentation de l'apathie (Eisenberger et al., 2010; Swardfager et al., 2016).

Concernant les traitements non pharmacologiques, c'est-à-dire principalement les thérapies psychologiques et les remédiations cognitives, ceux visant à améliorer la motivation pourraient être bénéfiques spécifiquement à l'apathie émotionnelle. Dans la schizophrénie, si l'effet de ces traitements n'a jamais été testé sur l'apathie multidimensionnelle, une méta-analyse a récemment montré que la remédiation cognitive basée sur l'amélioration du *wanting* est le plus efficace pour réduire l'apathie (Cella et al., 2023). Concernant les techniques de neuromodulation, la stimulation du cortex orbitofrontal pourrait également être une alternative thérapeutique prometteuse, et plus spécifiquement encore dans la schizophrénie. A notre connaissance, aucune étude publiée de ce type n'existe dans la schizophrénie. En revanche, dans la dépression, où l'apathie exécutive et d'initiation pourraient être plus sévères (un résultat à confirmer en poursuivant, notamment, l'étude 4), plusieurs études ont été menées. Plus précisément dans quatre études, la stimulation du cortex préfrontal dorsolatéral n'a été bénéfique pour diminuer le score d'apathie que chez la moitié des patients dépressifs (Feffer et al., 2018; Fettes et al., 2017; Kolken et al., 2023; Vinne et al., 2021). Les résultats montrent cependant une efficacité de la rTMS du cortex orbitofrontal chez 30 % des patients résistants, présentant des troubles motivationnels dominants (Fettes et al., 2017; Kolken et al., 2023). L'hypothèse qu'une forme différente d'apathie dominante existe chez ces patients est tentante : une forme exécutive chez les 50 % de patients dépressifs pour qui la stimulation du cortex préfrontal dorsolatéral est efficace, et, au contraire, une forme émotionnelle chez les 15 % de patients pour qui c'est la stimulation du cortex orbitofrontal qui l'est le plus.

2.2. Perspectives thérapeutiques pour l'apathie exécutive

Concernant l'apathie exécutive, nos résultats ont identifié le dysfonctionnement des processus de contrôle proactif comme spécifiquement associé à cette forme d'apathie, une forme qui pourrait s'avérer plus fréquente dans la dépression. Dans la mesure où ce mode de contrôle proactif est sous-tendu par le système dopaminergique (Braver et al., 2009; Lopez-Garcia et al., 2016), les traitements dopaminergiques semblent être une piste thérapeutique à privilégier. En effet, quatre études ont d'ores et déjà montré chez des patients souffrant de pathologies neurodégénératives que l'efficacité de ce traitement sur l'apathie était supérieure en cas d'apathie exécutive dominante, comparativement aux autres formes (Czernecki et al., 2008; Herrmann et al., 2008; Padala et al., 2017; Thobois et al., 2013).

En outre, la neuromodulation des régions sous-tendant les processus de contrôle cognitif pourrait également être une alternative thérapeutique prometteuse, et plus spécifiquement encore dans la dépression puisque les résultats de l'étude 4 suggèrent une sévérité plus importante de l'apathie exécutive dans la dépression. Néanmoins les études existantes ne s'appuient que sur une évaluation unidimensionnelle de l'apathie. En effet, dans la dépression, une étude en IRMf a montré que le neurofeedback, lors de la réalisation d'une tâche de contrôle cognitif, permettait d'améliorer l'apathie et d'augmenter la connectivité fonctionnelle du réseau de contrôle cognitif (Gunning et al., 2021). De la même façon, une étude de rTMS appliquée sur le cortex préfrontal dorsolatéral bilatéral a également permis de réduire spécifiquement l'apathie, et non les symptômes dépressifs, chez les patients souffrant de dépression (Bodén et al., 2021). L'absence d'effet chez les patients souffrant de schizophrénie pourrait en partie être expliquée par la présence de profils d'apathie différents. En effet, dans la schizophrénie, quelques études ont montré des effets d'une stimulation par rTMS du cortex dorsolatéral très variables d'un patient à un autre (Kumar et al., 2020; Lavallé & Aleman, 2019; Lisoni et al., 2022).

Conclusion

En nous appuyant sur la conception neuroanatomique de l'apathie multidimensionnelle la plus récente, notre travail a permis de progresser dans la connaissance des mécanismes cognitifs et neuronaux associés à chacune des trois formes émotionnelle - exécutive et d'initiation - de ce symptôme à la fois très fréquent et handicapant (Levy et Dubois, 2006). Pris ensemble, nos résultats confirment l'intérêt des stratégies thérapeutiques individualisées, prenant en compte le profil apathique de chaque patient lors de l'élaboration de son protocole de soins, afin d'améliorer les chances de succès thérapeutique. L'approche phénotypique de l'apathie privilégiée dans ce travail - c'est-à-dire en envisageant l'apathie comme un trait se distribuant sur un continuum entre la population normale et les patients en psychiatrie - a également permis d'envisager l'apathie, présente à des intensités variables dans la population jeune, comme potentiel marqueur de risque de développer un trouble psychiatrique. En effet, le trait stable d'apathie présent chez les sujets sains est à la fois associé aux mêmes difficultés dans la vie quotidienne que celles observées chez les sujets à risque de développer un trouble psychiatrique et chez les patients souffrant d'une pathologie psychiatrique, mais semble également associé à l'altération des mêmes mécanismes. Seules des études longitudinales complémentaires permettraient de tester et de préciser dans quelle mesure chaque phénotype d'apathie pourrait constituer un trait de vulnérabilité à l'apparition d'un trouble psychiatrique spécifique. Une meilleure exploration des conséquences et mécanismes des formes mixtes d'apathie, qui se sont révélées relativement fréquentes dans nos études, aiderait à répondre avec plus de précision à cette question. En contribuant à améliorer notre compréhension des mécanismes associés à ce symptôme caractéristique des phases prodromales de la schizophrénie et de la dépression, ce travail de thèse contribue également à une meilleure connaissance de la physiopathologie de ces deux pathologies psychiatriques.

