Université de Montréal

Rôle des symptômes neuropsychiatriques dans le déclin cognitif dû à la maladie d'Alzheimer

Associations structurelles cérébrales et neuropsychologiques

Par

Lucas Ronat

Faculté de Médecine

Thèse présentée en vue de l'obtention du grade de *Philosophiae Doctor*

Sciences Biomédicales, option Sciences du Vieillissement

Mai 2023

Université de Montréal

Unité académique : Faculté de Médecine

Cette thèse intitulée

Rôle des symptômes neuropsychiatriques dans le déclin cognitif dû à la maladie d'Alzheimer

Associations structurelles cérébrales et neuropsychologiques

Présentée par

Lucas Ronat

A été évaluée par un jury composé des personnes suivantes

Louis Bherer
Président-rapporteur

Alexandru Hanganu
Directeur de recherche

Sven Joubert
Membre du jury

Jean-François Gagnon
Examinateur externe pour une thèse

Résumé

Les symptômes neuropsychiatriques (SNP), des perturbations comportementales et psychologiques, surviennent fréquemment dans la démence de la maladie d'Alzheimer. En plus d'être un facteur de risque d'institutionnalisation précoce et de constituer une charge pour les aidants, ils peuvent aussi être associés à un déclin cognitif accéléré ou à des troubles cognitifs plus importants lorsqu'ils surviennent dans les stades pré-démentiels des maladies (avant ou pendant le trouble cognitif léger). Considérant la diversité des résultats d'études antérieures, la relation entre ces SNP, le déclin cognitif et la survenue/évolution des maladies neurodégénératives est encore pleine de mystères. En effet, il a pu être mis en évidence que la dépression, l'apathie, ou encore l'anxiété étaient des facteurs de risques de conversion en maladie d'Alzheimer, ou de déclin cognitif accéléré chez des individus ayant un trouble cognitif léger ou une cognition normale. Ils ont aussi pu être associés à des changements des structures ou du métabolisme cérébraux, limbiques et associatifs. Cependant, le rôle et la position exacte des SNP dans le décours temporel des maladies restent incertains : conséquences de la neurodégénérescence ? Conséquence psychologique de la survenue de troubles cognitifs ? Cause de troubles cognitifs par réorientation des ressources exécutives et comportementales ? Stade prodromal des maladies ? Conséquence d'une structure de personnalité antérieure ?

Ce travail propose d'aborder différentes problématiques de recherches liées aux SNP, notamment leurs associations cognitives en fonction de facteurs démographiques, psychologiques ou psychiatriques dans différents stades de déclins cognitifs ; leurs associations neurostructurelles ou métaboliques cérébrales, en devis transversal, rétrospectif ou longitudinal. L'objectif étant de conforter certaines données de la littérature sur l'impact des SNP sur les performances cognitives et leur évolution dans le vieillissement normal et pathologique, et comprendre l'apport de certaines analyses prédictives et de facteurs de risques afin d'en dégager des pistes d'applications cliniques dans une visée d'anticipation du déclin cognitif.

Pour cela, différentes bases de données sont traitées afin d'extraire différents types de variables d'intérêt (démographiques, neuropsychiatriques, neuropsychologiques, neuroimagerie, statuts

génétiques et diagnostiques, facteurs psychologiques…). Au total, c'est près de 5000 participants qui ont été extraits et analysés au travers des différentes bases de données.

Les principaux résultats ont permis de montrer : 1) des associations SNP/performances cognitives différentes entre les femmes et les hommes ; 2) des relations neurostructurelles différentes entre les SNP et les différents stades de déclin cognitif de la maladie d'Alzheimer ; 3) le rôle prédictif des SNP dans la conversion du trouble cognitif léger en maladie d'Alzheimer expliqué par l'altération des habiletés fonctionnelles des individus ; 4) des implications de traits de personnalité dans le déclin cognitif et cérébral chez des individus développant ou non démence de type Alzheimer.

Ces données consolident les résultats de la littérature et soutiennent l'utilité de certains modèles statistiques et de prédictions dans l'établissement des facteurs de risques de déclin et l'estimation de l'importance du déclin basé sur ces facteurs, à la fois chez des individus cognitivement sains, et des individus à risque de développer une démence.

Mots-clés : symptômes neuropsychiatriques, IRM, maladie d'Alzheimer, démence, trouble cognitif léger, déclin cognitif, modèles de prédiction.

Abstract

Neuropsychiatric symptoms (NPS), behavioral and psychological disturbances, occur frequently in Alzheimer's dementia. In addition to being a risk factor for early institutionalization and a burden to caregivers, they may also be associated with accelerated cognitive decline or greater cognitive impairment when they occur in the pre-dementia stages of the diseases (before or during mild cognitive impairment). Considering the diversity of results of previous studies, the relationship between these NPS, cognitive decline and the occurrence/evolution of neurodegenerative diseases is still full of mysteries. Indeed, it has been shown that depression, apathy, or anxiety were risk factors for conversion to Alzheimer's disease, or for accelerated cognitive decline in individuals with mild cognitive impairment or normal cognition. They could also be associated with changes in brain, limbic and associative structures or metabolism. However, the exact role and position of NPS in the temporal course of diseases remains uncertain: consequences of neurodegeneration? Psychological consequence of the onset of cognitive disorders? Cause of cognitive disorders by redirection of executive and behavioral resources? Prodromal stage of diseases ? Consequence of a previous personality structure?

This work proposes to address different research issues related to NPS, in particular their cognitive associations according to demographic, psychological or psychiatric factors in different stages of cognitive decline; their neurostructural or cerebral metabolic associations, in cross-sectional, retrospective or longitudinal specifications. The objective is to confirm certain data in the literature on the impact of NPS on cognitive performance and its evolution in normal and pathological aging, and to understand the contribution of certain predictive analyses and risk factors in order to identify avenues of clinical application with a view to anticipating cognitive decline.

For this purpose, different databases are processed in order to extract different types of variables of interest (demographic, neuropsychiatric, neuropsychological, neuroimaging, genetic and diagnostic status, psychological factors...). In total, nearly 5000 participants were extracted and analyzed through the different databases.

The main results showed: 1) different NPS/cognitive performance associations between women and men; 2) different neurostructural relationships between NPS and different stages of cognitive decline in Alzheimer's disease; 3) the predictive role of NPS in the conversion of mild cognitive impairment to Alzheimer's disease explained by the alteration of individuals' functional abilities; 4) implications of personality traits in cognitive and brain decline in individuals developing or not dementia of the Alzheimer’s type.

These data consolidate the findings of the literature and support the utility of certain statistical and predictive models in establishing risk factors for decline and estimating the magnitude of decline based on these factors, both in cognitively healthy individuals, and individuals at risk of developing dementia.

Keywords : neuropsychiatric symptoms, MRI, Alzheimer's disease, dementia, mild cognitive impairment, cognitive decline, prediction models.

Table des matières

Liste des tableaux

Liste des figures

Liste des sigles et abréviations

MA : Maladie d'Alzheimer

IRM : Imagerie par résonance magnétique

TEP : Tomographie par émission de positons

TCL : Trouble cognitif léger

SNP : Symptômes neuropsychiatrique

NPI : Inventaire Neuropsychiatrique

TCI : Inventaire de Tempérament et de Caractère

APOE-ε4 : Allèle ε4 de l'Apolipoprotéine E

Remerciements

Lundi matin, 7h30, le réveil sonne et ma seule envie est de dormir une heure de plus, peut-être même deux… ça sent le Level 100 de procrastination aujourd'hui ! Après un gros café (crème + sucre, il ne faut pas déconner non plus), 2 entretiens associatifs et une attente interminable du bus, me voilà au labo à presque 10h. Maintenant au boulot ! Ma motivation ? Oubliée à l'appart'... Ou dans mon lit. Bon, quitte à ne pas être productif, autant faire autre chose : rédiger mes remerciements par exemple !

Des semaines, des mois que j'y songe mais pas moyen de s'y coller ! Pourtant j'imaginais ça fun de faire des remerciements. Puis finalement j'ai plein de doute qui me gonflent : qui ? Pourquoi ? Sans oublier la trouille d'oublier des gens importants ! Je me dis qu'en ne remerciant personne, au moins personne ne sait s'il a été oublié ! D'un autre côté ça fait tellement plaisir d'être remercié et de remercier, de savoir qu'on a contribué de près ou de loin au travail d'un proche, à son bien-être, ou autre, n'importe quoi. Et réciproquement cela fait tout autant plaisir de réaliser tout l'entourage qui nous accompagne tous les jours sans s'en rendre compte. Donc par avance : famille, ami(e)s (non je n'écris pas en écriture inclusive…), connaissances, collègues clinicien(ne)s, professeur(e)s et superviseur(e)s actuel(le)s ou ancien(ne)s, désolé si je vous ai oublié(e)s en ces temps de surcharge cognitive (en vrai ça va, mais je me cherche des excuses).

De manière générale, je suis reconnaissant d'avoir pu réaliser un doctorat sans difficultés majeures, sans proximité avec le burn-out ou tout autre risque de troubles mentaux, sans décrochage ni découragement et désespoir significatifs. Pourtant, ce n'était pas gagné ! Trois années de candidatures successives, des refus qui pleuvent, jusqu'à une admission et un départ dans des conditions non-optimales… Un départ qui par ailleurs fut le premier hors de l'Europe ! Premier vol en avion, première vie dans un pays étranger, des complications à l'arrivée : problèmes relationnels avec les colocataires locaux ainsi qu'avec la propriété… Bienvenue ! Et alors que ces éléments n'étaient pas en route pour se résoudre, une pandémie nous tombe sur le râble… Bref j'en ai terminé avec les éléments négatifs non dus au doctorat en tant que tels.

Reprenons dans l'ordre voulez-vous, et les bavards du fond essayez de suivre un peu !

Mes premiers remerciements iront à Alexandru, mon superviseur, pour m'avoir donné ma chance, et pour avoir été d'une si grande bienveillance pendant ces 5 années (4 années de doctorat + l'année qui a précédé le doctorat, incluant notre rencontre), et ce malgré mes piètres compétences de programmation qu'il a vite pu constater lors de nos premiers échanges ! Il n'est pas toujours aisé d'être dans une relation optimale de travail, et encore moins de se dire avec confiance que l'on se sent apte à travailler avec un directeur pendant 4-5 ans à partir de quelques entrevues en ligne, et d'autant moins lorsque l'on sait, par expériences et retours d'expériences universitaires, à quel point les relations étudiants/directions peuvent devenir conflictuelles ou sources de tensions. Par chance, j'ai passé 4 superbes années de doctorats, avec des hauts des bas comme tout un chacun, où j'ai fait bien plus que jamais je ne l'aurai cru possible lors d'un programme comme celui-ci. Par son ouverture d'esprit et à la discussion, je me suis toujours senti libre d'exprimer mes désaccords et mes points de vue, entreprendre des initiatives etc. Bref, je n'aurai pas pu espérer meilleure expérience grâce à lui, à la fois sur le plan humain et sur le plan de la recherche.

Dans cette même lignée, je souhaiterai remercier du fond du cœur une très chère amie et future collègue psychologue, Mme Sarah Kraimeche, pour avoir été tant présente lors de ma venue au Québec. Nous étions alors les seuls membres "permanents" du laboratoire en dehors d'Alexandru et avons évolué ensemble dans ce jeune milieu de recherche ainsi qu'au travers de cours communs. Malgré l'éloignement généré d'abord par la pandémie puis par nos obligations distinctes issues de nos programmes universitaires respectifs, je conserverai toujours pour toi une profonde reconnaissance pour ton accueil, ton aide, ton soutien, tes encouragements, ta réassurance, ou tout simplement ta présence. Je te souhaite le meilleur et espère avoir la chance de te recroiser.

En parlant de ma première année quelque peu délicate, j'en profite pour remercier les personnes qui ont contribué à mon intégration et qui font aujourd'hui les premières amitiés que j'ai construites au Québec, Pauline Chambon (ma première colocataire, étudiante en muséologie à l'Université du Québec à Montréal), Lidia Zanetti Domingues (post-doctorante en histoire à ce moment-là et actuellement Professeure assistante à l'Université d'Amsterdam), Huong Pham (étudiante internationale venant du Vietnam), Karine Jauvin (Doctorante en psychologie et

partenaire de travail en cours de psychopharmacologie clinique), Emilie Espagne (Étudiante en Sciences Biomédicales à ce moment-là).

C'est à partir des premières accalmies postpandémie que le laboratoire a connu ses premières évolutions via l'accueil de stagiaires et auxiliaires de recherches, et c'est là que je souhaite transmettre mes remerciements à ces personnes impliquées qui ont contribué à la vie des locaux ainsi qu'à l'avancée des travaux de recherches, dont une partie des miens entre autres. Mais ce que j'en retiendrai le plus, ce sont nos échanges, car notre présence est avant tout sociale, et notre communication fait pratiquement tout l'intérêt que je porte à la recherche : parler avec des personnes pour en tirer quelque chose, pour moi, pour les autres, les deux… Donc un grand merci à Lyna, Adriana, Elisabeth, Loreena, Amina, Christéva, Nour… Qui avez traversé notre laboratoire à un moment donné, que ce soit pour du recrutement, des analyses, de la rédaction d'articles, de l'élaboration de projets, ou autres… J'en retiendrai pour l'essentiel nos échanges, de la private joke au débat animé, et les sécrétions dopaminergiques que cela a pu susciter durant ces mois/ces années.

Pour être certains de ne pas les oublier, je tiens aussi à remercier certain(e)s de mes anciens professeur(e)s qui ont grandement contribué à mon envie de m'orienter en neuropsychologie, intégrer un doctorat et devenir plus tard professeurs des universités (oui bon ce n'est pas pour demain mais on y travaille !), à commencer par Fabrice Robichon, Professeur de Neuropsychologie à l'Université de Bourgogne et neuropsychologue, pour m'avoir donné goût à la neuropsychologie et sa pratique clinique (les meilleurs cours de neuropsycho que j'ai eu !!!) mais aussi pour son humanité et ses connaissances à n'en plus finir, à Renaud Brochard, Professeur (récemment !) de Psychologie cognitive à l'Université de Bourgogne, pour ses cours de grande qualité certes mais surtout pour les premières opportunités de recherche que j'ai pu avoir avec lui, sans compter les nombreux échanges complices que l'on a pu avoir depuis, ainsi qu'à Ingrid Banovic, Professeure de Psychologie Clinique et Psychopathologie à l'Université de Rouen (anciennement à l'Université de Bourgogne), seule professeure capable de faire aussi peur tout en étant aussi captivante dans le même cours… En amphithéâtre comme en travaux dirigés, elle est une des rares professeures que j'aurai aimé avoir H24 juste pour parler psychopatho ! A

elle, merci aussi pour son soutien et son accompagnement lorsque j'ai quitté l'Université de Bourgogne, à destination de l'Université de Lille.

(Déjà 3 pages et il ne me reste pas loin de 300 personnes à remercier… Allez, on s'accroche et en avant Guingamp !)

Si la contribution des personnes rencontrées lors du doctorat est évidente, il ne faut pas oublier autre chose de plus subtile, à la participation bien plus importante encore, à savoir ma famille. Même si son rôle dans mon travail est très indirect, voire implicite, elle est en première ligne pour avoir orienté mes motivations, et plus encore ma personnalité. Pour le cadre sécure de développement et d'éducation qu'elle m'a procuré, j'ai pu appréhender l'école et les relations sociales en général en toute confiance (même carrément sans crainte si j'en remémore mon premier jour d'école où il semble que j'ai lâché la main de ma mère pour m'installer et dessiner, comme si j'en avais perdu ma permanence de l'objet). Entre scolarité aisée, adolescence merveilleuse sans guère de soucis et une entrée dans la vie adulte toute en douceur, je n'aurai pu espérer mieux dans ce monde pourtant plein de défauts grâce à mes parents en premier lieux, mais aussi grâce à mes frères, mes grands-parents, parrain, marraine, oncles et tantes, et cousinage. Tout cela paraît bien éloigné du propos de ce document, mais c'est par leur biais en partie que se construit la personnalité, l'intellect, la qualité des relations sociales futures… Donc de près ou de loin, je dois à toutes et tous ce que je suis, au moins un peu, et les remercie pour tout ce qu'ils ont pu m'apporter.

Je ne sais pas si ça vient de moi ou pas, mais j'ai complètement l'impression de raconter ma vie là-dedans… En même temps pour comprendre le contexte des remerciements il faut bien au moins un peu ! Bon, reprenons…

En parlant de raconter ma vie, il y a de nombreuses personnes que je ne peux passer sous silence pour leur importance dans ma vie avant le début de mon aventure doctorale, qui ont, en plus d'être des ami(e)s cher(e)s, aussi contribué au développement de mon esprit critique, qu'il soit scientifique, social, politique… A commencer par mes anciens camarades (et le terme est particulièrement bien choisi croyez-moi !) et colocataires de Marseille, Cassandre Vielle et Julien Poitreau, pour ces presque deux années passées avec eux (je cumule les temps partagés en cours,

hors cours, en colocation etc…), ces échanges scientifiques, politiques et sociologiques riches ! Et particulièrement à Cassandre pour m'avoir aidé à consolider et développer certaines convictions politiques que tu connais très bien ! Merci pour ces soirées, ces sorties, ces rires et les nombreux moments de gastronomie ! (Et non les dimanches végan ça ne compte PAS !).

Tant d'autres personnes ont contribué et contribuent encore à faire de ma vie ce qu'elle est et sans qui elle ne saurait être aussi bonne, des personnes rencontrées à l'université, par réseautage, ou par le biais d'associations, d'événements d'intégration étudiante… Leurs présences n'ont rendu que plus facile la réalisation du doctorat : toujours disponibles et à l'écoute en cas de besoin, je sais que malgré la distance il me sera toujours possible de les joindre, et que nos retrouvailles resteront riches d'émotions et de souvenirs. Merci à ces personnes à ces personnes d'apporter autant de coloration émotionnelle aux souvenirs et aux instants présents : Alexandre D'Amico, Clara De La Cruz, Jérémy Decroix, Jessica Rouco, Isolde English, Julie Ferreira, Thibault Chiron, Colline Grégoire (C'est là que je commence à avoir une grosse trouille d'oublier des gens…).

Un des derniers remerciements, et pas des moindres, va à la plus importante rencontre de mon doctorat. Celle qui a amené aux plus grands changements, à la plus importante étape de vie à ce jour : la rencontre avec celle qui partage ma vie actuellement et avec qui j'ai eu la chance d'emménager récemment ! Celle qui me soutien et qui m'estime plus que je n'ai jamais pu l'être avec moi-même (il y a très certainement de l'idéalisation là-dedans mais laissons de côté les biais cognitifs pour l'instant), que j'ai vu évoluer au cours de sa dernière année et demie de baccalauréat de psychologie : Emanuelle Paquin, ma brillante et déterminée amoureuse (tant dans ses projets que dans notre relation attention !). Merci infiniment à toi pour tous les compliments et éloges exagérés et idéalisés que tu peux me faire, pour ton soutien, ton attachement et ton dévouement sincère dans notre relation.

Pour terminer, je souhaite remercier les personnes qui ont participé à ma formation doctorale par le biais de séjours de recherche à l'étranger, ces personnes qui m'ont aidé à élaborer des projets de recherche, qui m'ont accueilli au sein de leur équipe de laboratoire pendant quelques mois, qui ont fait preuve de pédagogie, d'écoute et de patience : Christine Bastin, Chercheuse au

Centre de Recherche du Cyclotron à l'Université de Liège, et Sara Pudas, Chercheuse au département de biologie médicale intégrative de l'Université de Umeå.

Introduction générale

Les symptômes neuropsychiatriques - apparition et problématique globale

1906, un article paraît dans une revue neurologique allemande. Le Dr. Alois Alzheimer y décrit le cas d'une patiente de 51 ans présentant depuis 5 ans une détérioration cognitive progressive, des symptômes psychotiques de type hallucinations et délires, ainsi qu'une atteinte sévère du fonctionnement social. Une nouvelle entité clinico-pathologique est alors identifiée et dénommée comme la maladie d'Alzheimer[1]. Si la caractérisation de la maladie s'est essentiellement focalisée sur les troubles cognitifs, notons que ce cas princeps présentait aussi des symptômes neuropsychiatriques (SNP) et un fonctionnement social altéré.