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Annexes

Annexe 1

Traduction française du *Dimensional Apathy Scale* (DAS)

DAS – *Dimensional Apathy Scale*

Echelle d'apathie dimensionnelle

Choisissez la réponse à partir de ce que vous avez pu **ressentir, faire ou penser**, en fonction de leur fréquence de survenue au cours du dernier mois.

1) J'ai besoin d'un peu d'encouragement pour commencer quelque chose.
   - Quasiment toujours
   - Souvent
   - Occasionnellement
   - Presque jamais

2) J'initie le contact avec mes ami(e)s.
   - Quasiment toujours
   - Souvent
   - Occasionnellement
   - Presque jamais

3) J'exprime mes émotions.
   - Quasiment toujours
   - Souvent
   - Occasionnellement
   - Presque jamais

4) Je pense aux nouvelles choses à faire pendant la journée.
   - Quasiment toujours
   - Souvent
   - Occasionnellement
   - Presque jamais

5) Je me sens concerné(e) par les sentiments de ma famille.
   - Quasiment toujours
   - Souvent
   - Occasionnellement
   - Presque jamais

6) Je me trouve en train de regarder dans le vide.
   - Quasiment toujours
   - Souvent
   - Occasionnellement
   - Presque jamais

7) Avant de commencer quelque chose, je réfléchis à comment les autres pourraient le percevoir.
    - Quasiment toujours
    - Souvent
    - Occasionnellement
    - Presque jamais

8) Je planifie mes activités quotidiennes à l'avance.
    - Quasiment toujours
    - Souvent
    - Occasionnellement
    - Presque jamais

9) Quand j'apprends une mauvaise nouvelle, je me sens mal.
    - Quasiment toujours
    - Souvent
    - Occasionnellement
    - Presque jamais

10) Je suis capable de me concentrer sur une tâche jusqu'à ce qu'elle soit terminée.
    - Quasiment toujours
    - Souvent
    - Occasionnellement
    - Presque jamais

11) Je manque de motivation.
    - Quasiment toujours
    - Souvent
    - Occasionnellement
    - Presque jamais

12) J'ai des difficultés à éprouver de l'empathie pour d'autres personnes.
    - Quasiment toujours
    - Souvent
    - Occasionnellement
    - Presque jamais

13) Je me définis des buts.
    - Quasiment toujours
    - Souvent
    - Occasionnellement
    - Presque jamais

14) J'essaie de nouvelles choses.
    - Quasiment toujours
    - Souvent
    - Occasionnellement
    - Presque jamais

15) Je ne me sens pas concerné(e) par ce que les autres peuvent penser de mes comportements.
    - Quasiment toujours
    - Souvent
    - Occasionnellement
    - Presque jamais

16) J'agis sur les choses auxquelles j'ai pensé pendant la journée.
    - Quasiment toujours
    - Souvent
    - Occasionnellement
    - Presque jamais

17) Quand je réalise une tâche complexe, j'ai des difficultés à planifier ce que je dois faire.
    - Quasiment toujours
    - Souvent
    - Occasionnellement
    - Presque jamais

18) Je me garde occupé(e).
    - Quasiment toujours
    - Souvent
    - Occasionnellement
    - Presque jamais

19) Je suis facilement perdu(e) quand je dois faire plusieurs choses en même temps.
    - Quasiment toujours
    - Souvent
    - Occasionnellement
    - Presque jamais

20) Je deviens facilement émotif (émotive) quand je regarde quelque chose de joyeux ou triste à la télévision.
    - Quasiment toujours
    - Souvent
    - Occasionnellement
    - Presque jamais

21) Je trouve difficile de me focaliser sur des choses.
    - Quasiment toujours
    - Souvent
    - Occasionnellement
    - Presque jamais

22) Je suis spontané(e).
    - Quasiment toujours
    - Souvent
    - Occasionnellement
    - Presque jamais

23) Je suis facilement distrait(e).

- Quasiment toujours
- Souvent
- Occasionnellement
- Presque jamais

24) Je me sens indifférent(e) à ce qui se passe autour de moi.

- Quasiment toujours
- Souvent
- Occasionnellement
- Presque jamais

Annexe 2

Module d’évaluation écologique de l’apathie

Module d'évaluation écologique de l'apathie

Questionnaire d'activité - Sujet 31

*Indiquez l'activité que vous êtes en train de faire :

Veuillez sélectionner une réponse ci-dessous

- ○ Travail / Scolarité
- ○ Loisirs (film, musique, lecture, sport ...)
- ○ Manger / Dormir
- ○ Activités sociales (parler, téléphoner, ...)
- ○ Activités domestiques (cuisine, ménage, vaisselle, ...)
- ○ Rien en particulier

*Indiquez votre niveau de motivation pendant cette activité :

Veuillez sélectionner une réponse ci-dessous

- ○ Très motivé
- ○ Moyennement motivé
- ○ Peu motivé
- ○ Pas du tout motivé

*Indiquez votre niveau de plaisir pendant l'activité en cours :