Cependant, c'est surtout à partir des années 1990 que les SNP sont décrits et étudiés dans les maladies neurodégénératives. Il s'agit de symptômes non cognitifs tels que l'apathie, la dépression ou la psychose. Originellement décrits dans la démence, ils ont fait l'objet de création de matériel d'évaluation clinique ayant une bonne validité et fidélité, comme le Neuropsychiatric Inventory (NPI)[2]. Ce type de matériel a permis de comprendre certains corrélats de neuroimagerie, neuropathologiques, neurochimiques, neurogénétiques et neurocognitifs des SNP.

Alors qu'ils sont nécessaires aux diagnostics de démence frontotemporale et de démence à corps de Lewy, ils ne le sont pas pour la maladie d'Alzheimer et la maladie de Parkinson, malgré leurs prévalences élevées.

Au contraire des troubles psychiatriques idiopathiques, les SNP sont souvent multiples et simultanés dans les démences, et participent à la détresse psychologique des personnes qui les manifestent ainsi qu'à la charge des aidants (naturels ou non). Ils augmentent les nécessités de soins médicaux, et par conséquent les coûts, ainsi que les risques d'institutionnalisation précoce. En plus de cela, ils ont très tôt été identifiés comme marqueurs de démence : ils y sont associés[3] et en augmentent aussi l'incidence chez les personnes ne présentant pas de démence[4]. Au début

des années 2000 était déjà évoquée l'idée que les SNP pourraient donc être prodromaux à la démence[5].

Assal et Cummings (2002) mentionnent même que ces symptômes pourraient être similaires entre la démence et le stade pré-démentiel de trouble cognitif léger (TCL). C'est en effet ce qu'ont pu démontrer les travaux de Hwang et al. (2004) et Geda et al. (2008)[6,7]. Par ailleurs, Geda et al. rapportaient aussi que 25% des participants cognitivement sains présentaient des SNP non psychotiques dont notamment de la dépression, des comportements nocturnes, des changements de l'appétit, de l'irritabilité et de l'anxiété. D'autres travaux ont aussi mis en évidence ces symptômes dans cette population[8–11].

Certains de ces travaux ont même démontré les implications de ces SNP dans les performances cognitives, en devis transversaux et longitudinaux, suggérant que dans la maladie d'Alzheimer, en stades pré-démentiels ou pré-cliniques, ils seraient associés à des performances cognitives plus faibles ou un déclin cognitif accéléré[8,9,12].

La maladie d'Alzheimer

Comme souvent dans les manuscrits, qu'il s'agisse d'études ou de travaux universitaires, il y a une petite partie d'épidémiologie sur la ou les maladies abordées… Afin de ne pas déroger à cette règle, nous n'y couperons pas. Donc : l'état clinique de démence se caractérise par une détérioration progressive des fonctions cognitives, comportementales et du fonctionnement des activités de vie quotidienne. Pour ces raisons, cet état représente une charge notable pour les individus, les proches, les soignants et la société. Elle concerne plus de 24 millions de personnes à travers le monde en 2005[13], et pourrait quadrupler d'ici 2050. La cause principale en est la maladie d'Alzheimer et concerne 70% des cas de démence.

Les marqueurs pathologiques centraux de la MA sont les dépôts extracellulaires de peptide β-amyloïde (βA), les agrégats neurofibrillaires dus à l'altération et l'hyperphosphorylation de la protéine tau. D'autres changements comme des pertes neuronales, synaptiques, des modifications de l'activité microgliale ont pu être observées[14].

Critères et biomarqueurs

Depuis les critères diagnostiques de McKhann et al. (1984), le diagnostic de la MA se base sur la présence ou non de patterns cliniques et neuropathologiques permettant de distinguer les diagnostics de MA possible, probable et certaine[15].

Actuellement, le champ des diagnostics s'est élargi et comprend maintenant les diagnostics de MA, de MA pré-clinique, de TCL dû à la MA et de démence due à la MA.

La MA préclinique[16]

Contrairement aux critères de 1984, la MA pré-clinique ne peut se baser sur la symptomatologie et se focalise donc sur l'analyse des biomarqueurs. Les auteurs distinguent 3 stades de catégories précliniques : le stade 1 se caractérise par une amyloïdose cérébrale asymptomatique observée à un examen du liquide céphalo-rachidien ou de Tomographie par Émission de Positons au PiB (rétention élevée du traceur de l'amyloïde au TEP, ou faible taux de βA_{1-42} dans le LCR), sans marqueurs de lésions neuronales (observable aux examens de la protéine tau [taux élevés de tau/p-tau dans le LCR], du métabolisme cérébral du glucose via la TEP au Fluorodésoxyglucose [hypométabolisme des régions hippocampiques, temporales médianes ou associatives corticales], ou à l'IRM structurelle [amincissement cortical ou atrophie hippocampique]), ni preuve de changement cognitif ; le stade 2 se caractérise par une amyloïdose asymptomatique et le début d'une neurodégénérescence (marqueur tau, TEP-FDG, IRM structurelle) sans preuve de changement cognitif ; le stade 3 se caractérise par les marqueurs du stade 2 avec un déclin cognitif/comportemental subtil (preuve d'un changement subtile de la cognition par rapport au niveau de base, performances faibles aux tests cognitifs les plus difficiles, sans remplir les critères du TCL).

Le TCL dû à la MA[17]

Concernant les diagnostics de déclin cognitif dans la MA, dont le TCL, il est nécessaire de confirmer chez un individu des critères à la fois cliniques et cognitifs. Tout d'abord le déclin doit être subjectif et sujet à inquiétude de la part de la personne, d'un de ses proches ou d'un clinicien,

témoignant un changement perçu de la cognition par rapport à un état antérieur. Ensuite, ce déclin subjectif doit être confirmé objectivement par des évaluations neuropsychologiques. Les déficiences peuvent concerner un ou plusieurs domaines cognitifs dont la mémoire. Enfin, le diagnostic de TCL repose aussi sur la préservation de l'autonomie de la personne dans les activités de vie quotidienne et donc l'exclusion de diagnostic de démence.

Dans un second temps, le diagnostic repose sur l'examen de l'étiologie en lien avec une MA (et ses processus physiopathologiques). Pour cela les causes de déclin cognitif vasculaires, traumatiques et médicales autres sont éliminées, des preuves de déclin longitudinal de la cognition sont à fournir si possible ainsi que, le cas échéant, des preuves d'antécédents génétiques de MA.

Aussi, comme dans la MA pré-clinique, le diagnostic peut-être soutenu par la présence de biomarqueurs : dépôts βA (taux βA_{42} dans le LCR ou imagerie TEP amyloïde), atteintes neuronales (taux tau/p-tau dans le LCR, imagerie TEP-FDG, volumétrie des régions hippocampiques/temporales médianes, volumétrie cérébrales globale, imagerie de perfusion ou autres), ou encore des changements biochimiques associés comme des marqueurs inflammatoires, du stress oxydatif ou d'autres marqueurs de dommages synaptiques ou de neurodégénérescence.

La démence due à la MA[18]

Similairement au TCL, le diagnostic de démence de la MA repose sur le repérage des signes cliniques et cognitif de la démence, puis dans un second temps sur l'examen des biomarqueurs de la MA. Contrairement au TCL, le diagnostic de démence comprend aussi des symptômes comportementaux/neuropsychiatriques qui, comme les symptômes cognitifs, interfèrent avec le fonctionnement dans les activités quotidiennes. Les symptômes représentent aussi un déclin par rapport au fonctionnement antérieur de la personne et ne s'expliquent pas par un trouble psychiatrique majeur ou un délirium. Comme le TCL, les troubles cognitifs sont diagnostiqués à l'aide de l'anamnèse de la personne (ou d'un proche) et d'une évaluation objective.

Les troubles doivent concerner au moins deux domaines parmi la mémoire, le raisonnement/jugement, les habiletés visuo-spatiales, le langage et les changements de personnalité/conduites. Concernant ces derniers, il peut s'agir de fluctuations (humeur, agitation, motivation) pouvant mener à de l'apathie, de l'isolement social ou une réduction de l'empathie. Certains comportements nouveaux peuvent aussi émerger comme des comportements obsessionnels-compulsifs ou des comportements socialement inacceptables.

Enfin, les auteurs distinguent, à la manière de la MA préclinique, différents seuils de probabilité avec la démence de la MA probable, caractérisée par un début insidieux des symptômes, des symptômes initiaux proéminents de type amnésique ou non amnésique (présentation langagière, visuo-spatiale ou dysexécutive). Ce diagnostic probable peut être soutenu par des évaluations cognitives successives objectivant le déclin, la présence d'une mutation génétique causant la MA, ou la présence de biomarqueurs soutenant les processus pathophysiologiques de la MA. La démence de la MA possible est plutôt caractérisée par un parcours atypique de la maladie comme un début soudain des troubles ou des preuves insuffisantes historiques ou objectives de la progression du déclin cognitif. Par ailleurs l'étiologie peut adopter une présentation mixte, avec une maladie cérébrovasculaire concomitante (accident vasculaire cérébral ou infarctus correspondant à l'apparition des troubles cognitifs), des caractéristiques de démence à corps de Lewy ou des éléments d'autres maladies neurologiques ou non-neurologiques.

SNP associés

S'ils ne sont pas caractéristiques des diagnostics de MA ou de TCL dû à la MA, les SNP ont pu y être associés (prévalences plus élevées) et étudiés en tant que précurseurs (augmentation du risque de déclin).

Basé sur l'évaluation du NPI, Zhao et al. (2016) ont établi une revue systématique de littérature ainsi qu'une méta-analyse afin d'estimer la prévalence des SNP chez les personnes présentant une maladie d'Alzheimer[19]. L'analyse de 48 études communiquant des données basées sur le NPI montrait que les symptômes les plus fréquents étaient l'apathie, la dépression, l'agitation/agressivité, l'anxiété, et les troubles du sommeil (respectivement 42% (95% CI 37–46%), 40% (95% CI 33–46%), 39% (95% CI 32–46%) and 39% (95% CI 30–47%)). Les auteurs

soulignent aussi que la prévalence des SNP était influencée par la durée de la maladie, l'âge, le niveau d'éducation, l'origine de la population et la sévérité des troubles cognitifs. En effet, il a été montré que la prévalence des SNP est plus élevée dans la MA que dans le TCL, et plus élevée dans le TCL que chez les personnes cognitivement saines[9]. Cependant, la prévalence des SNP dans le TCL reste parfois élevée : entre 35 et 85% des personnes présentant un TCL ont au moins un SNP selon l'état des lieux de la littérature de Martin et Velayudhan (2020)[20].

Agitation

Selon Assal et Cummings (1994), l'agitation est étroitement liée à l'agressivité et peut se manifester par une résistance aux activités de vie quotidienne, une violence verbale ou physique envers les proches ou les soignants.

Alors que l'agitation fait partie des SNP les plus fréquents dans la MA, elle est moins représentée dans le TCL, entre 11.3 et 38% selon les travaux (échantillon basé sur la population vs. basé sur la clinique)[20]. Malgré cela, elle a pu être associée à des troubles mnésiques et visuospatiaux plus importants chez ces personnes ainsi qu'un risque de déclin cognitif deux fois plus grand[21,22]. L'agitation peut aussi émerger avant le début d'un TCL[23].

Anxiété

L'anxiété peut se manifester de différentes manières, dans la MA ou non, et notamment par une apparence anxieuse/inquiète, un sentiment de peur, de tension interne, d'agitation motrice. Dépendamment des manifestations, l'anxiété peut être présente chez 37 à 71% des patients ayant une MA [19,24].

Tout comme l'agitation, elle est bien moins présente dans le TCL, entre 11.6 et 26.3% selon la revue de Martin et Velayudhan (2020)[20]. Lorsque présente dans le TCL, elle augmente le risque de conversion en MA ainsi que la vitesse de déclin[25]. En revanche, plusieurs interprétations peuvent être faites des relations entre l'anxiété et le TCL. Elle peut être associée à la sévérité des déficits cognitifs du TCL, à la conscience que les personnes ont de leurs difficultés, ou encore interférer avec les ressources cognitives et ainsi produire des symptômes cognitifs.

Apathie

Entre perte d'énergie, de motivation, d'émotions/sentiments, ou d'intérêts, l'apathie a été et reste parfois considéré comme le SNP le plus fréquent de la MA[19,26]. Dans le TCL, elle est présente dans 14.7 à 39.5% des situations selon les échantillons[20]. En plus d'être hautement présente, l'apathie est aussi un facteur de risque important de conversion en MA chez les individus ayant un TCL. En comparaison avec l'anxiété qui augmente le risque de MA par 2 fois, l'apathie l'augmente par 7 fois[25,27]. Elle a aussi été associée à des troubles exécutifs plus importants, notamment lors de prise de décision, et ces troubles limiteraient la possibilité pour les personnes d'employer des moyens compensatoires pour mieux retenir des informations et ainsi interfèreraient avec le fonctionnement de la mémoire[28].

Dépression

Parfois difficile à distinguer du trouble dépressif majeur, les SNP de dépression tels que la tristesse, une variation diurne de l'humeur, un sentiment de désespoir, des idées suicidaires, une perte d'intérêt, d'énergie, une insomnie, une perte de poids, un ralentissement psychomoteur ou des difficultés à se concentrer peuvent se retrouver dans la démence de la MA, sans remplir les critères de dépression majeure[29].

Très fréquent dans la MA, il s'agit du SNP le plus fréquent dans le TCL avec une prévalence pouvant aller de 20 à 83% des situations selon les échantillons[20]. En plus d'être très présent, c'est aussi le SNP le plus étudié dans le TCL : il a pu être associé à certaines perturbations cognitives (performances en fluence catégorielle et en mémoires logique et visuelle plus faibles) ainsi qu'à un risque de progression en démence de la MA doublé ; par ailleurs les patients présentant de la dépression développaient une démence plus tôt que ceux sans dépression[30]. Si la dépression a pu être associée à des troubles cognitifs plus importants dans le TCL ainsi qu'à des risques accrus de conversion en démence ou en MA, les données ne sont pas unanimes. Cela laisse en suspens la question de la dépression comme conséquence du processus neurodégénératif, comme conséquence de la survenue des troubles cognitifs ou comme cause des troubles cognitifs suggérant une allure de TCL dont les symptômes seraient réversibles après prise en charge de la dépression[20,31,32].

Perturbations du sommeil / comportements nocturnes

Ces comportements comprennent les difficultés à l'endormissement, les réveils matinaux précoces ou encore l'errance nocturne. Quoi que très fréquent dans la MA et le TCL dû à la MA (13.8 à 48% selon les échantillons), ils sont moins étudiés que d'autres SNP[20]. Pourtant ils semblent d'une importance non négligeable dans la survenue des troubles cognitifs et dans l'accélération du déclin. En effet, ces symptômes sont des facteurs de risques de démence (toutes causes) et de MA[33]. Par ailleurs, il a aussi pu être montré des associations négatives entre la somnolence diurne / perturbation du sommeil avec la vitesse de réactions, l'attention et la mémoire dans le TCL[34].

Irritabilité

Similairement aux troubles du sommeil, l'irritabilité est fréquente à la fois dans la MA et dans le TCL, à des prévalences presque égales (12.9 à 44.7% selon les échantillons). Elle a cependant moins été l'objet d'études que d'autres SNP comme la dépression ou l'apathie[20]. Elle a pu être associée avec un déclin cognitif accéléré dans le TCL[22], à une plus haute incidence de TCL chez les individus sans TCL[23], et présente un risque accru de conversion en TCL ou en démence chez les individus sains[35].

Implications dans le déclin cognitif

Plusieurs études ont en effet pu démontrer l'association entre les SNP et le déclin cognitif dans le cadre de la MA, même lorsqu'ils survenaient chez des individus cognitivement sains ou ayant un TCL, augmentant leur probabilité de développer une démence[8,12,36]. Leur utilisation a même été exploitée dans le cadre de modèles prédictifs de la démence de la MA, en association avec les données de neuroimagerie structurelle[37]. Les auteurs ont notamment comparé différents algorithmes d'apprentissage machine (Arbre de classification, forêt aléatoire, proches voisins, machine à vecteur de support) pour classer les individus sains et les individus avec troubles cognitifs : les facteurs issus du score total de l'échelle comportementale utilisée, le Mild Behavioral Inventory, et le volume hippocampique gauche étaient significativement impliqués dans la prédiction de la classification.

Associations avec les structures et le métabolisme cérébral

Étant donné leurs prévalences élevées dans les maladies neurodégénératives, les SNP ont fait l'objet de nombreuses études et revues de littératures permettant d'en comprendre les substrats cérébraux, à la fois structurels et métaboliques.

Récemment, un important travail de recension mettait d'ailleurs en évidence le décours temporel des SNP dans les différents stades de la maladie d'Alzheimer et leurs associations cérébrales structurelles/métaboliques[38]. Ces données montrent à la fois le recouvrement de certaines régions cérébrales impliquées dans différents symptômes ainsi que des régions distinctes entre ces symptômes. On voit déjà par ce travail de recension que de nombreux symptômes se manifestent dans les stades précliniques/TCL de la MA comme l'apathie, la dépression, l'anxiété, l'irritabilité, les perturbations du sommeil, l'agitation et les comportements moteurs aberrants. De manière intéressante, certains symptômes qui partagent des substrats structurels similaires ne se manifestent pas aux mêmes stades de la maladie. C'est le cas par exemple des perturbations du sommeil, de l'appétit, les comportements moteurs aberrants, l'euphorie ou la désinhibition. En bref, il semble que l'apathie soit préférentiellement associée avec une réduction de l'anisotropie fractionnelle, de la substance grise, du métabolisme glucidique, et une plus grande charge neurofibrillaire et dépôts amyloïde dans le cortex cingulaire antérieur[39–43]. D'autres régions ont pu y être associées comme le striatum, le thalamus, le cortex orbitofrontal, d'autres régions préfrontales, temporales (supérieure, moyenne, parahippocampe), ou de l'insula[40,41,44,45].

La dépression a été davantage associée à des atrophies frontales (dorsolatérale, médial, orbitofrontal, cingulaire antérieur) et temporales (moyen, inférieur, entorhinal, hippocampe, parahippocampe), ou encore de l'insula, et hypométabolismes frontaux[44,46–53].

L'état d'anxiété a en revanche été associé à une atrophie de l'amygdale, de l'insula, des putamen, du cingulaire postérieur et du parahippocampe, et semble prédire des diminutions volumiques entorhinales[44,54,55]. Des hypométabolismes ont aussi pu y être associés, notamment dans les régions entorhinales, hippocampiques antérieures, temporales supérieures et dans l'insula[56]. Les patients plus anxieux présentent aussi de plus importants dépôts amyloïdes dans le précuneus, le cingulaire postérieur, et les cortex frontaux, pariétaux, et cingulaire antérieur[57].

Comme mentionnés précédemment, les symptômes d'agitation, d'irritabilité, de comportements moteurs aberrants, d'euphorie et de désinhibition, parfois appelés comme syndrome d'hyperactivité[58], partagent des associations cérébrales comme le cingulaire antérieur, l'insula, les régions frontales, amygdaliennes ou hippocampiques[42,55,59–62]. On voit que ces régions concernent les réseaux fronto-limbiques, dont les altérations ont aussi été associées aux symptômes dépressifs.

Enfin, les perturbations du sommeil ont été démontrées comme bi-directionnelles avec la MA. En effet, il existe une interaction entre les agrégats amyloïde et les troubles du sommeil : ces perturbations augmentent la génération des agrégats et réduisent leur élimination par le cerveau, une fois l'accumulation amyloïde présente dans le cerveau, il y a une augmentation des perturbations du sommeil[63,64]. Ces effets sur les agrégats s'observent même chez des participants âgés sains : la réduction de la quantité de sommeil augmente les charges amyloïdes dans les régions hippocampiques et thalamiques[65]. De même, des agrégats de protéines tau peuvent s'observer dans les aires cérébrales impliquées dans la régulation du sommeil comme le tronc cérébral, le thalamus, l'hypothalamus, le mésencéphale et les régions antérieures basales[66].

Par ailleurs, il a été mis en évidence que la morphologie des structures cérébrales pouvaient être associée positivement à certains SNP comme la dépression, l'apathie et l'anxiété, chez les TCL mais pas chez les MA[67].

D'autres travaux ont mis en évidence des signatures cérébrales des agrégats tau en fonction de chaque SNP et montraient aussi des différences entre les différents stades de la MA[68]. Ces données seront davantage décrites dans l'annexe des travaux supplémentaires.

Autres implications majeures : qualité de vie et charge des aidants

Comme mentionné précédemment, les SNP sont des facteurs pouvant réduire la qualité de vie des personnes qui en souffrent, augmenter la charge des aidants et des proches, ou encore augmenter le risque d'institutionnalisation précoce[5,69,70]. La charge de l'aidant englobe la mesure subjective de la pression physique, psychologique, émotionnelle, sociale et économique de la prestation de soins[71]. La prestation de soins est associée à des taux accrus de dépression,

d'anxiété et d'utilisation de médicaments psychotropes, à une moins bonne santé auto-évaluée et à des taux plus élevés de maladies médicales et de mortalité pour les aidants eux-mêmes[72–75]. Les effets négatifs de la charge de l'aidant se répercutent également sur le patient (taux accrus d'institutionnalisation), pouvant entraîner de la dépression, une réduction de la qualité de vie et des soins[76–79]. Il semble par ailleurs que, dans la MA, les SNP soient le plus important prédicteur de la charge des aidants[80–82].

D'autres travaux décrivent que la détresse des proches-aidants a pu être corrélée aux SNP, de même que la charge ressentie peut être liée à différents scores comme celui de l'évaluation du Neuropsychiatric Inventory ou de la Cornell Scale for Depression in Dementia (Lima-Silva et al., 2015). La détresse moyenne était particulièrement élevée face à l'anxiété et à la dépression des patients (Score moyen de détresse entre 1 et 2 à l'échelle de détresse du NPI alors que pour les autres symptômes elle était inférieure à 1). Cela étant, les mauvaises relations entre les proches-aidants et les patients peuvent aussi être générateurs de SNP. C'est ce qu'ont pu montrer Isik et al. (2018) : selon les auteurs, les SNP tels que l'anxiété, l'agitation, la désinhibition, les comportements agressifs et les troubles du sommeil sont plus étroitement liés à la charge des aidants. Ces SNP sont aussi associés au déclin de l'état de santé général, de la qualité de vie et de l'isolement social des aidants. Inversement, la charge des aidants détériore aussi leur relation avec les patients ayant une MA[83]. Cette relation peut donc augmenter la fréquence et la gravité des SNP. Similairement, certains travaux montraient que la relation entre SNP et charge des aidants était médiée par les stratégies de coping des aidants, par le stress perçu des aidants et leurs symptômes dépressifs[84,85]. Un désengagement plus important ou un engagement plus faible étaient prédicteurs de SNP plus élevés chez les patients[84]. Sous une autre perspective, les aidants plus jeunes, ayant un niveau de scolarité plus faible, des symptômes dépressifs et une charge plus élevés, ou qui passaient plus d'heures par semaine à prodiguer des soins avaient tendance à signaler davantage de SNP chez les patients bénéficiaires[86].

D'autres facteurs étaient aussi prédictifs de la charge comme le fait d'être une femme, un conjoint, ou une personne âgée avec des mécanismes d'adaptation immatures, l'isolement social, des connaissances insuffisantes sur la démence, une mauvaise relation pré-morbide avec le patient et des niveaux élevés d'émotions négatives exprimées[83]. D'autres résultats montraient

que les délires, les hallucinations, l'agitation, l'anxiété, l'euphorie, la désinhibition, les comportements moteurs aberrants, les troubles du sommeil et les changements liés à l'appétit étaient les meilleurs prédicteurs de la charge des aidants[87]. De manière intéressante, les auteurs ne montraient pas de corrélation entre la charge et la cognition, le stade de la maladie ou d'autres SNP comme l'apathie et la dépression.

De manière intéressante, la présence de SNP augmente aussi la charge des aidants de patients présentant un TCL. Les aidants rapportent notamment une plus faible satisfaction de vie, moins de soutien social et un besoin accru de services de soutien[88].

En plus de l'impact et des défis qu'ils apportent aux patients et à leurs proches, les SNP sont aussi facteurs d'admission en maison de repos pour les patients, et représentent un coût sociétal important[89,90]. Ils ont aussi pu être associés par un risque de mortalité plus grand, notamment pour la dépression et l'apathie, des pertes de poids, une réduction des qualités de soins et des possibilités de réhabilitations[43,90,91]. Plus particulièrement, l'apathie peut interférer avec la capacité pour les patients à s'engager et s'investir dans les traitements et les soins visant à améliorer les autres symptômes, qu'ils soient cognitifs, moteurs ou comportementaux[90].

Objectifs généraux

Considérant les occurrences importantes des SNP dans les différents stades de la MA, ainsi que leurs associations cognitives et cérébrales, en devis transversaux ou longitudinaux, ce travail vise à étudier ces associations à partir de différentes bases de données. Les résultats permettront de comprendre davantage les paramètres neuropsychiatriques et associés qui expliquent en partie les performances cognitives des individus au cours du vieillissement normal et pathologiques à un instant T (chapitre 1), les caractéristiques cérébrales d'un grand nombre de SNP (chapitre 2), la conversion ultérieure en un stade clinique plus sévère (chapitre 3), les relations entre le trouble dépressif majeur avec les SNP et les performances cognitives dans différents stades de déclin cognitif (chapitre 4), et l'implication de la personnalité dans l'émergence de SNP ainsi que dans le déclin cognitif chez les personnes développant ou non une démence au cours d'un suivi longitudinal (chapitre 5). Un travail supplémentaire sur la prédiction du TCL et de sa conversion

en MA basé sur l'association entre des mesures de dépression et de métabolisme cérébral du glucose, et sur la prédiction du déclin cognitif accéléré chez des individus âgés sains basés sur des mesures de dépression, d'anxiété et de taux protéiques amyloïde et tau cérébraux sera aussi décrit à la fin du manuscrit (Annexes - Travaux supplémentaires).

Ces données complètent celles existantes dans la littérature afin de contribuer à l'identification des personnes à risque de développer des troubles cognitifs ainsi qu'un déclin cérébral dans le vieillissement en se basant notamment sur les SNP et leur sévérité.

Ce premier chapitre abordera les associations cognitives des SNP chez des individus âgés, cognitivement sains, ayant un trouble cognitif léger, ou un diagnostic de maladie d'Alzheimer, en fonction de leur sexe ; l'objectif étant de déterminer les différences entre les femmes et les hommes en termes de prévalences des SNP, et les différentes associations avec les performances cognitives de ces symptômes.

Chapitre 1 – Neuropsychiatric symptoms influence differently cognitive decline in older women vs. men (Published in Journal of Psychiatric Research)

Running title: Impact of neuropsychiatric symptoms in older women vs. men

Ronat Lucas[a,b], Monchi Oury[a,c,d], Hanganu Alexandru[a,e], for the Alzheimer's Disease Neuroimaging Initiative* and National Alzheimer's Coordinating Center

[a]Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, Montréal, Québec, Canada

[b]Département de Médecine, Faculté de Médecine, Université de Montréal, Québec, Canada

[c]Département de Radiologie, Radio-Oncologie et Médecine Nucléaire, Faculté de Médecine, Université de Montréal, Québec, Canada

[d]Hotchkiss Brain Institute, Cumming School of Medicine, Calgary, AB, Canada

[e]Département de Psychologie, Faculté des Arts et des Sciences, Université de Montréal, Québec, Canada

*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at:

http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Corresponding Author:

Alexandru Hanganu, M6828, 4545 ch. Queen Mary, H3W 1W6, Montréal, QC

Telephone: (514) 340-3540 #4897

E-mail: alexandru.hanganu@umontreal.ca

Abstract

Objective: The potential impact of sex on cognitive performance in normal aging and participants with Alzheimer's disease (AD) has been outlined previously. Nevertheless, differences in neuropsychiatric symptoms have been also outlined. We aimed to study a potential association between NPS and cognitive performances according to sex, in older individuals with and without cognitive impairment.

Methods: Demographic, neuropsychiatric and neuropsychological data from the ADNI and NACC databases were merged into a dataset of 505 participants with healthy cognitive performance, 467 patients with mild cognitive impairment, and 239 patients with AD. Cognitive performance in each group was evaluated according to sex and the presence of NPS.

Results: Based on sex, cognitive performance differed according to clinical stage: in the healthy controls and AD groups, women had better fluency performance, while in the mild cognitive impairment group, women had better working memory and men better oral naming. Regardless of sex, depression showed a negative effect on processing speed in AD. Finally, there was an interaction between sex and NPS in mild cognitive impairment, where women with apathy had better working memory performance, and in AD, women with depression had better fluency performance. The opposite pattern was observed in men, where men with depression have worse focused attention.

Conclusion: Cognitive performance is influenced by sex, yet this influence has different manifestations at normal cognition, MCI or AD. Furthermore, apathy and depression seem to influence differently women and men at different types of cognitive decline.

Keywords: Neuropsychiatry, Sex, Aging, Mild Cognitive Impairment, Alzheimer’s Disease

Introduction

It has been reported that during the lifespan, sex differences in cognitive functions are stable with women performing better than men for episodic memory, semantic fluency and visual recognition and men performing better for visuospatial functions[92]. There are also sex differences with respect to risks of developing Alzheimer's Disease (AD): women account for nearly two-thirds of AD patients[93]. Prevalence and incidence are higher in women than men and these data increase with age[94,95]. Also, with same high Aβ-42 and total tau levels, Women showed more rapid hippocampal atrophy and cognitive decline than Men, particularly in Mild Cognitive Impairment (MCI)[96]. Neuropsychiatric Symptoms (NPS) are commonly defined as behavioral and psychological disturbances and they were shown to occur during pre-dementia syndromes such as MCI[97]. Some studies reported that NPS can precede the occurrence of MCI, may accelerate cognitive decline and could increase the risk of dementia[12,36]. Though NPS in the elderly has been previously investigated[9,98,99], the influence of NPS on cognitive performance with respect to sex, has received much less attention. Specifically, most NPS such as depression or apathy appeared to be associated with poorer memory and executive performance, while visuospatial and language reductions appeared to be more specific to psychotic symptoms[100–105].

Previous prevalence-based studies have shown that NPS in women are more varied and more severe[98]. Their types are also different, Women with MCI have higher prevalence of delusions, while Women with AD exhibit predominantly anxiety, irritability, delusion, depression and disinhibition[106–109]. In men, on the other hand, MCI was associated with more irritability, while AD was linked to irritability, agitation and apathy. From a cognitive perspective, longitudinal studies showed that women with mild anxiety and healthy cognitive performance (HC) had a higher likelihood of developing dementia compared to men with HC. Furthermore, anxiety led to a greater reduction in mental flexibility but not a higher risk of dementia after a follow-up of 5 and 3.4 years[110,111]. Other trends were reported regarding depression. Men with HC and with depression had a higher incidence of cognitive impairment after 2 years of follow-up[112]. In patients with mild amnestic MCI or mild AD, duration of cognitive decline was positively correlated with delusions severity in women, whereas the severity of irritability was negatively correlated with global cognition in men (assessed with the MMSE)[106]. To our knowledge, no other

study than those mentioned above has investigated the impact of NPS on cognitive performance according to sex. Moreover, these studies did not consider both the full range of neuropsychiatric differences between the sexes and the effects on a broader neuropsychological assessment.

Objective and hypothesis

Several significant limitations impede the proper interpretation of previous results, specifically the (1) small sample size; (2) single-site protocols (3) inclusion of a single ethnic group (4) brief assessments of cognitive performance (5) usage of clinical scales that are not adapted to the elderly population. Today, NPS are quantified using subjectively answered questionnaires, in which questions are answered either by the participant or by a caregiver. The realization of a multi-site study, using different databases, makes it possible to remedy the limitations previously mentioned (large sample size, more comprehensive neuropsychological assessment, assessment of numerous NPS). In the present study, we aimed to verify three hypotheses: 1) NPS have a different prevalence in women and men at different types of cognitive performance (HC, MCI or AD); 2) NPS influence differently cognitive performance when quantified per specific cognitive functions; and 3) sex and NPS have a different impact on cognitive performance in HC, MCI and AD.

Methods

Participants

Participants were selected from the ADNI (Alzheimer's Disease Neuroimaging Initiative) and NACC (National Alzheimer's Coordinating Center) databases. The ADNI database is a large compilation of longitudinal data, that was started in 2003 and is led by the principal investigator Michael W. Weiner, MD[113,114] (http://www.adni-info.org/). The NACC database was established in 1999 and is a large compilation of longitudinal data (https://naccdata.org). Participants that were included in our study from this database originated from the NACC UDSv1-2 dataset.

Three distinct groups were selected from each of the databases. Participants with HC included only those with cognitive performance within the expected range for their age, sex, and level of education. The Mild Cognitive Impairment group (MCI) from the ADNI database consisted of

individuals whose cognitive characteristics meet the criteria for MCI[115]. Entry criteria for patients with amnestic MCI included a Mini-Mental State Examination score of >24 and a Memory Box score of at least 0.5. The MCI participants from the NACC database had to have cognitive changes from the person's previous assessment (complaint) and a disorder in at least one cognitive domain[116].

Patients with Alzheimer's disease (AD) from the ADNI database were composed of individuals meeting the National Institute of Neurological and Communication Disorders/Alzheimer's Disease and Related Disorders Association criteria for probable AD[15]. They were only mildly impaired, based on the Mini-Mental State Examination score (>20, <26), global Clinical Dementia Rating (0.5-1) and sum-of-boxes Clinical Dementia Rating (>1.0, <9.0). The AD patients from the NACC database have met the NINCDS/ADRDA criteria for probable or possible AD[15].

Exclusion criteria used for this study were: (i) incomplete assessments, (ii) incomplete neuropsychiatric and neuropsychological assessments, (iii) presence of psychiatric history (major depression, schizophrenia, bipolar disorder, substance abuse, post-traumatic stress, obsessive-compulsive disorder), (iv) presence of neurological history (stroke, head injury, brain tumor, anoxia, epilepsy, alcohol dependence and Korsakoff, neurodevelopmental disorder), (v) prematurity, (vi) diagnostic criteria in favor of other neurodegenerative or neurological etiology (Parkinson's disease, frontotemporal degeneration, progressive supranuclear paralysis, corticobasal degeneration, Lewy body dementia, amyotrophic lateral sclerosis, multiple sclerosis, multi-system atrophy, vascular dementia). After the exclusion, the final sample for analyses consisted of 505 HC, 467 MCI, 239 AD (HC/MCI/AD: ADNI = 223/ 367/ 175; NACC = 282/ 100/ 64) (Table 1).

Ethics committee approval and individual patient consents were received by the ADNI and NACC databases (http://adni.loni.usc.edu/methods/documents/ & https://naccdata.org/data-collection/forms-documentation/uds-3) for each participant. This study was approved by the Comité d'éthique de la recherche vieillissement-neuroimagerie CER VN 19-20-06.

Neuropsychiatric and Neuropsychological Assessments

All participants underwent a comprehensive neuropsychological examination and a neuropsychiatric assessment via the Neuropsychiatric Inventory, that was completed by participants' relatives/caregiver in both datasets. We assessed the presence vs. absence of 12 neuropsychiatric symptoms: delusions, hallucinations, agitation/aggressiveness, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviors, nighttime behaviors and appetite/eating changes. The potential bias from relatives' answers was accounted for by ADNI using an interrater reliability assessment in different domains, which achieved and was reconfirmed to be excellent[117,118].

The neuropsychological assessment assessed eight cognitive functions, as per available tests present in both datasets: (1) global cognitive efficiency (assessed with the total score of Mini-Mental State Examination), (2) focused attention (completion time of Trail Making Test A), (3) processing speed (Total items correct of Wechsler Adult Intelligence Scale, Coding), (4) mental flexibility (completion time of Trail Making Test B), (5) visuoconstructive planning (copy score of the Clock test), (6) working memory (raw scores of the Digit Span forward and backward Tests), (7) verbal fluency (assessed based on the total correct words of the Semantic Lexical Evocation animal and vegetable) and (8) oral naming (total correct responses of the Boston Naming Test). Only assessments common to both databases were included. Thus, memory tests were not considered because of the different tests used in the databases (Rey auditory verbal learning test in ADNI and Logical Memory in NACC).

Statistical analysis

Independent variables were the (1) sex (woman or man), (2) clinical group (HC, MCI, or AD) and (3) NPS. Dependent variables were the raw cognitive performance. Data was analyzed using IBM SPSS Statistics version 26. First, the prevalence of NPS were compared between women and men in each clinical group using chi-square tests. Secondly, we determined the model for analyzing the effects of sex and NPS on cognitive performance (ANOVA vs. ANCOVA) accounting for age, years of education, and the MMSE score based on Student's t tests. Since the groups were not completely equal on these parameters, we used an ANCOVA model. Finally, the NPS that showed

a significantly different prevalence between women and men were included in our ANCOVA model with the confounding variables: age, years of education, and MMSE score. This allowed us to test the interaction effects of sex and NPS on cognitive performance. Three ANCOVAs were performed, comparing in each clinical group the differences in cognitive performance according to sex, NPS and the interaction of the two. The significance level was .05 for all tests. A Bonferroni correction was applied to comparisons of the estimated marginal means of the model.

Results

Demographic comparisons

Demographic data and comparisons within each group by sex are summarized in Table 1. Student's t tests reported a significant difference between women and men regarding age in the MCI group (W/M: 74.01 / 75.76, t = 2.409), MMSE score in the HC group (W/M: 29.17 / 28.94, t = -2.206) as well as number of years of education in all clinical groups (W/M: HC, 15.56 / 16.86, t = 3.213; MCI, 14.95 / 16.06, t = 3.938; AD, 14.07 / 15.64, t = 3.888).

Table 1.1. Demographic characteristics and comparison in each group depending on sex

Group	HC (N=505)		MCI (N=467)		AD (N=239)	
Sex	W	M	W	M	W	M
	(N = 281)	(N = 224)	(N=176)	(N=291)	(N=118)	(N=121)
ge, m (sd)	74.13 (7.93)	74.7 (7.09)	74.01 (7.65)	75.76 (7.55)*	75.38 (7.93)	76.06 (7.05)
ation, m (sd)	15.56 (2.68)	16.86 (6.13)***	14.95 (3.01)	16.06 (2.91)***	14.07 (3.06)	15.64 (3.16)***
MSE, m (sd)	29.17 (1.07)	28.94 (1.12)*	27.01 (1.89)	27.14 (1.82)	23.09 (2.53)	23.55 (2.68)

Legend: W = Women; M = Men; N = sample size per group and sex; m = mean; sd = standard deviation; *p<.05; ***p<.001

Prevalence of NPS

For each clinical group, the sample sizes as well as the prevalence of NPS by sex are presented in Table 2 and Figure 1-3. Women with HC presented less agitation than men with HC (0.7% vs. 3.6, Chi-square = 5.216, p = .022). Women with MCI, when compared to Men with MCI, showed less

apathy (8.5% vs. 15.1, Chi-square = 4.325, p = .038) and less irritability (16.5% vs. 32.0, Chi-square = 13.620, p < .001). Finally, in AD patients, women had less irritability than men (23.1% vs. 41.3, Chi-square = 9.048, p = .003), but a greater tendency to depression (32.5 vs 21.5%, Chi-square = 3.655, p = .056).

Table 1.2. Neuropsychiatric prevalence per group and sex.