Veuillez sélectionner une réponse ci-dessous

- ○ Très plaisant
- ○ Moyennement plaisant
- ○ Peu plaisant
- ○ Pas du tout plaisant

*Indiquez combien d'effort vous fournissez pour réaliser cette activité :

Veuillez sélectionner une réponse ci-dessous

- ○ Énormément d'effort
- ○ Beaucoup d'effort
- ○ Peu d'effort
- ○ Aucun effort

*Aviez-vous prévu à l'avance de faire cette activité :

○ Oui ○ Non

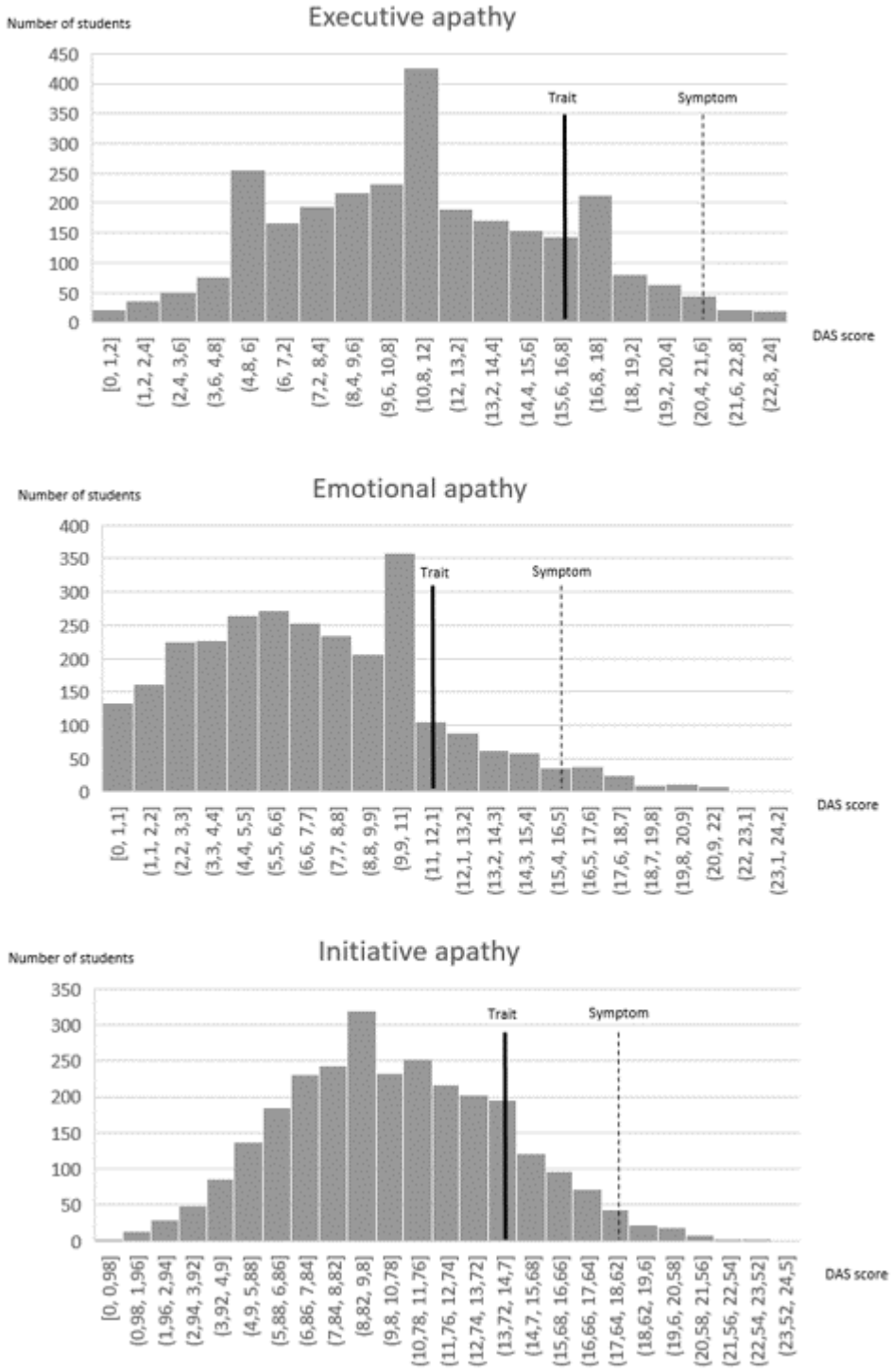
Envoyer

Annexe 3

Matériel supplémentaire de l’étude 1

The stability of multidimensional subclinical apathy during a pandemic and its relations to psycho-behavioral factors

Supplementary data 1-a: Distribution of the three DAS scores in the sample, with cut-offs for subclinical (trait) and clinical (symptom) apathy



Supplementary data 1-b: Table of the three DAS cut-offs for subclinical (trait) and clinical (symptom) apathy in Study 1 and Study 2

	Cut-off for subclinical apathy		Cut-off for clinical apathy	
	Study 1	Study 2	Study 1	Study 2
DAS executive	16	16	21	21
DAS emotional	12	12	16	16
DAS initiative	14	14	18	18

Supplementary data 2: Online survey

1- Sociodemographic characteristics

Gender: ☐ male ☐ female ☐ neutral

Age? : …….

Is French your mother tongue? ☐ Yes ☐ No

2- Education

Are you currently enrolled at the University of Strasbourg? ☐ Yes ☐ No

In which field? …….

In the event of a double course, indicate your main course

In which level?

- First year
- Diploma of Higher Education
- BA, BS/BSc
- MS/MSc, MA
- Master's Degree
- PhD

What were your results in the baccalaureate?