Group	HC (N=505)		MCI (N=467)		AD (N=239)	
Sex	W (N = 281)	M (N = 224)	W (N=176)	M (N=291)	W (N=118)	M (N=121)
NPS, n (%)						
Delusion	0 (0)	0 (0)	2 (1.1)	3 (1.0)	13 (11.1)	8 (6.6)
Hallucination	0 (0)	1 (0.4)	0 (0)	1 (0.3)	4 (3.4)	3 (2.5)
Agitation	2 (0.7)	8 (3.6)*	24 (13.6)	54 (18.6)	26 (22.2)	32 (26.4)
Depression	11 (3.9)	9 (4.0)	32 (18.2)	49 (16.8)	38 (32.5)	26 (21.5)†
Anxiety	11 (3.9)	6 (2.7)	34 (19.3)	49 (16.8)	32 (27.4)	37 (30.6)
Euphoria	0 (0)	0 (0)	2 (1.1)	10 (3.4)	3 (2.6)	6 (5.0)
Apathy	1 (0.4)	2 (0.9)	15 (8.5)	44 (15.1)*	33 (28.2)	42 (34.7)
Disinhibition	0 (0)	1 (0.4)	9 (5.1)	23 (7.9)	17 (14.5)	20 (16.5)
Irritability	13 (4.6)	15 (6.7)	29 (16.5)	93 (32.0)***	27 (23.1)	50 (41.3)**
Aberrrant motor behavior	0 (0)	2 (0.9)	6 (3.4)	13 (4.5)	19 (16.2)	16 (13.2)
Nightime Behaviors	13 (4.6)	12 (5.3)	20 (11.4)	36 (12.4)	20 (17.1)	29 (24.0)
Appetite changes	3 (1.1)	1 (0.4)	15 (8.5)	30 (10.3)	13 (11.1)	21 (17.4)

Legend: W = Women, M = Men, n = sample size per NPS, N = sample size per group and sex, †.05<p<.10; *p<.05; **p<.01; ***p<.001

Impacts of sex and NPS on cognitive performance

From the 12 neuropsychiatric symptoms only depression, agitation, apathy and irritability showed a significantly different prevalence between women and men and were included in further analysis (See Table 3 below).

Table 1.3. ANCOVA results with main effect of sex, NPS and interaction between them for each clinical group on cognitive performances

Effect of Sex												
	HC				MCI				AD			
Cognitive variable	Women	Men	F	p	Women	Men	F	p	Women	Men	F	p
Vegetable fluency	16.60	12.63	4.423	**0.004**	11.08	10.49	0.955	0.380	8.35	6.77	4.274	**0.011**
Digit span backward	6.69	6.48	0.006	0.937	7.11	6.06	7.558	**0.006**	5.17	4.54	1.762	0.061
BNT	26.98	27.74	0.358	0.996	23.37	26.05	12.850	**<0.001**	20.76	22.06	2.158	0.264

Effect of NPS																				
	HC								MCI								AD			
Cognitive Variable	No-Agi	Agi	F	p	No-Apa	Apa	F	p	No-Irr	Irr	F	p	No-Dep	Dep	F	p	No-Irr	Irr	F	p
Digit Symbol	47.05	44.50	0.684	0.523	37.44	36.98	0.018	0.823	37.30	37.14	0.026	0.937	30.57	25.35	4.35	**0.030**	28.15	27.94	0.007	0.928

Interaction Sex and NPS												
	MCI						AD					
Cognitive variable	Women No-Apa	Women Apa	Men No-Apa	Men Apa	F	p	Women No-Dep	Women Dep	Men No-Dep	Men Dep	F	p
Digit span backward	6.49	7.81	6.31	5.80	5.321	**0.022**	5.26	5.08	4.83	4.21	<0.001	0.988
TMTA	41.58	51.08	43.59	42.99	1.545	0.215	61.05	56.55	56.15	87.86	6.011	**0.015**
Animals Fluency	14.89	14.37	15.97	16.27	2.199	0.139	10.71	12.90	13.58	10.71	5.373	**0.021**

Legend: HC = Healthy Control; MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease; F = ANCOVA statistical value; p = p-value; BNT = Boston Naming Test; NPS = neuropsychiatric symptom; No-Agi/Agi = Absence/presence of agitation; No-Apa/Apa = Absence/presence of apathy; No-Irr/Irr = Absence/presence of irritability; No-Dep/Dep = Absence/presence of depression; TMTA = Trail Making Test version A.

In the HC group, the ANCOVA model showed a simple effect of sex on the semantic lexical evocation domain (specifically vegetable fluency), with women performing better than men (F = 4.423, ddl = 1, p = .036). This simple effect was confirmed by comparison of the estimated marginal means (p = .004).

In the MCI group, women showed better performance compared to men in the working memory domain (F = 7.558, ddl = 1, p = .006) and worse performance in the oral naming domain (F = 12.850, ddl = 1, p < .001). This performance was further shown to be influenced by apathy, since the single interaction analysis showed that women with apathy performed better in working memory compared to both women and men without apathy as well as men with apathy (F = 5.321, ddl = 1, p = .022).

In the AD group, women performed better than men on semantic lexical evocation (vegetable fluency) (F = 4.274, ddl = 1, p = .040), confirmed with the estimated marginal means (p = .011).

This effect was also influenced by the presence of depression, as women with depression showed better semantic lexical evocation (animal fluency) performance than women without depression, while in men, those with depression had worse performance than those without ($F = 5.373$, ddl = 1, $p = .021$). On the other hand, depression was shown to influence focused attention in men, but not in women. Specifically, men without depression showed better performance on focused attention compared to depressed men ($F = 6.011$, ddl = 1, $p = .015$), while no effect was observed in women. These results should also be regarded in light of a potential impact of a simple effect of depression on processing speed ($F = 4.350$, ddl = 1, $p = .038$), since the presence of depression reduced the performance in all participants.

Discussion

Our results indicate that: 1) NPS have a different prevalence in women and men at different stages of cognitive performance; specifically, agitation is more specific for men with HC, apathy – for Men with MCI, irritability is more prevalent in Men with MCI and Men with AD, depression is more prevalent in Women with AD; (2) sex and NPS have a different impact on cognitive performance at different cognitive clinical stages; specifically, regarding semantic lexical evocation (HC/Women with AD are better than HC/Men with AD, Women with AD with depression > Women with AD without depression, Men with AD with depression < Men with AD without depression), working memory (Women with MCI > Men with MCI, Women with MCI with apathy > Women with MCI without apathy), oral naming (Women with MCI < Men with MCI), focused attention (Men with AD with depression > Men with AD without depression).

Our results are in line with some of the previously published reports that observed that some certain NPS are more prevalent in men than in women, specifically agitation, apathy, and irritability in MCI and AD[106,108,119]. In addition, we show that NPS are also present in HC participants, and our results of prevalence in this group are in line with previously published data from Mortby et al. (2018)[97]. On the other hand, our results contradict the study of Xing et al. who found that NPS prevalence was similar in both women and men and the study of Inamura et al. that women had more delusions than men[106,109]. Concerning apathy, Zuidema et al. (2009) suggested that apathy is more prevalent in men because of the higher prevalence of vascular

disease in these patients[119]. Thus, apathy in women could be caused by other factors than vascular etiology. Nevertheless, previous findings used smaller sample sizes and the MCI group had different quantification criteria, significantly diminishing the potential comparisons to them.

To explain these neuropsychiatric differences, some studies point to genetic predispositions as well as hormonal fluctuations in men and women including the menopausal process[120–123]. Differences in NPS also appear to be due to the amyloid status of individuals or to hormone/amyloid status interactions, particularly in women[109,123]. Finally, these prevalence may vary depending on the presence of other NPS. For example, Tao et al. (2018) focused on patients with agitation/aggression. Among them, with equal levels of agitation, women appeared to have more anxiety and irritability than men[108].

Based on our sex related prevalence differences, associations between NPS and cognitive performance were tested according to agitation, irritability, apathy and depression. Our results showed that women performed better overall in semantic fluency (HC and AD groups), and oral naming (MCI group), as well as in verbal working memory (MCI group) than men. In this sense, these data are consistent with previous literature regarding better verbal performance in women. However, men were not found to have better visuospatial performance than women. This is quite distinct from other studies reporting that older women show better cognitive preservations than men in most cognitive domains, except for visuospatial and perceptual-motor domains[92,124]. Furthermore, cognitive aging, depending on sex, appears to be mediated by different brain changes[125].

Concerning sex and NPS interactions on cognitive performance, in the HC group, agitation did not show a different effect on cognitive performance by sex. This is not surprising given the lack of studies showing relationships between NPS and cognition in HC participants. Indeed, while the presence of NPS is frequently demonstrated in HC participants (at least one NPS in 42% from Fernandez-Martinez et al., 2010), their relationships with cognition are poorly studied, and do not show significant results[9,21]. Indeed, in MCI patients, Brodaty et al. (2012) reported associations between depression and dysexecutive disorders, anxiety and processing speed/selective attention, agitation and memory disorders as well as visuospatial disorders in relation to

agitation, anxiety and apathy; but no associations in HC[21]. Moreover, in controls and patients with MCI neither the neuropsychological test nor daily living scales were related to the presence of any NPS in the study of Fernandez-Martinez et al. (2010)[9]. In contrast, it appears that the presence of NPS shows long-term negative effects on future cognitive decline[8,21,112]. For example, more rapid decline in executive function was predicted by the presence of anxiety at baseline, whereas decline in language was predicted by agitation, whereas NPI total score at baseline was associated with accelerated memory and language decline and anxiety was related to accelerated decline of processing speed[21]. These data suggest that NPS would be better predictors of future cognitive decline than current cognitive performance.

In the MCI group, the interaction effect between apathy and sex on working memory showed a benefit in women. Indeed, those with apathy showed better performance than those without. This effect was not present in men. This could be due to the different apathy profiles between women and men. Indeed, apathy may involve different brain networks (cognitive, affective, motivational, goal-directed e.g.) and thus impact cognitive functions such as working memory in different ways[126,127]. However, most studies do not consider these subtypes of apathy and demonstrate, that in normal aging, mild cognitive impairment and Alzheimer's disease, frontal/dysexecutive disorders in association with apathy[103,104,128,129]. Also, some pharmacological and non-pharmacological treatments of apathy have been shown to improve cognitive performance in Alzheimer's disease[130]. However, these data were not considered in this study. By contrast, previous results reported associations between anxiety and accelerated memory decline and greater executive dysfunction[101,103,104]. We didn’t find any association with anxiety and cognitive performances.

Finally, in the AD group, depression had a different impact on women and men's performance in semantic fluency and focused attention. Regarding semantic fluency, the performance patterns were reversed between women and men; the former performed better with depression while the latter performed better when they were not depressed. Regarding focused attention, men with depression were slower. In contrast to what was found in women, the literature tends to show poorer executive performance in Alzheimer's disease when depression is present[131,132]. Other studies also showed broader associations of depression with executive function, memory

and language[103,133]. However, studies investigating the associations between NPS and cognitive performance remain scarce. Interestingly, high sex-dependent prevalence of NPS does not necessarily indicate strong cognitive associations. Thus, this suggests that group prevalence alone does not explain the association with cognitive performance. Indeed, other NPS, not considered in our study such as psychotic, euphoria or disinhibition symptoms, could also exhibit associations with cognitive performance, depending on sex, even if in our study they were not included due to prevalence limitations.

Strengths, limitations and perspectives

To our knowledge, this study is the first to consider a broad field of cognitive performance to investigate associations with NPS as a function of sex. In addition, the study of two large databases, ADNI and NACC, allowed the accumulation of a large population of more than 1200 participants, HC, MCI and AD. Despite this, the consideration of NPS whose prevalence was significantly different between women and men in each clinical group led to a great variability of the sample sizes, particularly with the HC group, where the prevalence of NPS is globally low. Another way to approach this issue would be to pay attention to the most prevalent NPS in each group rather than sex differences in prevalence.

It should be noted that the NPI design does not attempt to determine the origin of NPS or distinguish the triggers of the behaviors, whether they are due to the physical (new location) or psychosocial (interactions or care) environment[134]. Furthermore, the behaviors assessed are for the previous month and focus on behavioral changes, compared to the assessed individual's previous functioning[134,135].

Another limitation is the lack of consideration of the amyloid status of the participants. This parameter, when controlled, could show different results, as demonstrated in the study of Xing et al. (2015)[109]. Interestingly, most studies on sex differences in NPS and cognitive decline have focused on Alzheimer's disease or amnestic MCI[106,108,109]. To our knowledge, few studies have examined these differences in normal cognitive aging (i.e. in HC participants). However, the studies of Kassem et al. (2017; 2018) and Ng et al. (2009) showed that NPS at baseline like anxiety and depression affect longitudinally the cognitive decline in women and men groups

differently[110–112]. That's why these data need to be supplemented by longitudinal analyses as well as comparative analyses of neuropsychiatric profiles between clinically progressing participants (HC who convert to MCI, MCI who convert to AD e.g.) and those who do not progress (HC participants who remain HC in particular). The possibility that the magnitude and characteristics of inter-sex differences within NPS may vary during cognitive decline should also be considered[108]. Of particular interest could also be comorbidities between NPS. Indeed, especially in patients with MCI or AD, several NPS may be present in the same individual. From this perspective, taking into consideration the NPS as co-occurring rather than independently, might allow a better understanding of the neural processes involved in the cognitive performance of participants, even in the pre-MCI stages. Finally, a limitation can be mentioned regarding gender-specific biases in the evaluation of NPS: even if these biases are not systematically described in previous studies, it remains possible that gender-related social expectations such as communication in women or impulsivity in men bias the evaluation of NPS by relatives. In addition, sex differences in the manifestations of the same NPS have been described, such as physical aggression in men and verbal agitation in women[119]. This is in line with the results of Orengo et al. (1997) who showed a positive relationship between plasma testosterone levels and physical aggression in men with dementia while this relationship was not found with verbal aggressive behavior and physically nonaggressive behavior[136]. Also, in the same perspective, estrogen levels are positively associated with affective symptoms (emotional lability) in women with Alzheimer's disease but not in men[137]. Despite this, it has previously been suggested that gender differences in NPS may be due to gender bias on the part of the reporting caregiver, but Ott et al. (1996) found that the sex of the patient rather than the informant is the strongest predictor of sex differences in behavior[138].

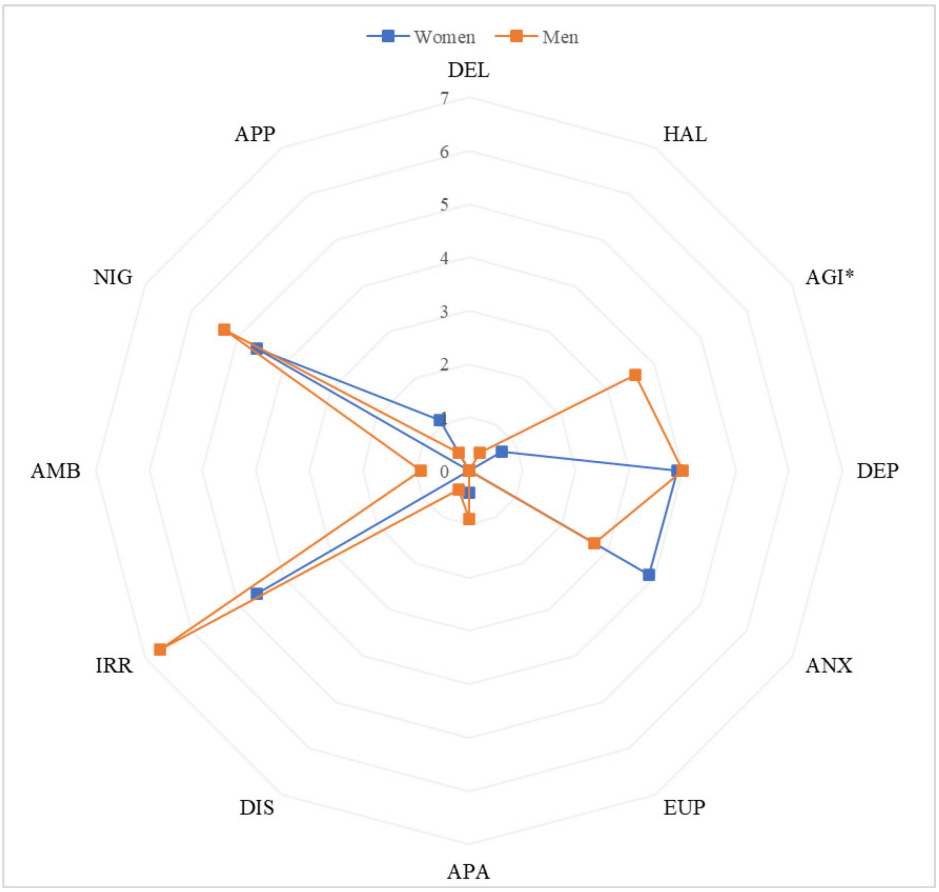
The relationships between NPS and sex-dependent cognitive performance could depend on genetic (APOE status), hormonal (estradiol, testosterone), cerebrospinal biomarkers (tau, phospho-tau, amyloid), and stage of cognitive decline (MCI, moderate or severe AD) factors. Thus, the study of these processes would require more integrative approaches.

Conclusion

In order to explore the effect of sex and NPS on cognitive performance at different stages of cognitive decline, we compared different cognitive functions in women and men at different clinical cognitive groups (HC/MCI/AD) with and without NPS. Our results showed essentially cognitive differences due to sex, where women performed better overall in semantic fluency (HC and AD groups), and oral naming (MCI group), as well as in verbal working memory (MCI group) than men. Some differences were due to NPS: apathy influenced working memory in Women with MCI and depression had an impact on verbal fluency in HC/Women with AD and Men with AD, as well as an impact on focused attention in Men with AD. These results might suggest (1) that some NPS might have a potential compensatory effect on the cognitive performance, (2) some NPS have a detrimental effect, and (3) some NPS must be considered in light of sex when assessing their impact on cognitive performance.

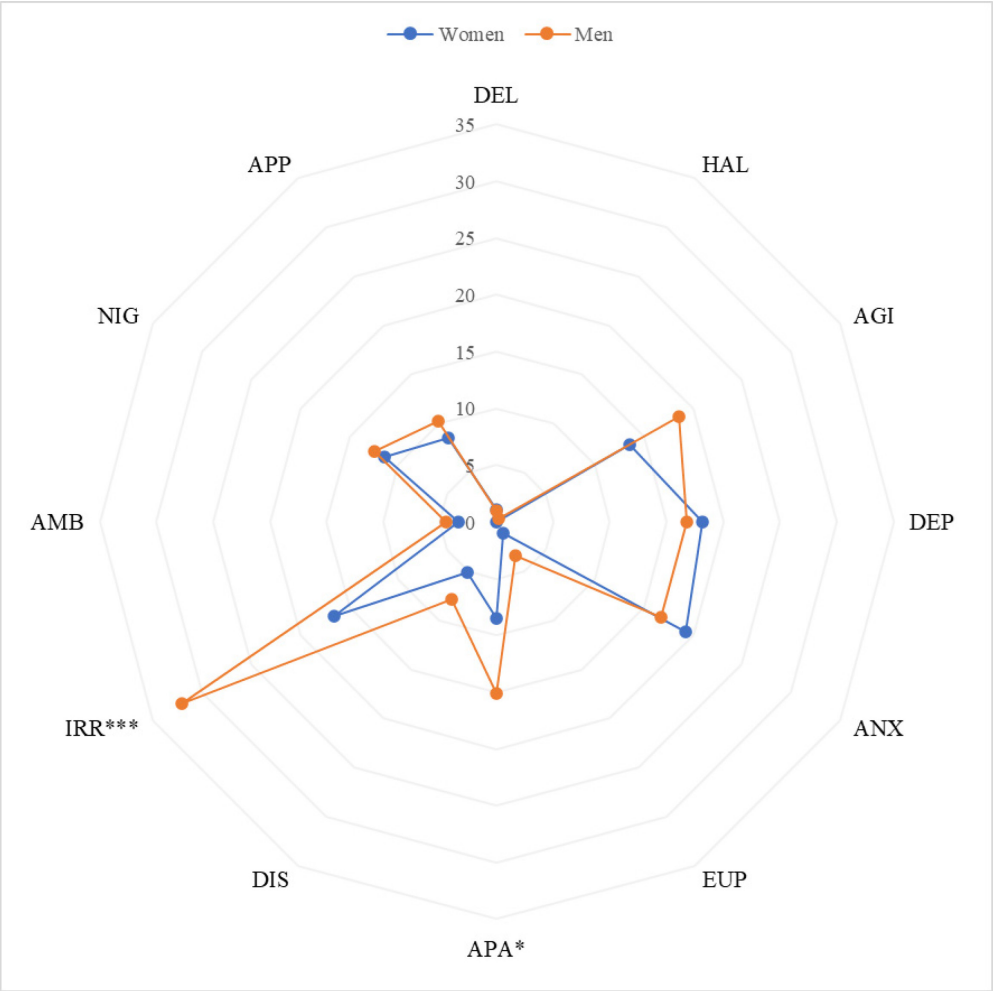
Figures

Figure 1.1. Radar of neuropsychiatric symptoms prevalence in HC group (in %).



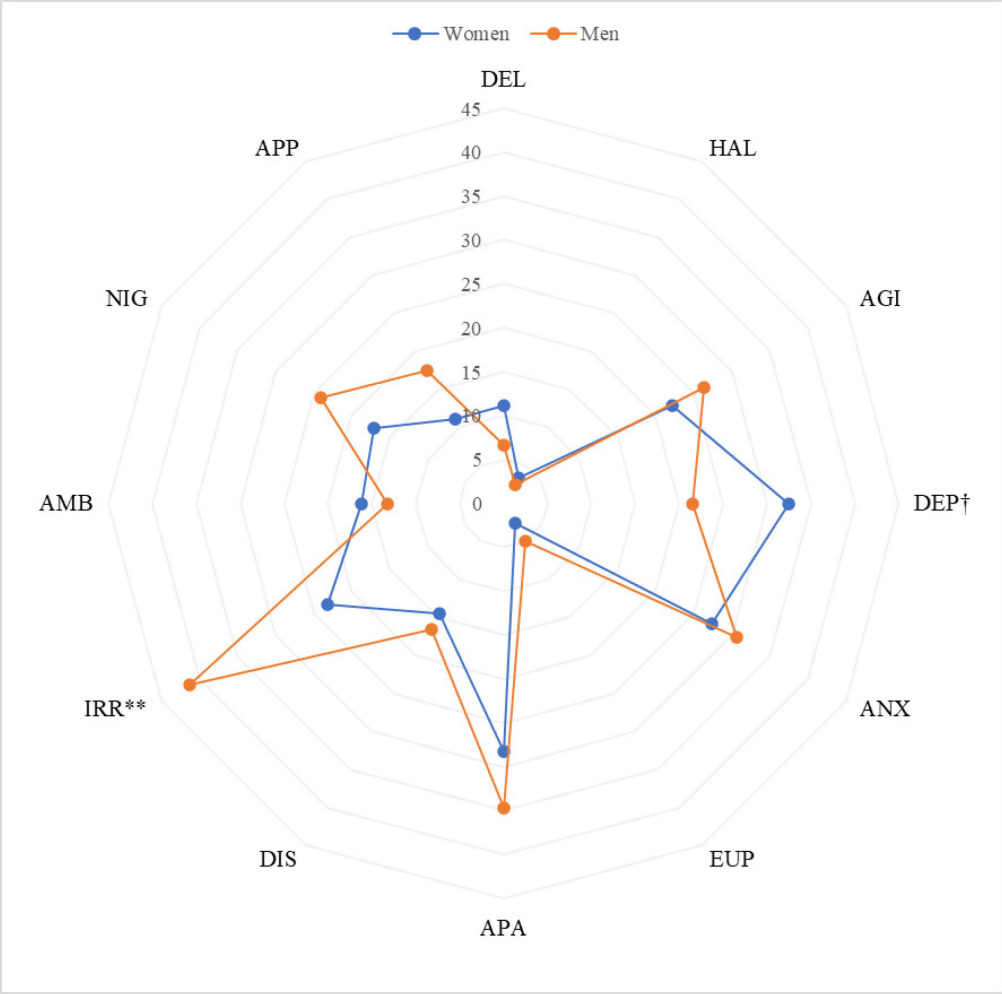
Legend: DEL = Delusion; HAL = Hallucination; AGI = Agitation; DEP Depression; ANX = Anxiety; EUP = Euphoria; APA = Apathy; DIS = Disinhibition; IRR = Irritability; AMB = Aberrant Motor Behaviors; NIG = Nighttime Behaviors; APP = Appetite Changes; *Chi² p-value for comparison of NPS prevalence between women and men <.05. **NOTE: all 3 radar figures have different scales.**

Figure 1.2. Radar of neuropsychiatric symptoms prevalence in MCI group (in %).



Legend: DEL = Delusion; HAL = Hallucination; AGI = Agitation; DEP Depression; ANX = Anxiety; EUP = Euphoria; APA = Apathy; DIS = Disinhibition; IRR = Irritability; AMB = Aberrant Motor Behaviors; NIG = Nighttime Behaviors; APP = Appetite Changes; *Chi² p-value for comparison of NPS prevalence between women and men <.05; ***p<.001.
NOTE: all 3 radar figures have different scales.

Figure 1.3. Radar of neuropsychiatric symptoms prevalence in AD group (in %).



Legend: DEL = Delusion; HAL = Hallucination; AGI = Agitation; DEP Depression; ANX = Anxiety; EUP = Euphoria; APA = Apathy; DIS = Disinhibition; IRR = Irritability; AMB = Aberrant Motor Behaviors; NIG = Nighttime Behaviors; APP = Appetite Changes; †Chi² p-value for comparison of NPS prevalence between women and men <.10; **p<.01.
NOTE: all 3 radar figures have different scales

Transition

Cette première étude a soulevé plusieurs éléments : les prévalences de symptômes neuropsychiatriques diffèrent entre les femmes et les hommes, au travers des différents stades de déclin cognitif étudiés, et même chez les individus cognitivement sains. Globalement, les hommes présentent plus souvent ces symptômes (agitation, apathie, irritabilité), et lorsque ces symptômes sont présents, ils sont associés à des performances cognitives plus faibles. Ces données soulignent l'importance de porter attention aux différences symptomatologiques entre les femmes et les hommes même au sein de processus pathologiques similaires, ainsi qu'à considérer le sexe comme variable à contrôler dans les études comportementales et cognitives du vieillissement normal et pathologique.

Dans cette lignée, le chapitre suivant visera à étudier les associations cérébrales, corticales et sous-corticales, des SNP dans différents échantillons d'individus cognitivement sains, ayant un trouble cognitif léger, ou un diagnostic de maladie d'Alzheimer.

Chapitre 2 – Cortical and subcortical association of neuropsychiatric symptoms in cognitive decline (In Prep)

Running title: Neuropsychiatry in cognitive decline

Ronat Lucas[a,b], Hoang Van-Tien[a], Hanganu Alexandru[a,c] for the ADNI*

[a]Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, Montréal, Québec, Canada

[b]Faculté de Médecine, Département de Médecine, Université de Montréal, Montréal, Québec, Canada

[c]Faculté des Arts et des Sciences, Département de Psychologie, Université de Montréal, Montréal, Québec, Canada

*Alzheimer's Disease Neuroimaging Initiative#

Corresponding Author:

Alexandru Hanganu, 4545 Chemin Queen Mary, Montréal, QC H3W 1W6.

Telephone: +1514-340-3540 #4897

E-mail: alexandru.hanganu@umontreal.ca

[#]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at:

http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Abstract

Objectives: Neuropsychiatric symptoms (NPS) were reported to have a significant impact on brain morphology in older people. These behavioral patterns were shown to especially influence the anterior parts of the brain such as prefrontal and cingulate regions. Nevertheless, the interplay between NPS and brain morphology at different stages of cognitive performance has not been eluded so far.

Method: Using the Alzheimer's Disease Neuroimaging Initiative database cohorts 2 and 3, we investigated 659 participants with normal cognition, 561 with mild cognitive impairment (MCI) and 215 with Alzheimer's disease (AD). The NPS were assessed using the Neuropsychiatric Inventory while brain morphology was quantified using MRIs processed with FreeSurfer. We used a general linear model and multivariate linear regression analysis using covariates to establish the associations between the severity of NPS and brain morphometry in cortical and subcortical structures in each clinical group.

Results: In cognitively normal participants, agitation and depression were mainly associated with posterior structures (parietal, cingulate and occipital), apathy with anterior structures (prefrontal, insula) and irritability with both anterior and posterior structures (prefrontal and parietal). In MCI, agitation, apathy and irritability were mainly associated with anterior structures (prefrontal), anxiety with posterior structures (cingulate, parietal). In AD, anxiety, apathy and nighttime behaviors were associated with both anterior and posterior structures (prefrontal, cingulate, insula, temporal, parietal and occipital).

Conclusion: These results show that associations between brain structures and NPS differed across both NPS and clinical stages.

Keywords**:** Neuropsychiatric symptoms, MRI, Alzheimer's Disease, Mild Cognitive Impairment.

INTRODUCTION

Neuropsychiatric symptoms (NPS) are common in Alzheimer's disease (AD). Among the most common and early symptoms are agitation, depression, anxiety, apathy, irritability and nocturnal behaviors[19,38]. These symptoms lead to significant distress in carers and relatives, reduce quality of life and increase the risk of institutionalization[139,140]. Thus, exploring the pathophysiological correlates of these symptoms in AD is essential to their clinical improvement. These symptoms are verbal, physical, or mood and emotional behavioral changes. Although their prevalence is variable in AD depending on the method of the studies, they affect more than one third of patients[19], can be persistent over months[141] and occur in different stages of AD (pre-clinical, mild cognitive impairment, dementia)[8,11,12,142,143]. Numerous studies are attempting to identify the biological basis of these NPS in order to advance their understanding and make their therapeutic targets more effective[144,145]. Some have focused on specific NPS, others have considered broader sets of symptoms[62,146].

In their work focusing on agitation/aggression, Trzepacz et al (2013) report frontal and temporal associations with these symptoms (atrophies and hypometabolism) confirmed by their results based on the ADNI cohort 1 database[62]. Indeed, their analyses of patients' MRIs showed greater frontal, insular, amygdala, cingulate and hippocampal atrophies in individuals with more agitation/aggression. Other work supports the findings of Trzepacz et al. or has also been able to show associations between agitation and dysconnectivity of the salience network, involving the cingulate and insula regions[42,147].

Irritability is often associated with agitation, both of which are considered symptoms of hyperactive syndrome. However, few studies have looked at this or demonstrated neuroanatomical correlates. However, it seems that irritability is associated with a decrease in the integrity of the white matter of the anterior cingulate[42].

Interestingly, apathy, considered a motivational disorder, has also been associated with anterior cingulate structures. Indeed, whether it is work on fractional anisotropy, grey matter, or white matter density, it appears that reduction or atrophy of the anterior cingulate has been associated with apathy in AD[39,45,147,148]. However, it appears that other structures may have been associated

but not systematically, such as the right thalamus, the parietal and frontal lobes (including the left medial, superior, and ventrolateral prefrontal cortices) and the left inferior temporal.

Similarly, depression in AD also appears to involve limbic cortical regions, such as atrophies of the frontal (dorsolateral, medial, orbitofrontal and anterior cingulate), temporal (inferior) and parietal lobes[48,49,52,53]. In addition, other medial temporal and subcortical associations have been linked to the severity of depression in AD, including with the right hippocampus, entorhinal cortex, and striatum[51,53,149].

As in a continuum with apathy and depression, anxiety has been associated with subcortical regions such as via putamen and amygdala atrophies[44,55], but also cortical, involving the right parietal (inferior lobule and precuneus)[150], insular, parahippocampal and right posterior cingulate regions[44] as well as the entorhinal cortex[54].

Finally, sleep disorders, recognised as a risk factor for AD, consist of a wide range of disorders: sleep apnoea, rapid eye movement sleep behavior disorder, sleepiness, insomnia, restless legs syndrome. Some of these disorders could be associated with bilateral temporal and occipital cortices atrophies in RBD[151], insula volume reductions in relation to more frequent nocturnal awakenings in healthy older adults[152], hippocampal volume reductions in other populations with insomnia-like sleep disturbances[153,154], or right superior frontal volume reductions in poor quality sleep[155]. In AD, the literature review by Liu et al. (2021) indicates inconsistent findings regarding structural changes in AD with sleep disorders, possibly affecting the default mode circuit, sensorimotor cortex, hippocampi, brainstem, or pineal gland[156].

Furthermore, recent work showed significant limitations of previous results requiring further investigation. In particular, it has been shown that cortical volume is determined by surface area and thickness, which are influenced by different factors[157]. Thus, the analysis of the three measures would provide a better understanding of the potential underlying pathology, considering that the volumetric changes of the brain are explained by thickness, surface area, or both. In fact, it has been pointed out that these three features are key elements in the diagnosis of MCI and AD[158].

This study proposes to determine cortical and subcortical associations of a broad range of the most predominant NPS in AD (agitation, depression, anxiety, apathy, irritability and nighttime behaviors) on brain morphology, at several stages of cognitive decline including CN participants, patients with MCI and patients with AD from the ADNI database (cohort 2-3); and to compare these results in light of previously published data.

Affective (depression, anxiety) and hyperactive (agitation, irritability) symptoms are expected to share associations with cortical (notably prefrontal and temporal) and subcortical (striatum, amygdala and hippocampus) structures, whereas apathy is thought to be primarily associated with prefrontal and cingulate morphology. Finally, sleep disorders would be associated with posterior (temporal, hippocampus, occipital), as well as prefrontal structures.

METHODS

Study design

This study is based on the extraction and cross-sectional analysis of healthy participants and those with pathological cognitive decline (MCI or AD) from the ADNI cohort 2-3 databases.

Setting

The cleaning and extraction of data relevant to the study as well as the descriptive and inferential statistical analyses were carried out from the first half of 2020 and the end of 2021.

Participants

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI, launched in 2003 and led by Principal Investigator Michael W. Weiner, MD, aims to combine imaging data, biological markers, and clinical and neuropsychological assessments to measure the progression of MCI and early AD. At the time of extraction in February 2023, the database contained 16304 observations, including 2428 baseline visits, with participants aged 50.4 to 91.4 years, who meet entry criteria for a clinical diagnosis of probable AD (n = 411), early MCI (n = 421), late MCI (n = 689), subjective memory complaint (n = 352) or CN (n = 541). For our study, early and late MCI participants were grouped as MCI, and

SMC and CN participants were grouped as CN. Participants received neurological, biological, and neuropsychological assessments at baseline and follow-up visits. (for reviews and more details, see Shaw and colleagues, Mueller and coauthors, and http://www.adni-info.org/)[113,114]. All patients with AD met the NINCDS/ADRDA criteria for probable AD with a Mini-Mental State Examination score between 20 and 26, a global Clinical Dementia Rating of 0.5 or 1, a sum-of-boxes Clinical Dementia Rating of 1.0 to 9.0, and, therefore, are only mildly impaired. Entry criteria for patients with amnestic MCI include a Mini-Mental State Examination score of 24 to 30 and a Memory Box score of at least 0.5, whereas other details on the ADNI cohort can be found online.

Each participant had demographic data (age, sex, ethnicity, race, years of education, marital status), and neuropsychiatric assessment via the Neuropsychiatric Inventory (NPI). The NPI consists of 12 subscales assessing 12 NPS. Each of these scales has a general “yes/no” question. If the answer to this general question is “yes”, sub-questions are used to specify the manifestations of the symptoms. They are also answered by “yes” or “no”. For each manifestation of a symptom, the respondent must then estimate the frequency (on a scale from 1 (occasionally, less than once per week) to 4 (very frequently, once or more per day or continuously) as well as the severity (from 1= mild to 3 = severe). The multiplication of these two scores constitutes the score of a symptom on a total of 12 points. The sum of the 12 symptom scores constitutes the total NPI score. Here, we considered as a continuous variable the total score of each symptom. Six NPS were retained considering their higher prevalence in normal and pathological aging compared to other NPS: agitation/aggressiveness, depression, anxiety, apathy, irritability, and nighttime behavior disorders. From the 2428 participants at baseline, 1469 from the cohorts ADNI 2 and 3 were assessed with the NPI.

The exclusion criteria have been reported in Table 1.

Data processing and statistical analysis

MRI data were processed on the Digital Research Alliance of Canada's Cedar cluster (http://www.alliancecan.ca), on CentOS Linux version 7 (Centos 7.0_x86_64), with FreeSurfer 7.1.1 (http://surfer.nmr.mgh.harvard.edu) and managed and verified by an automated internal

pipeline (github.com/alexhanganu/nimb). The processing extracted volume, thickness and area of cortical regions based on multiple segmentation atlases[159,160]. Cortical thickness was calculated as the average of (1) the distances between each vertex on the white surface and the corresponding nearest point on the pial surface (not necessarily at a pial vertex) and (2) the distance between the corresponding pial vertex and the nearest point on the white surface[161]. The cortical surface was obtained based on the triangular face of the surface representation with the *abc* coordinates of the corresponding triangle vertices and by dividing the vector norm of the cross product of the differences between the vertex coordinates by two: |(a-c) x (b-c)| /2[162]. Finally, the cortical volumes are based on the definition of oblique truncated triangular pyramids that were divided into three irregular tetrahedrons and their volumes were calculated[163]. Each voxel of the normalized brain volume was assigned to one of the labels in the atlases used based on probabilistic atlas obtained from a manually labelled training set[159]. To adjust the subcortical volumes to the intracranial volume we performed simple regressions between each nucleus and the intracranial volume, and then calculated an adjusted volume according to the formula volume(adjusted) = volume(observed) - *a*(eTIV[observed] - eTIV[mean]), where *a* is the simple regression coefficient between each nucleus and the intracranial volume[164,165]. Among the 1469 selected participants, 1451 MRI could be extracted. During the processing of the images, 16 were error prone in the process and were excluded from the final analyses.

Managing missing data

After merging the neuropsychiatric and imaging data frames, 2 participants remained without neuropsychiatric data. These missing data were for one CN participant and one patient with AD. Scores based on the mean of each group were assigned. Each averaged NPI subscale score was rounded to the nearest integer and their sum was used to estimate the total score for these participants.

Statistical analysis

To assess the effect of each NPS on brain morphology within each clinical group, we performed a whole-brain general linear model analysis with FreeSurfer mri_glmfit for each NPS, based on the Desikan cortical atlas, that includes 34 regions[160]. Analysis was performed for three cortical

measurements: volume, thickness and area and considered age, sex, education as covariates. Results underwent a Monte-Carlo correction with a vertex-level threshold of $p<0.05$.

In a second step, considering that FreeSurfer mri_glmfit didn't take into account subcortical structures, multiple linear regression were performed to analyze the relation between NPS and subcortical nuclei volumes, within each group. The nuclei included in the analysis were: caudate, putamen, pallidum, thalami, nucleus accumbens, ventral diencephalon, hippocampi, and amygdala[159]. Age, sex and education were also included in each model and considered as covariates. For these regressions, a False Discovery Rate correction was applied by considering the number of structural variables and the number of NPS factors. The corrections were applied using the python-based package "statsmodel", and the function stats.multitest.fdrcorrection with: a Benjamini/Hochberg method and a Family-wise error rate of 0.05.

Standard Protocol: Approvals, Registrations, and Consents

Ethics committee approval and individual patient consents were received by the corresponding registration sites according to ADNI rules (http://adni.loni.usc.edu/methods/documents/).

Data availability

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). Ethics committee approval and individual patient consents were received by the corresponding registration sites according to ADNI rules (http://adni.loni.usc.edu/methods/documents/). All data are available on the ADNI websites upon demand (http://adni.loni.usc.edu/data-samples/access-data/).

RESULTS

Clinical groups consisted of CN participants (mean age: 75.83 ± 5.08), patients with MCI (mean age: 74.83 ± 7.39) and AD (mean age: 75.46 ± 7.47) (Table 1). Groups were similar according to age. The MCI group included more males (63.7%). The mean MMSE score was higher in the CN group compared to MCI and higher in MCI compared to the AD group.

Table 2.1. Demographic and neuropsychiatric features across control and clinical groups

	CN	MCI	AD	F/Chi²	p-value
N	659	561	215		
Age	71.12±6.68	71.85±7.38	74.56±8.19	18.63	<.001
Education	16.66±2.37	16.29±2.55	15.68±2.60	12.95	<.001
MMSE	29.03±1.24	27.81±1.88	22.98±2.30	1033.17	<.001
Women (%)	59.03	45.10	41.86	32.01	<.001
Agitation	0.08±0.50	0.40±1.18	0.95±2	50.00	<.001
Depression	0.15±0.68	0.57±1.19	0.89±1.55	48.51	<.001
Anxiety	0.08±0.52	0.45±1.37	0.81±1.66	38.47	<.001
Apathy	0.06±0.45	0.57±1.58	1.43±2.32	83.22	<.001
Irritability	0.16±0.69	0.58±1.42	1.06±2.16	42.47	<.001
Nighttime Behaviors	0.33±1.09	0.84±2.07	0.60±1.47	15.04	<.001

Whole-brain general linear model analysis

GLM based intragroup analysis revealed significant association between brain's morphology and the NPS studied in the different groups (Table 2).