- Mention very well with congratulations from the jury
- Honours
- Mention well
- Mention good enough
- Without honours
- I do not remember

Did you repeat a year during your schooling?

- No
- Yes
    - in kindergarten
    - in elementary school
    - in middle-school
    - in high school
    - at university

If so, how many times so far? …….

Did you skip a class during your schooling?

- No
- Yes
    - in kindergarten
    - in elementary school
    - in middle-school
    - in high school
    - at university

If so, how many times so far? …….

Did you choose your field this year?

- Yes and I like what I study
- Yes but, in the end, I don't like what I'm studying
- No and I don't like what I'm studying
- No, but in the end, I like what I study

3- General functioning

On average, how many people do you initiate social contact with in a day:

- 0
- 1 to 2
- 3 to 6
- More than 6

Face to face, phone calls or messages are considered social contacts.

Would you say you are socially isolated?

- Yes and I suffer from it
- Yes but it’s ok for me
- No

Do you have any hobbies? : ☐ Yes ☐ No

If so, list them:

Do you go out at night?

- Almost every evening
- Often (several evenings per week)
- Rarely (a few evenings per month)
- Almost never

Do you like to discover new things? ☐ Yes ☐ No

Would you describe yourself as a dynamic and enthusiastic person in your daily life?

☐ Yes ☐ No

Do you feel pleasure in your daily life?

- Almost all the time
- Often
- Rarely
- Almost never

Do you live?

- Alone in an apartment
- Alone in a dormitory
- With your family
- With a roommate
- With a partner
- In a guest room
- No fixed address

Do you consider yourself independent on a daily basis? ☐ Yes ☐ No

Do you do the housework? ☐ Yes ☐ No

Do you do your grocery shopping? ☐ Yes ☐ No

Do you cook your meals?

- Yes, lunch and dinner
- Yes, lunch or dinner
- No, I eat at the (university) restaurant
- No, someone makes me my meals

How much time do you spend sitting or lying down on a typical day?

Indicate the approximate number of hours: …….

This question includes time spent sitting at a desk, traveling in car, bus, train, reading, playing cards or watching TV. <u>It does not include the time spent asleep</u>.

4- Psychopathology

Qualitative measures

Do you currently suffer from a somatic disease? ☐ Yes ☐ No

For example, are taken into account for this question: a motor or sensory disability, a thyroid disorder, a sleep disorder, a neurological disease,

Do you have a neurodevelopmental disorder? ☐ Yes ☐ No

For example: ADHD, dyslexia, dyspraxia …

If so, specify the neurodevelopmental disorder(s): …….

Do you suffer or have you ever suffered from a psychiatric disorder or a mood disorder?

☐ Yes ☐ No

For example: depression, bipolarity, schizophrenia …

Do your parents or siblings suffer or have they suffered from a psychiatric disorder or a mood disorder? ☐ Yes ☐ No

Have you taken any psychotropic drugs in the past three months? ☐ Yes ☐ No

By psychotropic drugs are meant: antidepressants, anxiolytics, sleeping pills, antipsychotics and mood regulators

Do you take any of the following substances?

- Alcohol : ☐ Yes ☐ No

If so, number of drinks per week: ……

- Cannabis : ☐ Yes ☐ No

If so, how many times per month: …….

Was the last intake in the past month? ☐ Yes ☐ No

- Other illicit drugs : ☐ Yes ☐ No

Was the last intake in the past month? ☐ Yes ☐ No

Do you feel tired every day <u>for no reason?</u>

- Always
- Often (several times per week)
- Rarely (once a week, or not every week)
- Never

Are you worried about your future? ☐ Yes ☐ No

Validated scales

Scale 1: The Rosenberg Self-Esteem Scale (RSE) (Rosenberg, 1965)

Scale 2 : Dimensional Apathy Scale (Radakovic & Abrahams, 2014)

Scale 3: The Temporal Experience of Pleasure Scale (TEPS) (Gard and al, 2006)

Scale 4: The Beck Depression Inventory II (BDI-II) (Beck et al., 1996)

Supplementary data 3: Correlations between all the questionnaires for both studies

Study 1						
	DAS emotional	DAS initiative	BDI-II	RSE	TEPS anticipatory	TEPS consummatory
DAS executive	r=-0.06 p>.05	r=0,40 p<.001	r=0,55 p<.001	r=-0,49 p<.001	r=-0,08 p<.001	r=-0.01 p>.05
DAS emotional		r=0,20 p<.001	r=-0,01 p>.05	r=0,08 p<.001	r=-0,34 p<.001	r=-0,26 p<.001
DAS initiative			r=0,40 p<.001	r=-0,39 p<.001	r=-0,36 p<.001	r=-0,25 p<.001
BDI-II				r=-0,78, p<.001	r=-0,26 p<.001	r=-0,13 p<.001
RSE					r=0,22 p<.001	r=0,10 p<.001
TEPS anticipatory						r=0,41 p<.001
Study 2						
	DAS emotional	DAS initiative	BDI-II			
DAS executive	r=-0,04 p>.05	r=0,46 p<.001	r=0,28 p<.001			
DAS emotional		r=0,18 p<.001	r=0,02 p>.05			
DAS initiative			r=0,18 p<.001			

DAS - The Dimensional Apathy Scale (Radakovic and Abrahams, 2014) ; BDI-II - The Beck Depression Inventory II (Beck et al., 1996) ; RSE - The Rosenberg Self-Esteem Scale (Rosenberg, 1965) ; TEPS - The Temporal Experience of Pleasure Scale (Gard and al, 2006)