In CN participants, agitation severity showed negative associations with the left inferior parietal volume, specifically due to changes in the surface area, and with the left isthmus cingulate area, and positive association with the right superior temporal area and left lingual thickness. Depression severity was associated negatively with left postcentral, right occipital lateral and parietal superior surface area, and positively with right insula, left *pars opercularis* and bilateral precuneus thickness. Anxiety severity was only negatively associated with left fusiform volume. Apathy severity was positively associated with left *pars opercularis*, right superior frontal and temporal volumes, right insula and left medial orbitofrontal surface area, and right superior

parietal thickness. Finally, irritability severity was positively associated with left *pars opercularis*, right superior frontal and parietal volumes, left frontal pole and right postcentral surface area. No association was found with the severity of nighttime behaviors.

In patients with MCI, agitation severity showed negative associations with the right superior frontal volume, the left superior frontal, caudal middle frontal supramarginal and inferior temporal thickness. Depression was only negatively associated with right superior parietal volume. Anxiety was negatively associated with left isthmus cingulate volume, inferior parietal, precuneus and right rostral middle frontal surface area. Apathy severity was negatively associated with bilateral caudal middle frontal, left superior frontal, right supramarginal volumes, specifically due to changes in the surface area, left paracentral, right postcentral surface area, left paracentral and right middle temporal thickness. Irritability severity showed negative associations with left precentral, right lateral orbitofrontal, superior temporal (specifically due to changes in the thickness), rostral middle frontal, supramarginal and *pars opercularis* volumes. Finally, nighttime behaviors were associated negatively with right lingual volume.

In patients with AD, agitation was positively associated with left superior temporal surface area. Anxiety was positively associated with left superior temporal, parietal and precentral volumes, and negatively associated with right medial orbitofrontal thickness. Apathy severity showed positive association with left occipital lateral volume (specifically due to changes in the thickness) negative association with right rostral middle frontal volume, and negative associations with left caudal anterior cingulate, right postcentral, middle temporal, insula and superior frontal thickness. Finally, nighttime behaviors were positively associated with right precentral volume, left superior temporal and *pars triangularis*, right insula, inferior parietal, pericalcarine surface areas, and right lateral orbitofrontal thickness. No association was found with the severity of depression or irritability.

Table 2.2. Regressions between neuropsychiatric severity and cortical brain structures in CN group (controlled for age, sex and education).

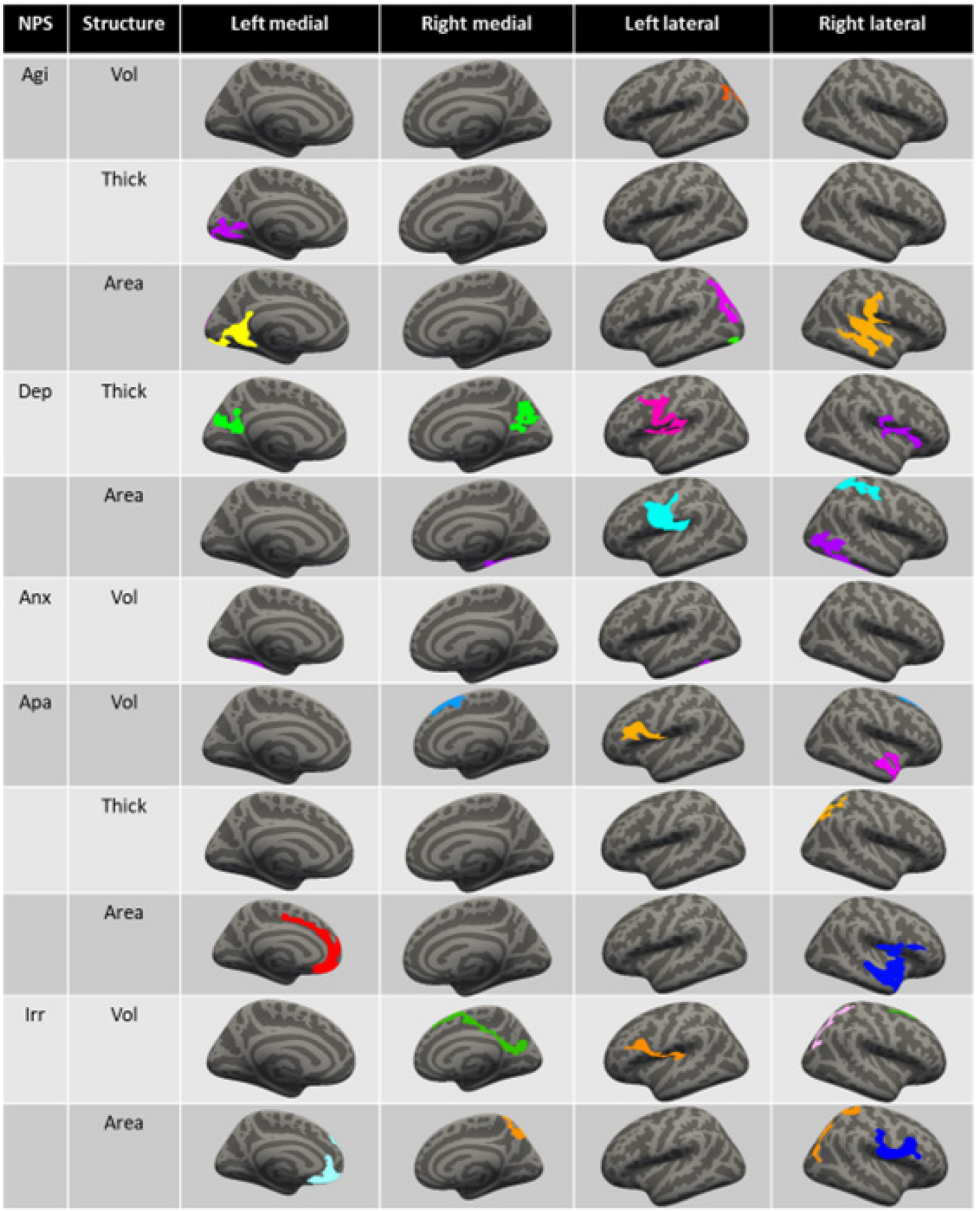
Brain Structure	Measure	Talairach coordinates	p (log(p))	PCC R	R^2

		x	y	z			
Agitation							
Parietal inferior L	Vol	-38.3	-66.9	41.3	<.005 (-2.45)	-0.16	0.03
Occipital lingual L	Thick	-8.6	-73.8	0.6	<.00001 (5.73)	0.18	0.03
Parietal inferior L	Area	-31.3	-67.7	41.4	<.005 (-2.62)	-0.16	0.03
Cingulate isthmus L	Area	-19.0	-47.3	1.4	<.005 (-2.81)	-0.16	0.03
Temporal superior R	Area	58.9	-21.4	6.4	<.0005 (-3.37)	-0.17	0.03
Depression							
Insula R	Thick	30.3	23.2	7.2	<.00001 (5.73)	0.13	0.02
Pars opercularis L	Thick	-37.7	5.6	11.6	<.0005 (3.36)	0.12	0.01
Precuneus L	Thick	-6.4	-53.4	11.4	<.005 (2.99)	0.13	0.02
Precuneus R	Thick	5.5	-59.9	37.4	<.001 (3.05)	0.12	0.01
Postcentral L	Area	-62.8	-11.3	14.2	<.0005 (-3.90)	-0.14	0.02
Occipital lateral R	Area	46.4	-75.7	6.1	<.0005 (-3.44)	-0.12	0.01
Parietal superior R	Area	25.9	-49.9	61.1	<.005 (-2.43)	-0.12	0.01
Anxiety							
Fusiform L	Vol	-26.7	-44.7	-12.3	<.001 (-3.24)	-0.18	0.03
Apathy							
Pars opercularis L	Vol	-37.8	17.0	19.4	<.00001 (5.39)	0.25	0.06
Frontal superior R	Vol	7.0	24.7	51.1	<.0005 (3.99)	0.22	0.05
Temporal superior R	Vol	57.1	0.7	-7.7	<.0005 (3.33)	0.20	0.04
Parietal superior R	Thick	23.0	-58.8	47.1	<.005 (2.89)	0.19	0.04
Insula R	Area	37.1	-8.5	-9.1	<.00001 (5.34)	0.21	0.04
Orbitofrontal medial L	Area	-4.2	43.7	-20.0	<.005 (2.98)	0.18	0.03
Irritability							

Pars opercularis L	Vol	-40.7	8.3	18.6	<.00001 (5.53)	0.14	0.02
Frontal superior R	Vol	16.5	14.7	54.6	<.0001 (4.19)	0.13	0.02
Parietal superior R	Vol	31.8	-42.1	60.6	<.005 (2.80)	0.12	0.01
Frontal pole L	Area	-8.3	56.6	-17.1	<.001 (3.21)	0.12	0.01
Postcentral R 1	Area	21.5	-33.7	54.8	<.005 (2.87)	0.12	0.01
Postcentral R 2	Area	50.8	-9.1	13.1	<.0005 (3.62)	0.13	0.02

Legend. x/y/z = coordinates of the x/y/z axis of the Talairach atlas. L = left, R = right, Vol = cortical volume; Area = cortical surface area; Thick = cortical thickness; PCC R = mean partial correlation coefficient; R^2 = effect size (0.01 = small, 0.09 = medium, 0.25 = large). The log(p) value indicates the level of significance in the regression slope between cortical volume, thickness and surface area relative to NPS severity for each group. The sign indicates the regression direction.

Figure 2.1. Brain clusters associated with NPS in CN group.



Legend. NPS = Neuropsychiatric Symptoms; Agi = Agitation; Dep = Depression; Anx = Anxiety; Apa = Apathy; Irr = Irritability; Vol = Volume; Thick = Thickness.

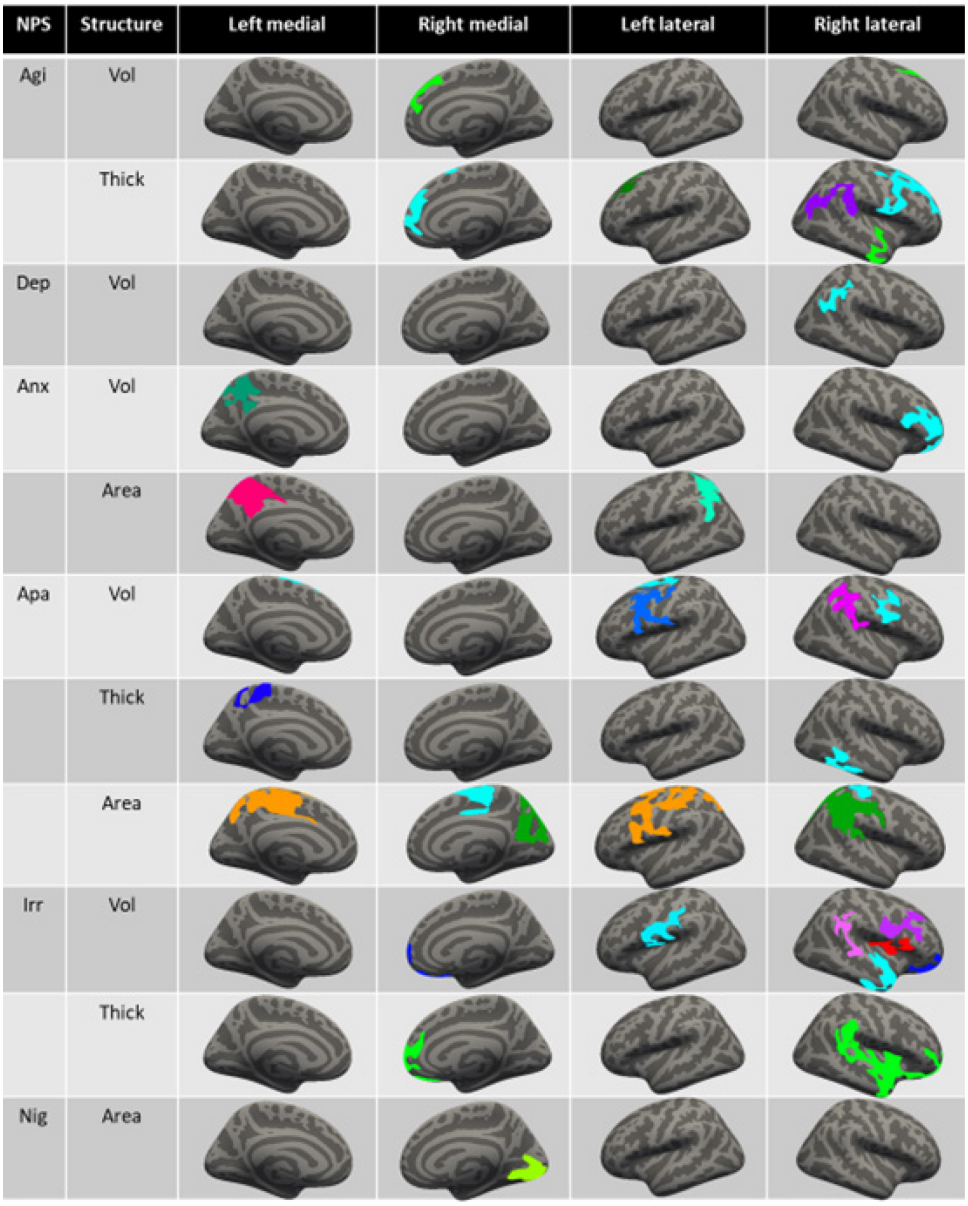
Table 2.3. Regressions between neuropsychiatric severity and cortical brain structures in MCI group (controlled for age, sex and education).

Brain Structure	Measure	Talairach coordinates			p (log(p))	PCC R	R^2
		x	y	z			
Agitation							
Frontal superior R	Vol	7.2	50.7	32.1	<.005 (-2.69)	-0.08	0.01
Frontal superior L	Thick	-15.6	34.6	43.3	<.0005 (-3.51)	-0.09	0.01
Frontal middle caudal R	Thick	39.6	20.4	42.6	<.0005 (-3.50)	-0.08	0.01
Supramarginal R	Thick	59.6	-33.3	33.6	<.0005 (-3.77)	-0.08	0.01
Temporal inferior R	Thick	47.2	-8.7	-25.5	<.0001 (-4.15)	-0.08	0.01
Depression							
Parietal inferior R	Vol	49.5	-58.0	23.8	<.001 (-3.11)	-0.08	0.01
Anxiety							
Cingulate isthmus L	Vol	-8.1	-40.1	31.0	<.0001 (-4.10)	-0.07	<0.01
Parietal inferior L	Area	-30.7	-54.9	37.1	<.0005 (-3.55)	-0.07	<0.01
Precuneus L	Area	-8.2	-46.8	48.1	<.0005 (-3.52)	-0.08	0,01
Frontal middle rostral R	Area	40.0	45.8	2.7	<.005 (-2.40)	-0.06	<0.01
Apathy							
Frontal middle caudal L	Vol	-37.4	8.8	36.3	<.00005 (-4.45)	-0.06	<0.01
Frontal superior L	Vol	-12.0	4.9	62.1	<.001 (-3.29)	-0.06	<0.01
Supramarginal R	Vol	49.9	-41.1	37.5	<.0005 (-3.85)	-0.06	<0.01
Frontal middle caudal R	Vol	38.7	6.2	39.8	<.01 (-2.28)	-0.06	<0.01
Paracentral L	Area	-10.7	-22.7	46.6	<.001 (-3.22)	-0.06	<0.01
Supramarginal R	Area	49.9	-40.2	39.1	<.00005 (-4.97)	-0.07	<0.01
Postcentral R	Area	27.6	-26.3	51.2	<.001 (-3.18)	-0.06	<0.01

Paracentral L	Thick	-15.6	-35.3	50.9	<.05 (2.89)	0.06	<0.01
Temporal middle R	Thick	62.5	-40.6	-4.8	<.0005 (-3.62)	-0.06	<0.01
Irritability							
Precentral L	Vol	-54.5	-0.8	6.9	<.001 (-3.02)	-0.07	<0.01
Orbitofrontal lateral R	Vol	27.9	36.4	-10.2	<.0005 (-3.50)	-0.07	<0.01
Temporal superior R	Vol	43.8	11.5	-21.7	<.0005 (-3.65)	-0.07	<0.01
Frontal middle rostral R	Vol	35.1	29.5	34.7	<.001 (-3.10)	-0.07	<0.01
Supramarginal R	Vol	59.0	-38.9	24.2	<.005 (-2.33)	-0.06	<0.01
Pars opercularis R	Vol	43.0	18.2	7.0	<.001 (-3.02)	-0.07	<0.01
Temporal superior R	Thick	54.0	-5.0	-3.0	<.0001 (-4.02)	-0.07	<0.01
Nighttime behaviors							
Occipital lingual R	Area	10.2	-87.5	-3.2	<.005 (-2.55)	-0.04	<0.01

Legend. x/y/z = coordinates of the x/y/z axis of the Talairach atlas. L = left, R = right, Vol = cortical volume; Area = cortical surface area; Thick = cortical thickness; PCC R = mean partial correlation coefficient; R^2 = effect size (0.01 = small, 0.09 = medium, 0.25 = large). The log(p) value indicates the level of significance in the regression slope between cortical volume, thickness and surface area relative to NPS severity for each group. The sign indicates the regression direction.

Figure 2.2. Brain clusters associated with NPS in MCI group.



Legend: NPS = Neuropsychiatric Symptoms; Agi = Agitation; Dep = Depression; Anx = Anxiety; Apa = Apathy; Irr = Irritability; Nig = Nighttime Behaviors; Vol = Volume; Thick = Thickness.

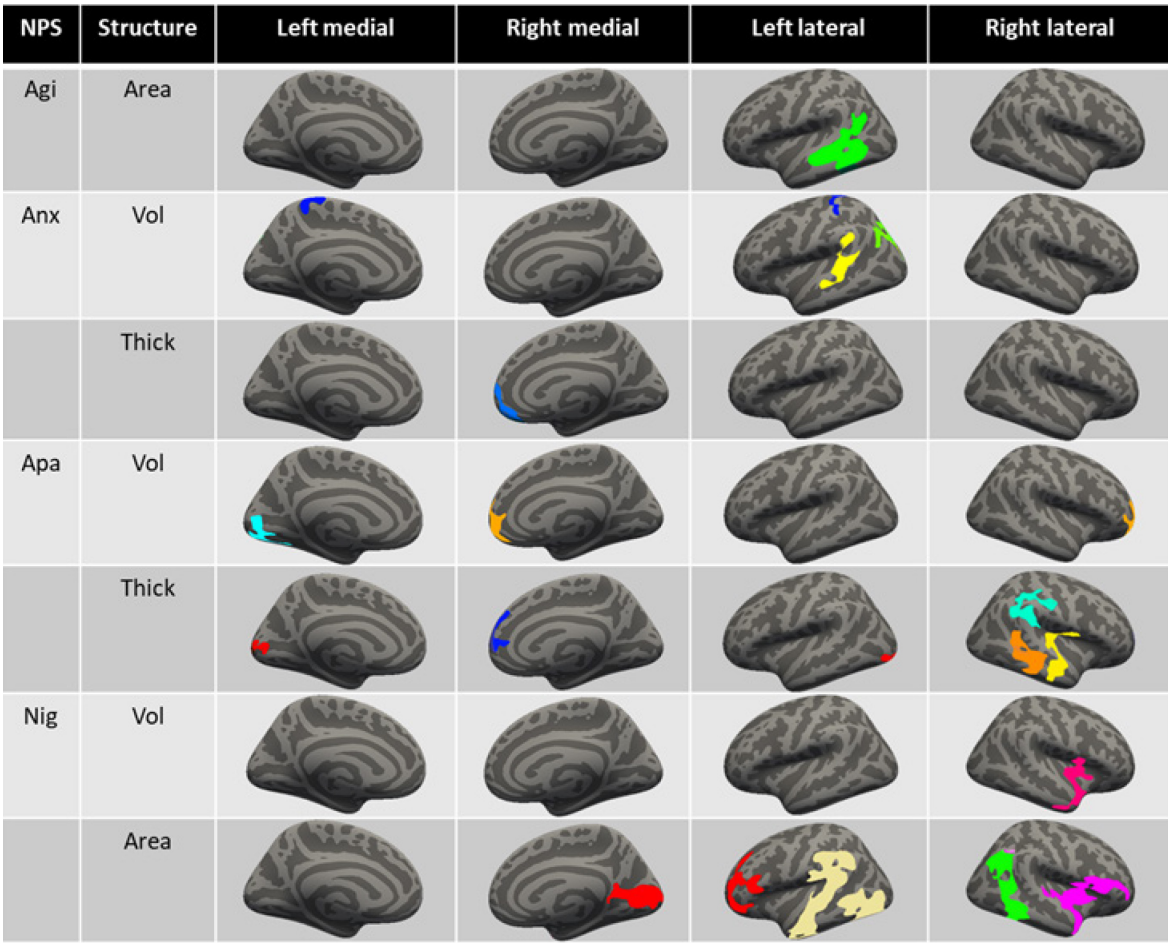
Table 2.4. Regressions between neuropsychiatric severity and cortical brain structures in AD group (controlled for age, sex and education).

Brain Structure	Measure	Talairach coordinates			p (log(p))	PCC R	R^2
		x	y	z			
Agitation							
Temporal superior L	Area	-48.7	-22.8	-4.7	<.001 (3.14)	0.08	0.01
Anxiety							
Parietal superior L	Vol	-26.5	-71.5	19.5	<.01 (2.21)	0.08	0.01
Temporal superior L	Vol	-49.4	-20.9	-5.0	<.005 (2.81)	0.09	0.01
Precentral L	Vol	-8.5	-33.2	61.3	<.001 (3.24)	0.09	0.01
Orbitofrontal medial R	Thick	6.8	50.9	-19.3	<.005 (-2.51)	-0.09	0.01
Apathy							
Frontal middle rostral R	Vol	24.9	50.3	6.0	<.001 (-3.22)	-0.07	<0.01
Occipital lateral L	Vol	-14.1	-87.6	-1.9	<.0005 (3.43)	0.07	<0.01
Occipital lateral L	Thick	-40.9	-81.9	-4.4	<.005 (2.75)	0.07	<0.01
Cingulate anterior caudal L	Thick	-7.0	19.1	26.3	<.001 (-3.09)	-0.07	<0.01
Postcentral R	Thick	52.1	-16.3	33.3	<.0005 (-3.57)	-0.07	<0.01
Temporal middle R	Thick	64.0	-40.1	-2.2	<.0005 (-3.98)	-0.07	<0.01
Insula R	Thick	33.9	-26.8	12.3	<.001 (-3.12)	-0.07	<0.01
Frontal superior R	Thick	10.4	53.4	4.8	<.005 (-2.72)	-0.06	<0.01
Nighttime behaviors							
Precentral R	Vol	42.9	6.7	8.0	<.001 (3.19)	0.11	0.01
Temporal superior L	Area	-61.0	-23.6	-0.4	<.0005 (3.88)	0.11	0.01
Pars triangularis L	Area	-50.0	24.9	4.1	<.005 (2.60)	0.10	0.01
Insula R	Area	37.7	-1.6	2.6	<.0005 (3.51)	0.10	0.01

Parietal inferiori R	Area	47.2	-56.2	25.4	<.005 (2.89)	0.10	0.01
Pericalcarine R	Area	9.4	-73.1	17.0	<.01 (2.01)	0.10	0.01
Orbitofrontal lateral R	Thick	15.7	15.2	-20.1	<.0001 (-4.17)	-0.12	0.01

Legend. x/y/z = coordinates of the x/y/z axis of the Talairach atlas. L = left, R = right, Vol = cortical volume; Area = cortical surface area; Thick = cortical thickness; PCC R = mean partial correlation coefficient; R^2 = effect size (0.01 = small, 0.09 = medium, 0.25 = large). The log(p) value indicates the level of significance in the regression slope between cortical volume, thickness and surface area relative to NPS severity for each group. The sign indicates the regression direction.

Figure 2.3. Brain clusters associated with NPS in AD group.



Legend: NPS = Neuropsychiatric Symptoms; Agi = Agitation; Anx = Anxiety; Apa = Apathy; Nig = Nighttime Behaviors; Vol = Volume; Thick = Thickness.

Subcortical regression analysis

Controlling for age, education, and sex, some associations are revealed between NPS and subcortical volumes.

In CN participants, left hippocampal volume was negatively associated with depression severity (coef = -46.95, p = 0.044, 95CI = [-92.46:-1.44], R^2 = 0.17). The right hippocampal and left putamen volumes were positively associated with the severity of apathy (coef = 79.89, p = 0.039, 95CI = [3.87:155.92], R^2 = 0.18; coef = 108.93, p = 0.040, 95CI = [4.93:212.93], R^2 = 0.08).

In patients with MCI, bilateral caudate volumes were negatively associated with agitation severity (coef = -40,46, p = 0.029, 95CI = [-76.67:-4.25], R^2 = 0.02; coef = -38.77, p = 0.035, 95CI = [-74.89:-2.65], R^2 = 0.02). Left putamen and bilateral pallidum were positively associated with irritability severity (coef = 57.66, p = 0.003, 95CI = [19.16:96.15], R^2 = 0.08; coef = 25.03, p = 0.002, 95CI = [9.43:40.63], R^2 = 0.06; coef = 18.73, p = 0.013, 95CI = [3.89:33.57], R^2 = 0.07).

In patients with AD, right pallidum was positively associated with nighttime behaviors severity (coef = 26.97, p = 0.032, 95CI = [2.39:51.55], R^2 = 0.08), right amygdala was negatively associated with agitation severity (coef = -21.46, p = 0.041, 95CI = [-42.03:-0.89], R^2 = 0.13) and positively associated with irritability severity (coef = 24.55, p = 0.022, 95CI = [3.65:45.46], R^2 = 0.13). Right accumbens area was negatively associated with apathy severity (coef = -8.63, p = 0.004, 95CI = [-14.44:-2.83], R^2 = 0.20).

However, none of these associations were confirmed by the FDR correction.

DISCUSSION

Based on the ADNI database (cohorts 2 and 3), this study aimed to investigate the relationships between neuropsychiatric symptoms assessed with the Neuropsychiatric Inventory and brain morphology (including cortical volumes, areas and thicknesses, and subcortical volumes) in different diagnostic groups (CN, MCI and AD).

It was expected that affective NPS such as depression and anxiety, and hyperactive symptoms such as agitation and irritability share associations with prefrontal, temporal and subcortical

structures (striatum, amygdala and hippocampus), whereas apathy is mainly associated with prefrontal and cingulate morphology. Finally, sleep disturbances would rather be associated with posterior (temporal, occipital), hippocampal, and prefrontal structures. It would also seem that these associations are dependent on the diagnosis (for example, positive associations in participants CN and with MCI, and negative associations in participants with AD).

Our results show discrepancies in associations between the three groups. Agitation showed negative and positive associations in CN participants, involving the inferior parietal and cingulate isthmus on the one hand, and the lingual and superior temporal regions on the other. The associations were only negative in MCI participants and involved the superior frontal, middle caudal, and inferior temporal regions. Finally, a single positive association with the superior temporal region was shown in the AD group. Negative associations with frontal and cingulate regions have also been demonstrated in the literature, including the work of Trzepacz et al. (2013) on ADNI cohort 1, among others[62,166]. However, the previously demonstrated cingulate regions belonged more to the anterior structures whereas our results showed an association with the posterior cingulate[42,147] (Bruen et al., 2008; Tighe et al., 2012). Also, while the amygdala was also negatively associated with agitation in the Trzepacz et al. study, this association only appeared in the AD group and did not survive statistical corrections[62].

Often associated with agitation, irritability also appears to show negative associations with anterior cingulate structures[42]. In this work, positive associations were observed with prefrontal and parietal structures in CN participants, and negative associations with prefrontal, temporal, and parietal structures in participants with MCI. In contrast, no associations were shown in the AD group. Irritability shared only one association with the inferior frontal *pars opercularis* between the CN and MCI groups, with the other associations involving different structures between them despite the involvement of many prefrontal structures (superior frontal and frontopolar in CN, orbitofrontal and middle frontal in MCI). Interestingly, in the AD group, only the amygdala was positively associated with irritability (without confirmation by statistical corrections). Some data may have shown positive associations between NPS and amygdala volume, including apathy, depression, and anxiety, but not with irritability[167].

Despite the more systematic nature of anterior cingulate involvement in apathy, many cortical and subcortical structures were also associated with it. In the CN group, it was positively associated with prefrontal (orbital, inferior, superior), insular, parietal (superior) and temporal (superior) regions. While the lobes involved were similar in the MCI, the associations there were negative and did not involve the same prefrontal (middle, superior), parietal (supramarginal, postcentral), and temporal (middle) structures. Finally, in the AD group, the associations were also negative, except for the lateral occipital gyrus (whose volume increased with apathy, due to an increase in thickness). In addition, the associated regions included the anterior cingulate cortex, superior and middle prefrontal regions, insula, postcentral gyrus and middle temporal. As described in the literature, the anterior cingulate is associated with apathy in AD[39,45,147,148], and other structures could be linked to it such as frontal and temporal regions in both AD and MCI [39,44,45,147,148,166,168]. Subcortical structures have also been highlighted in apathy by the work of Johansson et al. (2020), including hippocampus, nucleus accumbens, thalamus, amygdala and putamen[167]. Our results show a tendency to confirm these findings with a positive relationship with the hippocampus and putamen in CN and a negative relationship with the nucleus accumbens in AD. Similar to Siafarikas et al. (2021), the relationships differed according to the diagnosis of the participants[67].

Regarding depression, results showed negative associations with posterior, parietal, and occipital surfaces, and positive associations of anterior (insula and inferior frontal) and posterior (precuneus) thicknesses in CN participants, whereas in MCI, only an inferior parietal association was revealed. While positive associations with depression have been previously demonstrated, they were more likely to involve the amygdala and superior temporal sulcus[67,167]. Several studies also highlighted the association with signature structures of Alzheimer's disease such as the hippocampus, entorhinal and parahippocampal cortex, middle and inferior temporal gyrus[44,51,53,149,169]. However, the results only showed the involvement of the left hippocampus in the association with depression, and only in the CN participants (non-significance of the result after adjustment). Most studies suggest diffuse, prefrontal and parietal associations in AD. Although our data also indicate diffuse anterior and posterior associations[48,49,52,53], however, they do not involve the same regions outside of the precuneus[49] and were only found in the CN group.

In contrast, the latter relationship was negative. Nour et al. (2020) suggested an involvement of the salience network in depression in MCI, a network involved in the processing of emotions and in the encoding of interoceptive signals from the body's internal milieu that reflect autonomic activity[44]. This network is composed of the anterior cingulate and the insula, among others, and its atrophy seems to be associated with symptoms of anxiety and depression[170]. However, Nour et al (2020) point out that these structures are also significantly correlated with cognitive performance and could be more associated with it than with NPS[44].

Conversely to apathy and depression, anxiety has been more strongly associated with subcortical structures such as the putamen and amygdala[44,55,167], and also unsystematically with temporal, cingulate and parietal cortical structures[44,54,150]. Our results showed similar findings, including associations with inferior parietal and precuneus[150] and posterior cingulate[44] in MCI participants, as well as different associations, including negative with fusiform gyrus in CN participants and medial orbitofrontal cortex in AD, and positive with superior parietal and temporal and precentral regions also in AD.

Finally, nocturnal behaviors were negatively associated with the lingual gyrus in MCI, and the lateral orbitofrontal cortex in AD, and positively associated with the precentral frontal and *pars triangularis*, superior temporal, insular, inferior parietal, and pericalcarine regions in AD. A positive association with the pallidum was also found in AD but this result did not survive the significance adjustment. Other work showed associations with temporal and occipital[151] and insular[152], or global frontal regions in MCI[166]. However, the sleep disturbances, although diverse, were characterized by atrophy and not larger structures.

As mentioned by Lebedeva et al. (2014), the association of similar structures between different symptoms may be due to the overlap between these symptoms such as between depression and apathy in CN participants (positively associated with the inferior frontal *pars opercularis*, superior parietal and insula)[49]. Similarly, the same region may also be involved in different neural networks whose changes may be related to different NPS[49]. The authors also mention possible interactions between NPS and AD that may impact the results. In particular, they mention the example of the default mode network (including precuneus, posterior cingulate cortex and temporal cortex),

shown to have reduced functional connectivity in AD, and increased in patients with depressive disorder[171,172], highlighting the importance of combining structural and functional data in the study of NPS. Considering our results and the associations between these structures and several NPS, it may be that this network, among others, is involved in neuropsychiatric manifestations in aging and AD.

If our results show some variability from previous work, this may stem from the heterogeneity of the stages of AD studied in different studies. As mentioned by Johansson et al. (2020), the involvement of anterior cingulate and frontal structures frequently associated with apathy are from studies conducted with late stages of AD[173,174]. On the contrary, in a study of participants without cognitive impairment or with MCI, apathy was associated with temporal atrophies[175], suggesting that these regions are involved earlier than cingulate regions and thus may contribute to the variability of outcomes between the stages studied. Other studies highlighted subcortical associations with apathy, suggesting the involvement of interconnected networks involving the dorsal anterior cingulate and ventral striatum via involvement of the nucleus accumbens among others[176]. While our data suggested the involvement of the nucleus accumbens in association with apathy in AD, this result was not confirmed by significance adjustments.

Regarding positive associations between NPS and certain structures, Johansson et al. (2020) suggest the possibility of neurostructural adaptations in the early stages of the disease and mention data involving functional activations and volume increases of the amygdala in anxiety while the amygdala seems to reduce in volume in AD[167,177,178].

According to Siafarikas et al. (2021), MCI patients in whom brain structure and function are relatively preserved may be better able to understand and express depressive symptoms, among others, and have more resources to compensate for them[67]. In contrast, AD patients with generally smaller cortex and brain volumes may have lost these abilities. Other explanations can be proposed in relation to the salience network, whose connectivity could be shown to be higher in AD patients with hyperactivity syndrome (agitation, irritability, aberrant motor behavior, euphoria, and disinhibition)[59]. The authors hypothesized that the increased connectivity in these patients led to a misperception of events generating the manifestations of hyperactivity

syndrome. Thus, associations between NPS and brain morphology would change over the course of the disease. However, our data also show positive associations in the AD group, suggesting that either some participants have an early stage of AD or that some covariates not considered here would interact with these relationships.

Strengths and limitations

This study provides insight into the involvement of NPS in the neuroanatomical correlates of AD using a large sample size. These analyses revealed that distinct brain structures were associated with each SNP in participants with AD, MCI, and CN participants, contributing to a better understanding of these symptoms in AD. Our study has several strengths, including the use of the NPI, which is highly validated in several populations, including patients with different neurodegenerative diseases, dementia or MCI, and cognitively intact older adults. Although calculating NPI scores based on frequency x severity multiplication results in asymmetric scores, parametric and nonparametric analyses led to similar results, showing robustness of the scores[135]. Even when performing our whole-brain analyses, we decreased the risk of type I errors using Monte Carlo simulations for a more rigorous correction method and added covariates to the models, which are important methodological strengths.

Our study has some limitations that should be taken into account. First, in the CN group, the NPI scores are globally lower and the presence of NPS is lower than in the other groups, which limits the interpretation and generalization of the results from this group. Some covariates that may influence the size of brain structures and the severity of NPS were not included in the models, such as the duration of the disease or cognitive impairment in AD and MCI, or some biological data that may indicate AD risk in CN or MCI participants, such as APOE status or amyloid PET positivity. Despite the validity of the NPI, some symptoms do not appear to show reproducibility of their anatomical associations between studies[135]. Finally, because our study was cross-sectional, no causal relationship can be concluded from the significant associations. In fact, the observed results could be due to the pathophysiological decline of AD, which is correlated with symptom scores; as the disease progresses, the NPS are more likely to become more severe.

Conversely, it is possible that as the NPS score increases, the decline is greater and, therefore, the likelihood of belonging to the AD group rather than the MCI group is also greater.

CONCLUSION

In a large cohort of the ADNI database, we showed that NPS were mainly impacting cortical associative structures and to a lesser degree the subcortical structures. The influence of NPS was found even in CN participants. However, these impacts differed between groups and between NPS. Notably, positive associations of structure size were found with apathy and irritability in CN participants, with agitation, anxiety and nighttime behaviors in patients with AD. In most cases, NPS showed associations with the structures of different lobes, especially frontal and parietal. These data suggest that some NPS, in addition to occurring early in cognitive decline, may manifest themselves via brain changes. Further longitudinal studies should investigate the cognitive trajectories of CN and MCI participants according to the NPS/brain structure relationships they present.

Declaration of interest : none

Author contributions

Lucas Ronat: Conceptualization; Data curation; Methodology; Statistical analysis; Writing – original draft; Writing - review & editing. **Van-Tien Hoang**: Methodology; Imaging preprocess and process. **Alexandru Hanganu**: Methodology; Imaging preprocess and process; Statistical analysis; data visualization; Writing - review & editing.

ACKNOWLEDGEMENTS

Funding

L. Ronat reports having received a doctoral research scholarship from the IUGM Foundation and a merit scholarship from the Faculty of Medicine of the Université de Montréal. A. Hanganu has received funding from the IUGM Foundation, Parkinson Quebec, Parkinson Canada, FRQS, Lemaire Foundation.

Use of ADNI data

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals

Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Transition

Cette deuxième étude visait à investiguer les relations entre la sévérité des SNP et les structures cérébrales corticales et sous-corticales dans différents échantillons, cognitivement sain, avec un trouble cognitif léger ou un diagnostic de MA. Les résultats montraient que les associations différaient entre les trois groupes et impliquaient essentiellement des structures corticales, à la fois limbiques et associatives, connues pour être impliquées à la fois dans les émotions, l'exécution des comportements et les processus cognitifs. Cela suggère que les SNP sont au moins en partie induits par des modifications cognitives chez les individus.

C'est pourquoi l'étude suivante s'intéressera à l'utilisation des facteurs neuropsychiatriques, neurostructurels et cognitifs dans la prédiction de la conversion du vieillissement normal au TCL, et du TCL à la MA.

Chapitre 3 - Establishing an individualized model of conversion from normal cognition to Alzheimer's Disease after 4 years, based on cognitive, brain morphology and neuropsychiatric characteristics (Published in International Journal of Geriatric Psychiatry)

Running title : Model of conversion from CN to MCI to AD.

Ronat Lucas,[a,b] **Hoang** Van-Tien[a], ADNI group,[*] **Hanganu** Alexandru[a,c]

[a]Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, Montréal, Québec, Canada

[b]Faculté de Médecine, Département de Médecine, Université de Montréal, Québec, Canada

[c]Faculté des Arts et des Sciences, Département de Psychologie, Université de Montréal, Québec, Canada

[*]Alzheimer's Disease Neuroimaging Initiative

Corresponding Author:

Alexandru Hanganu, M6828, 4545 ch. Queen Mary, H3W 1W6, Montréal, QC

Phone: (514) 340-3540 #4897

Mail: alexandru.hanganu@umontreal.ca

Lucas Ronat, M7820, 4545 ch. Queen Mary, H3W 1W6, Montréal, QC

Phone: +1 (438) 408-6806

Mail: lucas.ronat@umontreal.ca

CONFLICT OF INTEREST/DISCLOSURE STATEMENT

The authors have no conflict of interest to report.

Abstract

Objectives: The impact of neuropsychiatric symptoms (NPS) on cognitive performance has been reported, and this impact was better defined in the aging population. Yet the potential of using the impact of NPS on brain and cognitive performance in a longitudinal setting, as prediction of conversion – have remained questionable. This study proposes to establish a predictive model of conversion to Alzheimer's disease (AD) and mild cognitive impairment (MCI) based on current cognitive performance, NPS and their associations with brain morphology.