Supplementary data 4: Independent variables and their modalities

	Independent variables	Modalities if categorical variables
Sociodemographic characteristics	Gender	3: Male; Female; Transgender
	Age	Years
Education	Field	5: Arts and Literature; Law, Health; Technical Sciences; Humanities and Social sciences
	Level of study	6: First year; Diploma of Higher Education; BA, BS/BSc, MS/MSc, MA; Master's Degree; PhD
	Bachelor's degree	6: Mention very well with congratulations from the jury; Honours; Mention well; Mention good enough; Without honours; I do not remember
	Number of grade repetitions	8: none; 1; 2; 3; 4; 5; 6; 7
	Type of grade repetition	5: in kindergarten; in elementary school; in middle-school; in high school; at university
	Number of classes skipped	5: none; 1; 2; 3; 4
	Type of classes skipped	5: in kindergarten; in elementary school; in middle-school; in high school; at university
	Choice of field	4: Yes and I like what I study; Yes but, in the end, I don't like what I'm studying; No and I don't like what I'm studying; No, but in the end, I like what I study
General functioning	Initiation of social contacts	4: 0; 1 to 2; 3 to 6; more than 6
	Social isolation	3: Yes and I suffer from it; Yes but it's ok for me; No
	Hobbies	2: Yes; No
	Night out	4: Almost every evening ; Often (several evenings per week); Rarely (a few evenings per month); Almost never
	Curiosity	2: Yes; No
	Dynamism	2: Yes; No
	Daily pleasure	4: Almost all the time; Often; Rarely; Almost never
	Dwelling	7: Alone in an apartment; Alone in a dormitory; With your family; With a roommate;

		With a partner; In a guest room; No fixed address
	Independence	2: Yes; No
	Housework	2: Yes; No
	Grocery shopping	2: Yes; No
	Cooking	4: Yes, lunch and dinner; Yes, lunch or dinner; No, I eat at the (university) restaurant; No, someone makes me my meals
	Sedentary lifestyle	Number of hours
Psychopathology – Validated scales	The Beck Depression Inventory II (BDI-II)	Score
	The Temporal Experience of Pleasure Scale (TEPS)	Score
	The Rosenberg Self-Esteem Scale (RSE)	Score
Psychopathology – Qualitative measures	Somatic disease	2: Yes; No
	Neurodevelopmental disorders	2: Yes; No
	Psychiatric disorders	2: Yes; No
	Psychiatric disorders in relatives	2: Yes; No
	Psychotropic drugs	2: Yes; No
	Alcohol	2: Yes; No
	Frequency of alcohol intake	Number of glass per week
	Cannabis	2: Yes; No
	Frequency of alcohol intake	Number of intakes per month
	Other illicit drugs	2: Yes; No
	Fatigue	4: Always ; Often (several times per week); Rarely (once a week, or not every week); Never
	Anxiety	2: Yes; No

Annexe 4

Matériel supplémentaire de l’étude 2

Specific mechanisms underlying executive and emotional apathy: A phenotyping study

Supplementary data 1: Results of the assumption tests for the ANOVAs

The indicators in bold do not respect the assumption tests for the ANOVAs.

		Shapiro-Wilk test	Levene's test
DPX			
	RT - AX trials	P<.001	p>.15
	RT - AY trials	P<.004	p>.248
	RT - BX trials	P<.001	p>.18
	FA – AX trials	P<.001	p>.08
	FA – AY trials	P<.001	p>.50
	FA – BX trials	P<.001	p>.20
	BSI - RT	P>.06	p>.416
	BSI - FA	P<.001	p>.08
	Omissions	P<.001	p>.07
	P2N2 – A cue	P<.02	p>.18
	P2N2 – B cue	P<.02	p>.95
	P3b – A cue	P>.59	p>.74
	P3b – B cue	P>.17	p>.78
	CNV – A cue	P>.23	p>.17
	CNV – B cue	P>.79	p>.16
	N2 – AX trials	P>.17	p>.14
	N2 – AY trials	P>.33	p>.32
	N2 – BX trials	P>.19	p>.45
	P3 a – AX trials	P>.23	p>.59
	P3 a – AY trials	P>.43	p>.91
	P3 a – BX trials	P>.12	p>.84
MID			
	RT – win cue	p>.08	p>.91
	RT – loss cue	P<.002	p>.63
	RT – neutral cue	P<.001	p>.39
	Anticipations – win cue	P<.001	p>.15
	Anticipations – loss cue	P<.001	p>.25
	Anticipations – neutral cue	P<.001	p>.16
	Omissions – win cue	P<.001	p>.14
	Omissions – loss cue	P<.001	P<.03
	Omissions – neutral cue	P<.001	P>.25
	P3b – win cue	P<.004	P>.16
	P3b – loss cue	P<.03	P>.62
	P3b – neutral cue	P<.002	P>.09
	CNV – win cue	P>.12	P>.16
	CNV – loss cue	P>.69	P>.22
	CNV – neutral cue	P>.28	P>.26
	RewP – actual win	P>.28	P>.26
	RewP – actual loss	P>.78	P>.26
	P3 a – actual win	P>.56	P>.84
	P3 a – neutral trials with positive feedback	P>.73	P>.94
	P3 a – actual loss	P>.64	P>.73
	P3 a – neutral trials with negative feedback	P>.18	P>.97
	LPP – actual win	P>.47	P>.19
	LPP – absence of win	P>.26	P>.77
	LPP – actual loss	P>.17	P>.85
	LPP – absence of loss	P>.57	P>.93
	LPP - neutral trials with positive feedback	P>.13	P>.58
	LPP - neutral trials with negative feedback	P>.21	P>.31

Supplementary data 2: Results of the ANCOVAs

1) DPX task

a- Behavioral data

ANCOVA - Goal maintenance index [FA_z(AY)-FA_z(AX)+z(BX)]

	Sum of Squares	df	Mean Square	F	p	η^2p
Group	6.060	2	3.0298	3.1004	0.042	0.092
Sex	0.106	1	0.1056	0.1080	0.744	0.002
Group ✻ Sex	0.192	2	0.0959	0.0981	0.907	0.003
Residuals	59.612	61	0.9772			

b- Probe-locked N2

ANCOVA - N2 amplitude [AX-AY]

	Sum of Squares	df	Mean Square	F	p	η^2p
Group	1253.7	2	626.8	3.128	0.031	0.098
Sex	46.9	1	46.9	0.234	0.630	0.004
Group ✻ Sex	174.1	2	87.1	0.434	0.650	0.014
Residuals	12424.9	62	200.4			

2) MID task

a- Cue-locked CNV

ANCOVA – CNV amplitude [all trials]

	Sum of Squares	df	Mean Square	F	p	η^2p
Group	246.6	2	123.31	3.663	0.031	0.106
Sex	35.6	1	35.60	1.058	0.308	0.017
Group ✻ Sex	15.6	2	7.82	0.232	0.793	0.007
Residuals	2087.1	62	33.66			

b- Feedback-locked P3a

ANCOVA – P3a amplitude [actual loss trials]

	Sum of Squares	df	Mean Square	F	p	η^2p
Group	1759	2	879.5	3.622	0.033	0.106
Sex	102	1	101.8	0.419	0.520	0.007
Group ✻ Sex	187	2	93.4	0.385	0.682	0.012
Residuals	14810	61	242.8			

ANCOVA - P3a amplitude [neutral trials with negative feedback]

	Sum of Squares	df	Mean Square	F	p	η^2p
Group	1271	2	635.7	3.326	0.042	0.097
Sex	241	1	241.4	1.263	0.265	0.020
Group ✻ Sex	106	2	53.0	0.277	0.759	0.009
Residuals	11852	62	191.2			

c- Feedback-locked LPP

ANCOVA - LPP amplitude [actual loss trials]

	Sum of Squares	df	Mean Square	F	p	η^2p
Group	522	2	261	1.440	0.245	0.045
Sex	88.3	1	88.32	1.677	0.200	0.026
Group ✻ Sex	114.6	2	57.32	1.088	0.343	0.034
Residuals	11056	61	181			

ANCOVA - LPP amplitude [neutral trials with negative feedback]

	Sum of Squares	df	Mean Square	F	p	η^2p
Group	127.2	2	63.6	0.668	0.516	0.021
Sex	66.9	1	66.9	0.703	0.405	0.011
Group ✻ Sex	464.2	2	232.1	2.439	0.096	0.074
Residuals	5804.8	61	95.2			

ANCOVA - LPP amplitude [neutral trials with positive feedback]

	Sum of Squares	df	Mean Square	F	p	η^2p
Group	107.6	2	53.8	1.036	0.361	0.032
Sex	58.4	1	58.4	1.125	0.293	0.018
Group ✻ Sex	37.6	2	18.8	0.362	0.698	0.012
Residuals	3220.5	62	51.9			

Annexe 5

Analyses complémentaires pour tester l'hypothèse d'une forme mixte dans l'apathie d'initiation

Analyses complémentaires

Hypothèse d'une forme mixte dans l'apathie d'initiation

1) DPX task

a- Behavioral results

The ANOVA performed on RT revealed a main effect of trial ($F(2,132)=140.16$, $p<.001$; $\eta^2=.68$), with slower RT for AY than AX and BX ($p<.001$), and for AX than BX ($p<.001$). No effect of group ($p>.54$) nor trial x group interaction ($p>.68$) was observed.

Regarding the FA rate, the ANOVA revealed a main effect of trial ($F(2,122)=14.55$, $p<.001$; $\eta^2=.19$), with higher FA rate for AX and AY than for BX ($p<.001$). No effect of group ($p>.63$) nor trial x group interaction ($p>.68$) was observed.

The ANOVA performed on the BSI for RT and FA revealed no effect of group (respectively, $p>.66$ and $p>51$).

The ANOVA performed on the total number of omissions revealed no effect of group ($p>.23$).

b- Electrophysiological results

b1- Cue-locked ERP

The ANOVA performed on the P2-N2 difference revealed the classic main effect of cue ($F(1,66)=3.26$, $p<.05$; $\eta^2=.04$); with larger P2-N2 difference after the B cue than the A cue. No effect of group ($p>.32$) nor cue x group interaction ($p>.30$) was observed.

The ANOVA performed on the P3b revealed the classic main effect of cue ($F(1,66)=162.64$, $p<.001$; $\eta^2=.71$), with a larger P3b after the B cue than the A cue. No effect of group ($p>.15$) nor cue x group interaction ($p>.13$) was observed.

The ANOVA performed on the CNV revealed the classic main effect of cue ($F(1,66)=3.66$, $p<.05$; $\eta^2=.04$), with larger CNV after the A cue than the B cue. No effect of group ($p>.31$) nor cue x group interaction ($p>.74$) was observed.

b2- Probe-locked ERP

The ANOVA performed on the P3a revealed a main effect of trial ($F(2,132)=51.89$, $p<.001$; $\eta^2=.44$), with larger P3a in AY trials than in AX and BX trials ($p<.001$). No effect of group ($p>.24$) nor trial x group interaction ($p>.15$) was observed.

2) MID task

One subject with initiative apathy was excluded from analyses because he anticipated more than 15% of the trials per block.

a- Behavioral results

The ANOVA performed on RT revealed the classic main effect of cue ($F(2,130)=21.06$, $p<.001$; $\eta^2=.25$), with faster RT for win than neutral cues, and for loss than neutral cues (all $p<.001$). No effect of group ($p>.81$) nor cue x group interaction ($p>.27$) was observed.

The ANOVA performed on the rate of anticipations revealed a main effect of cue ($F(2,130)=14.32$, $p<.001$; $\eta^2=.18$), with more anticipations after a win than loss and neutral cues ($p<.007$) and more anticipations after loss than neutral cues ($p<.05$). No effect of group ($p>.63$) nor cue x group interaction ($p>.58$) was found.

The ANOVA performed on omissions revealed there was no effect of cue ($p>.60$), group ($p>.38$), nor trial x group interaction ($p>.59$).

b- Electrophysiological results

b1- Cue-locked ERP

The ANOVA performed on the P3b revealed a main effect of cue ($F(2,130)=3.87$, $p<.02$; $\eta^2=.06$), with larger P3b after a win than a loss cue ($p<.01$). No effect of group ($p>.62$) nor cue x group interaction ($p>.59$) was observed.

The ANOVA performed on the CNV revealed a cue x group interaction ($F(4,130)=2.87$, $p<.03$; $\eta^2=.08$), with less negative CNV amplitude for the control group compared to the emotional group after a win cue ($p<.01$). The initiative group present a more negative CNV amplitude after the win and loss than the neutral cues ($p<.02$).

b2- Feedback-locked ERP

The ANOVA performed on the P3a between actual win trials and neutral trials with positive feedback revealed a main effect of feedback ($F(1,65)=6.17$, $p<.02$; $\eta^2=.09$), with larger P3a after an actual win than a positive neutral feedback ($p<.02$); as well as a main effect of group ($F(2,65)=6.72$, $p<.002$; $\eta^2=.17$), with larger P3a for the initiative group than the emotional and control groups ($p<.002$ and $p<.04$ respectively). No effect of feedback x group interaction ($p>.51$) existed.

The ANOVA performed on the P3a between actual loss trials and neutral trials with negative feedback revealed a main effect of feedback ($F(1,64)=11.75$, $p<.001$; $\eta^2=.16$), with larger P3a after an actual win than a positive neutral feedback ($p<.001$), as well as a trend for a main effect of group ($F(2,64)=2.91$, $p<.06$; $\eta^2=.08$), with larger P3a for the initiative group than the control and emotional groups (both $p<.05$). No trial x group interaction ($p>.62$) existed.

The ANOVA performed on the LPP between actual win trials and the absence of win trials revealed there was no effect of trial ($p>.99$), group ($p>.59$), nor trial x group interaction ($p>.60$).

The ANOVA performed on the LPP amplitude between neutral trials with positive and negative feedback revealed there was no effect of trial ($p>.73$), group ($p>.26$), nor trial x group interaction ($p>.92$).

Annexe 6

Matériel supplémentaire de l’étude 3

Initiative apathy trait underlies individual differences in the ability to anticipate and expend cognitive effort in cost-benefit decision-making tasks

Supplementary data 1: Results of the ANCOVAs

3) IE task

c- Behavioral data

ANCOVA - Efficiency for easy trials in the IE task

	Sum of Squares	df	Mean Square	F	p	η^2
Group (control vs initiative)	2.61e-7	1	2.61e-7	0.474	0.495	0.009
DAS executive	2.22e-6	1	2.22e-6	4.034	0.071	0.078
BDI	4.77e-7	1	4.77e-7	0.866	0.357	0.017
Age	2.57e-6	1	2.57e-6	4.667	0.037	0.090
Residuals	2.31e-5	42	5.51e-7			

ANCOVA - Efficiency for difficult trials in the IE task

	Sum of Squares	df	Mean Square	F	p	η^2
Group	3.87e-8	1	3.87e-8	0.0938	0.761	0.002
DAS executive	2.26e-6	1	2.26e-6	5.4842	0.024	0.094
BDI	2.23e-7	1	2.23e-7	0.5415	0.466	0.009
Age	4.28e-6	1	4.28e-6	10.3727	0.002	0.177
Residuals	1.73e-5	42	4.13e-7			

d- Effort anticipation

ANCOVA – CNV after an easy cue in the IE task

	Sum of Squares	df	Mean Square	F	p	η^2
Group	18.02	1	18.02	0.637	0.429	0.015
DAS executive	6.16	1	6.16	0.218	0.643	0.005
BDI	2.86	1	2.86	0.101	0.752	0.002
Age	12.29	1	12.29	0.434	0.513	0.010
Residuals	1188.17	42	28.29			

ANCOVA - CNV after a difficult cue in the IE task

	Sum of Squares	df	Mean Square	F	p	η^2
Group	200.1	1	200.1	7.003	0.011	0.130
DAS executive	53.2	1	53.2	1.861	0.180	0.034
BDI	68.6	1	68.6	2.400	0.129	0.044
Age	21.5	1	21.5	0.751	0.391	0.014
Residuals	1200.3	42	28.6			

e- Effort expenditure

ANCOVA – mPFC theta power for easy trials in the IE task

	Sum of Squares	df	Mean Square	F	p	η^2
Group	0.27325	1	0.27325	4.69390	0.036	0.100
DAS executive	0.00702	1	0.00702	0.12062	0.730	0.003
BDI	2.62e-4	1	2.62e-4	0.00450	0.947	0.000
Age	0.00129	1	0.00129	0.02209	0.883	0.000
Residuals	2.44499	42	0.05821			

ANCOVA – mPFC theta power for difficult trials in the IE task

	Sum of Squares	df	Mean Square	F	p	η^2
Group	0.05677	1	0.05677	0.936	0.339	0.021
DAS executive	0.04032	1	0.04032	0.665	0.419	0.015
BDI	0.05917	1	0.05917	0.976	0.329	0.022
Age	0.00727	1	0.00727	0.120	0.731	0.003
Residuals	2.54680	42	0.06064			

4) EDM task

d- Behavioral data

ANCOVA – Efficiency for difficult choices in the EDM task

	Sum of Squares	df	Mean Square	F	p	η^2
Group	5.51e-6	1	5.51e-6	5.505	0.024	0.113
DAS executive	3.17e-7	1	3.17e-7	0.317	0.577	0.006
BDII	1.86e-6	1	1.86e-6	1.854	0.181	0.038
Age	3.19e-6	1	3.19e-6	3.191	0.082	0.065
Residuals	3.80e-5	38	1.00e-6			

e- Effort expenditure

ANCOVA – mPFC theta for easy low reward choices in the EDM task

	Sum of Squares	df	Mean Square	F	p	η^2
Group	7.14e-4	1	7.14e-4	0.01993	0.889	0.001
DAS executive	1.21e-4	1	1.21e-4	0.00337	0.954	0.000
BDI	0.01884	1	0.01884	0.52569	0.473	0.014
Age	0.00129	1	0.00129	0.03590	0.851	0.001
Residuals	1.29043	36	0.03585			

ANCOVA - mPFC theta for easy high reward choices in the EDM task

	Sum of Squares	df	Mean Square	F	p	η^2
Group	0.00492	1	0.00492	0.1723	0.681	0.004
DAS executive	4.32e-4	1	4.32e-4	0.0151	0.903	0.000
BDI	0.06231	1	0.06231	2.1807	0.148	0.054
Age	0.06307	1	0.06307	2.2073	0.146	0.054
Residuals	1.02862	36	0.02857			

ANCOVA - mPFC theta for difficult low reward choices in the EDM task

	Sum of Squares	df	Mean Square	F	p	η^2
Group	0.00271	1	0.00271	0.0603	0.807	0.002
DAS executive	0.01325	1	0.01325	0.2946	0.591	0.008
BDI	0.00886	1	0.00886	0.1969	0.660	0.005
Age	0.03988	1	0.03988	0.8865	0.353	0.024
Residuals	1.61952	36	0.04499			

ANCOVA - mPFC theta for difficult high reward choices in the EDM task

	Sum of Squares	df	Mean Square	F	p	η^2
Group	0.0949	1	0.0949	3.1372	0.045	0.081
DAS executive	6.79e-4	1	6.79e-4	0.0224	0.882	0.001
BDI	0.03637	1	0.03637	1.1582	0.289	0.029
Age	0.0726	1	0.0726	2.4007	0.130	0.055
Residuals	1.0892	36	0.0303			

Giulia LAFOND-BRINA

Une conception multidimensionnelle de l'apathie permet-elle de mieux en comprendre les mécanismes ?

Approche cognitive et électrophysiologique

Résumé

L'objectif de ce travail était de progresser dans la compréhension des mécanismes de l'apathie. A cette fin, nous nous sommes appuyés sur une conception multidimensionnelle distinguant trois formes - émotionnelle, exécutive, d'initiation – sous-tendues par le dysfonctionnement de réseaux cérébraux distincts. Deux approches complémentaires ont été utilisées : phénotypique et transnosographique.

Nos résultats révèlent des déficits motivationnels au niveau du *liking* chez les sujets sains en cas d'apathie émotionnelle. Chez les patients schizophrènes ou dépressifs, c'est le *wanting* qui semble davantage affecté. L'apathie exécutive est associée, pour l'ensemble des sujets, à des troubles du contrôle cognitif proactif alors que l'apathie d'initiation est associée à des prises de décision coût-bénéfice aberrantes.

En identifiant des mécanismes spécifiques à chaque forme et en suggérant l'existence de formes distinctes potentiellement plus sévères dans la schizophrénie et la dépression, nos résultats plaident pour une meilleure prise en compte du profil apathique de chaque individu lors de l'élaboration de son protocole de soins.

Mots clefs : apathie, phénotype, dépression, schizophrénie, EEG, méta-analyse ALE, motivation, contrôle cognitif, prise de décision

Résumé en anglais

The purpose of this project was to improve our knowledge on the mechanisms of apathy. To this end, we relied on a multidimensional model, that distinguishes three forms – executive, emotional, initiative – underlying by the dysfunction of distinct brain networks. Two complementary approaches were used: phenotypic and transnosographic.

Our results reveal motivational deficits of the liking process in healthy subjects in the case of emotional apathy. In patients suffering from schizophrenia or depression, it is the wanting process that seems to be more affected. Executive apathy is associated, for all subjects, with disorders of proactive cognitive control, while initiation apathy is associated with aberrant cost-benefit decision-making.

By identifying mechanisms that are specific to each form and by suggesting the existence of potentially more severe forms that are distinct between schizophrenia and depression, our results plead for a better consideration of the apathetic profile of each individual when elaborating his treatment protocol.

Keywords : apathy, phenotype, depression, schizophrenia, EEG, ALE meta-analysis, motivation, cognitive control, decision-making