Methods: 156 participants with MCI from the Alzheimer's Disease Neuroimaging Initiative database cognitively stable after a 4-year follow-up were compared to 119 MCI participants who converted to AD. Each participant underwent a neuropsychological assessment evaluating verbal memory, language, executive and visuospatial functions, a neuropsychiatric inventory evaluation and a 3Tesla MRI. The statistical analyses consisted of 1) baseline comparison between the groups; 2) analysis of covariance model (controlling demographic parameters including functional abilities) to specify the variables that distinguish the two subgroups and; 3) used the significant ANCOVA variables to construct a binary logistic regression model that generates a probability equation to convert to a lower cognitive performance state.

Results: Results showed that MCI who converted to AD in comparison to stable MCI, exhibited a higher NPS prevalence, a lower cognitive performance and a higher number of involved brain structures. Functional abilities, memory performance and the sizes of inferior temporal, hippocampal and amygdala sizes were significant predictors of MCI to AD conversion. We also report two models of conversion that can be implemented on an individual basis for calculating the percentage risk of conversion after 4 years.

Conclusion: These analytical methods might be a good way to anticipate cognitive and brain declines.

Keywords: Neuropsychiatry; cognitive performance; cognitive decline; MRI; Alzheimer's Disease

Key points:

- Low functional abilities are a significant factor of MCI to AD conversion.
- Smaller volumes of inferior temporal region, hippocampus and amygdala are characteristic of MCI to AD conversion.
- Neuropsychiatric symptoms seem to play a diminished role in predicting the conversion from MCI to AD.

Introduction

Clinical states of age-related cognitive decline

Current clinical evaluations of cognitive decline include only two stages: (a) the mild cognitive impairment (MCI) and (b) dementia (or major cognitive impairment). These stages are based on cognitive markers[17,179,180] that are evaluated with comprehensive neuropsychological assessments. One of the leading clinical presentations of dementia is Alzheimer's disease (AD) type[181]. An MCI level that would lead to AD has been characterized by either subjective concern about a change in cognition, or a lower performance in one or more cognitive domains in comparison to those expected for the patient's age and educational background, without significant impairment in social or occupational functioning[17].

On the other hand, in the demented state, cognitive deficits are sufficiently extensive that the individual is no longer able to carry out his or her daily life tasks alone or without supervision. These cognitive stages are frequently accompanied by psychological suffering for participants, relatives and caregivers[182,183] as well as psychological and behavioral disturbances called neuropsychiatric symptoms (NPS)[2].

Neuropsychiatric symptoms in cognitive decline

Most of NPS are clearly observed in dementia[2], but they also occur in the MCI stage[12] and can be present in cognitively healthy individuals[97]. NPS presence was shown to increase the risk of AD in MCI[36]. Indeed, these NPS are found in the cognitively healthy (CH) population[7,97,184], and their prevalence increases with the advancement of clinical stages: it is higher in the MCI population and even higher in the AD population[184]. Also, they may increase the likelihood of MCI progressing into AD[36] and thus increase the likelihood of developing dementia[12]. These include depression[185,186], apathy[187] and anxiety[188–190], but the latter is more controversial[191,192]. However, the impact of depression on cognitive decline is greater in MCI than in AD[193].

In addition, several studies have looked at longitudinal follow-ups of participants and participants with NPS. For example, the study by Moon et al (2017) confirms a greater progression from MCI to AD in participants with depressive symptoms according to the amyloid status of MCI

participants: the study is based on the analysis of longitudinal ADNI data and shows, in MCI participants with amyloid-positive amyloid and depression, a higher rate of AD conversion than participants without depression[194]. In addition, cognitive decline is accelerated over the 2-year follow-up period. Also based on the ADNI database, Zahodne et al. (2013) studied the atrophy pathways of MCI subjects with and without depression and apathy on a longitudinal level. Their results show that depression is associated with greater baseline entorhinal atrophy and accelerated anterior cingulate atrophy[53]. To our knowledge, fewer studies have looked at the factors of conversion from normal cognition to MCI and the course of cognitive decline in healthy individuals. However, these studies were able to highlight that healthy individuals with mild behavioral impairment exhibited greater attentional and working memory decline after one year of follow-up[195]. Also, the presence of NPS, including depression, apathy, and anxiety, is also associated with faster global and domain-specific decline[8,196]. In addition, MRI data were also exploited as predictors of conversion from MCI to AD. Thus, it has been shown that MCI that convert to AD have reduced volumes in the medial temporal lobe (hippocampus, amygdala, and entorhinal cortex), the insular, posterior cingulate, precuneus and orbitofrontal cortex[197–199]. However, these data do not appear to have been addressed in the conversion from CH to MCI. This shows the importance of screening for NPS and to more investigate MRI in CH subjects.

For this study, we hypothesized that (1) participants who convert to a lower cognitive performance state would exhibit increased variation in NPS; (2) these variations would be associated with brain morphology and cognitive performance; and (3) these correlations can be used to predict the conversion.

The purpose of this work is to propose probabilistic models for predicting conversion to Alzheimer's disease in participants with MCI, and conversion to MCI in CH participants. From a clinical perspective, the construction of models with good psychometric characteristics would allow to estimate, for an individual evaluated in a clinical context, an objective probability of conversion.

Materials and Methods

Participants

275 participants with MCI and 185 cognitively healthy participants (CH) from the ADNI database were extracted. Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI, launched in 2003 and led by Principal Investigator Michael W. Weiner, MD, has for main objective to understand the progression of MCI and early AD by combining imaging, biological and neuropsychological data[113,114] (http://www.adni-info.org/). Entry criteria for participants with amnestic MCI include a Mini-Mental State Examination score of 24 to 30 and a Memory Box score of at least 0.5, whereas other details on the ADNI cohort can be found online. All participants with AD met National Institute of Neurological and Communication Disorders/Alzheimer's Disease and Related Disorders Association criteria for probable AD with a Mini-Mental State Examination score between 20 and 26, a global Clinical Dementia Rating of 0.5 or 1, a sum-of-boxes Clinical Dementia Rating of 1.0 to 9.0, and, therefore, are only mildly impaired. Exclusion criteria at baseline and follow-up included any serious neurological disease or neurodegenerative disease other than possible AD, any history of brain lesions or head trauma, or psychoactive medication use (including antidepressants, neuroleptics, chronic anxiolytics, or sedative hypnotics).

Sample size is dependent on participants completing a neuropsychiatric examination, a comprehensive neuropsychological assessment, a 3 Tesla MRI and having a change in diagnosis available (MCI to AD or CH to MCI). Participants whose change in diagnosis was remittent (e.g., MCI to CH, AD to CH) were not included nor were CH participants converting to AD because of their too low prevalence.

The clinical status was available until 4-years follow-up for all participants. Based on the clinical stage at follow-up, four groups were created in order to distinguish participants who converted to a worse cognitive performance compared to those that maintained their previous cognitive level. Our groups consisted of: 156 MCI remained MCI at follow-up (MCI-non-converted), 119 MCI

participants that converted to AD (MCI-converted), 170 CH both at baseline and at follow-up (CH-non-converted) and 15 CH that converted to MCI (CH-converted) (Table 1). As mentioned above, others neurological diagnosis or conversions were not considered.

Data acquisition and processing

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012).

The neuropsychiatric changes were evaluated using the Neuropsychiatric Inventory[2]. The inventory consists of the evaluation of the presence, severity and frequency of 12 neuropsychiatric symptoms (NPS): delusions, hallucinations, agitation/aggressiveness, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviors, nighttime behaviors and appetite changes. We included the evaluations performed by the participants' relatives and only the prevalence of each NPS is considered.

Neuropsychological assessment was based on the tests assessing: (1) anterograde verbal memory (Rey Auditory Verbal Learning Test - RAVLT), (2) focused attention (Trail Making Test A - TMTA), (2) processing speed (Wechsler Adult Intelligence Scale Code subtest), (3) mental flexibility (Trail Making Test B - TMTB), (4) visuoconstructive planning (clock test), (5) working memory (digit span), (6) semantic lexical evocation (animal and vegetable fluency) and (7) oral naming (Boston Naming Test - BNT). Moreover, the Mini-Mental State Examination score was used as a demographic factor of global cognitive efficiency.

MRI structural images were processed with FreeSurfer 7.1.1 software, on Linux Centos 7 on ComputeCanada environment, cluster Cedar and managed with our in-house pipeline (github.com/alexhanganu/nimb) that allowed automated exclusion of post-processed data with errors as well as extraction of statistical data, diminishing potential human error. Cortical thickness parameter was extracted based on the Destrieux et al. atlas (2010) while subcortical volumes were extracted for all regions as well as sub-regional based on the corresponding

atlases[200]; for the thalamus[201], amygdalas[202], and hippocampi[203]. The volumes of subcortical structures were corrected with the estimated Total Intracranial Volume (eTIV)[204].

Also, in order to consider and control the risk of neuropsychiatric symptoms due to difficulties in performing daily activities, the Functional Assessment Questionnaire (FAQ) score was compared between groups and included as a covariate in case of significant difference between groups.

Statistical analysis

The statistical analyses are based on the methodology of Orso et al. (2020)[205]. For this study, the data were analyzed using SPSS version 26.0 software. Descriptive analyses verified the similarity of the groups (MCI-converted vs. MCI-non-converted; CH-converted vs. CH-non-converted) in terms of age, years of education, MMSE score, FAQ and sex distribution (respectively mean comparisons by Student test and contingency Chi² analysis). Statistical analysis consisted of three steps. (I) First, the groups were compared based on (i) means of cognitive performances (Two sample t-tests), (ii) prevalence of NPS (Chi² tests) and (iii) means of neuroimaging structure sizes (Student t-tests of cortical thickness and subcortical volumes). (II) Features that were shown to be significant in the first three comparisons, were included in the Analysis of Covariance Model with age, sex, years of education, FAQ and MMSE scores as covariates. (III) Finally, features that were deemed significant in the ANCOVA model were imputed in a two binary logistic regression model to generate probability equations for AD and MCI conversion based on neuropsychiatric, cognitive and neuroimaging data.

Results

Demographical, neuropsychiatric and neuropsychological differences

At baseline, in comparison to MCI-non-converted, the MCI-converted group had a lower MMSE and higher FAQ scores, worse performance on some cognitive tests (clock test, RAVLT immediate recall A and B, RAVLT delayed recall, semantic lexical evocation for "vegetables", TMT A and B,

WAIS code) and a significantly higher prevalence of agitation and appetite changes (Table 1 near here).

On the other hand, the CH-converted and CH-non-converted groups showed similar results regarding age, years of education, sex distribution, MMSE and FAQ scores as well as distributions of neuropsychiatric symptoms. Several significant differences were depicted in the cognitive performance at baseline, with the CH-converted group having a worse performance in comparison to CH-non-converted on RAVLT 2nd recall, digit span backward and semantic lexical evocation of "vegetables".

Brain morphology differences

Considering the large number of structures compared between the converted vs. non-converted groups, the results for MCI and CH are summarized in Supplementary Tables 1 and 2 respectively. Briefly, the MCI-converted group showed multiple significant difference in comparison to the MCI-non-converted one. Significant changes were depicted in all brain lobes both on the cortical level in gyri and sulci as well as regarding the volumes of subcortical structures, notably the volumes of hippocampus, amygdala and thalamus subregions (Supplementary table 1).

By contrast, the CH-converted group exhibited smaller frontal inferior orbital gyrus and suborbital sulcus, cingulate ventral posterior gyrus, temporal pole and temporal middle gyrus thicknesses and some hippocampal, amygdala and thalamic subregions volumes than CH-non-converted group (Supplementary table 2).

ANCOVA model

After controlling for age, sex, years of education, FAQ and MMSE scores as covariates, ANCOVA showed a significantly lower performance in MCI-converted for every score of the RAVLT than in MCI-non-converted. Conversion interacted with agitation on the recall of the B-list of the RAVLT (non-converted with agitation perform better than those without while the opposite trend is present in converted)(Supplementary table 3). By contrast, the CH-converted group exhibited significantly lower performance on the 2nd recall of the RAVLT and in semantic lexical evocation of "vegetables" than CH-non-converted (Supplementary table 4).

Regarding brain structures, most of the structures (all lobes [except insula], hippocampi and amygdala) were smaller in MCI-converted than in MCI-non-converted. Presence of agitation was featured by greater cortical thicknesses (frontal, parietal, occipital, temporal) and subcortical volumes (hippocampus and amygdala) whereas appetite changes were featured by precentral and lingual thinning and larger hippocampus and amygdala volumes (Supplementary Table 3). An interaction effect between conversion and agitation showed a greater thickness in the MCI-converted with agitation than in those without agitation, while the opposite difference is found in the non-converted, at the inferior occipital, intraparietal, left parieto-occipital, right middle temporal and bilateral precentral levels. The opposite effect was found in the left subcallosal gyrus. Another interaction effect between conversion and appetite changes showed thinning in MCI-converts with appetite changes compared to those without, whereas the opposite pattern was found in non-converted, at the bilateral superior parietal, precuneus, subparietal, left intraparietal, right lingual and parieto-occipital structures (Supplementary table 3). In CH-converted, the previous structures (Supplementary table 2) remained significantly smaller than in CH-non-converted, except for the central lateral and paratenial thalamic nuclei (Supplementary table 4).

Prediction of AD from MCI and MCI from CH based on logistic regression

Binary logistic regression models (Tables 2, 3 near here) based on the significant results of the ANCOVA models provided probabilistic prediction equations for conversion of MCI participants to AD and CH participants to MCI.

The probability equation for an MCI participant to convert to AD is sustained by age, the FAQ score, the RAVLT 1st immediate recall score, the RAVLT 5th immediate recall score, the right inferior temporal gyrus thickness, the right molecular layer of the right hippocampus body volume, and the left amygdala accessory basal nucleus volume. The model had a sensitivity of 73,1%, specificity of 83,3% (Tables 3) and Yule Q coefficient indicating a very strong link between the diagnosis and the clinical characteristics.

Then, the probability equation for a CH participant to convert to MCI is sustained by age, the semantic lexical evocation for “vegetables” performance, the right subiculum body volume, and

the left medial pulvinar thalamic nucleus volume. The models were characterized by a sensitivity and specificity of 6.7% and 99.4% a (Table 5) and Yule Q coefficient was 0.85 indicating a very strong link between the diagnosis and the clinical characteristics (Tables 4, 5 near here).

Discussion

Our results show that (1) participants with MCI and CH who maintain their cognitive performance at the 4 years follow-up, tend to exhibited (i) a lower NPS prevalence (for MCI), (ii) a higher cognitive performance and (iii) a lower number of involved brain structures; (2) none of the NPS have potential of predicting MCI participants who might convert in AD over 4 years when considering functional abilities score; (3) from all cognitive performance tests, only poorer mnesic performances seems to predict MCI who convert to AD over 4 years, and only language performance might predict CH who convert to MCI over 4 years; (4) brain regions that seem to have the highest relevance in predicting conversion over 4 years, seem to be the hippocampus, amygdala, and temporal inferior in the case of MCI participants, and hippocampus and thalamus in the case of CH participants.

It was expected that agitation and appetite changes would be involved in predicting MCI to AD conversion. Indeed, agitation along with appetite changes first appeared to have a significant higher prevalence in the MCI-converted group. Previous studies also outlined this potential trend by reporting agitation a precursor to future AD development[12,36,206,207] and a sign in MCI participants that would correspond to an early AD diagnosis[23]. Yet no specific link was reported regarding appetite changes. However, these implications were not significant when functional abilities were considered. This suggests that in this sample of MCI participants, the NPS are at least partly explained by the reduction in functional abilities. Furthermore, the involvement of other NPS has been reported: depression, anxiety, apathy, irritability, psychotic symptoms. Though in our model these NPS did not survive the significant threshold for the prevalence, nor did they appear in the prediction model, they did show a non-significant up to double increase in prevalence. Whereas several studies have been able to describe that the presence of NPS in CH increased the risk of conversion to MCI[97,185–188], our results did not show any difference between the CH-converted group in comparison to CH-non-converted.

Cognitively, our results show lower verbal mnesic performance and semantic lexical evocation in MCI-converted vs. MCI-non-converted. Interestingly, we do not find executive weaknesses in MCI-converted although these deficits are frequent in MCI in relation to NPS (Rosenberg et al. 2011) as well as in AD[208]. In addition, mnesic difficulties occur much earlier than the diagnosis of AD in comparison to executive difficulties[208]. The CH-converted vs. CH-non-converted showed worse verbal mnesic, working memory and semantic lexical evocation performance. These performances remains within the populational norms but they can probably be cognitive fragilities and signs of a beginning of cognitive decline, potentially in line with subjective cognitive complaints, not objectified by the neuropsychological tests[209–211]. As such, only verbal memory performance remained significantly involved in predicting conversion to AD and to MCI in our logistic regression models.

Regarding this significant role of memory performance, this is in line with the results of Baerresen et al. (2015)[212]. The use of this type of model, with predictive purposes, is more frequent in recent years and could be applied in individuals with non-amnestic MCI[193], MCI due to Parkinson's disease[213] [46] or even multiple sclerosis[214]. Unfortunately, these studies do not systematically mention the reliability criteria of their models.

Concerning brain difference between MCI-converted and MCI-non-converted, brain characteristics were broader and involve cortical structures of all lobes and subcortical regions of the hippocampus and amygdala. This suggests that diffuse cerebral frailties may already be present at the MCI stage, prior to the diagnosis of AD. However, only right temporal inferior, right hippocampus and right amygdala remained significantly predictive of conversion in the logistic regression model. Other studies have also shown cortical thinning of several lobes in MCI participants and even more so in AD, with a more important involvement of the left hemisphere[215,216]. The opposite asymmetry was found in our data.

When analyzing specific brain changes from the perspective of involved NPS (agitation and appetite changes) and their potential to influence the brain in MCI-converted participants, previous studies showed that agitation was characterized by insular, superior frontal, middle, orbital, parieto-occipital, hippocampal, and amygdala atrophies in MCI[62,217,218]. Furthermore,

these atrophies were broadly similar between MCI and AD participants. Our data comparing the effect of agitation in converters and non-converters showed occipital, cingulate, precentral, intraparietal, and temporal involvement in conversion. Note that the interaction between conversion status and agitation revealed that converters with agitation had thicker cortical structures than converters without agitation, whereas the opposite association were found in non-converters. This might suggest that the underlying physiological processes are not the same (e.g., atrophy vs. compensation or inflammation). According to Bateman et al. (2020), pro-inflammatory vs. anti-inflammatory processes have respectively a positive and negative correlation with agitation in AD. Since the increase in brain structures here is only observed in our converted group, we should look at the age of the agitation[219]. It could be assumed that in the converted group, agitation is older and could have allowed the development of inflammatory processes.

Interestingly, appetite changes seem more prevalent in MCI converted in AD than in non-converted but them were also not retained by regression models as significant factor who predict the conversion. Frequently, these behavioral changes are mainly associated with posterior structures. Particularly, them have been described in participants with posterior cortical atrophy but associated with posterior structures also in typical AD[220], indicating that posterior brain damage is not specific to these disorders. Overall, these are understudied disorders and often dependent on other NPS such as anxiety or depression[221,222]. This makes these disorders more complicated to study, especially on a neuroanatomical level.

In the CH to MCI conversion, the poorer performance in memory suggested that the brain structures involved in memory would be reduced in people who convert to MCI. However, the cortical and subcortical structures involved appear to be broader and involved in emotional (cingular, amygdala, frontal orbital), memory (temporal, hippocampus) and multimodal functions (thalamus). According to regression model, smaller volumes in the right hippocampus and the left thalamus predicted better the conversion to MCI. Previous studies that have looked at brain differences have focused on comparisons between CH individuals and individuals with MCI. These studies showed reductions in hippocampal, entorhinal and parahippocampal cortex volumes[223,224] and were supported by other studies showing cortical thinning in healthy

participants with subjective cognitive impairment compared to participants without, in hippocampal, parahippocampal, amygdala, entorhinal, fusiform, posterior cingulate, and inferior parietal regions[225–227]. These reductions may have been associated with poorer performance in verbal memory[225].

To our knowledge, most studies have focused on regions of interest known to be involved in AD, whereas our study looked at the entire cortex and subcortical structures. Furthermore, our results may suggest brain changes that precede medial temporal damage, which is usually considered as an anatomical precursor of cognitive decline due to AD.

Because the risk of developing MCI was dependent on certain demographic data, we chose to include them in the regression model, whereas these variables were controlled in the ANCOVA model to isolate differences related to cognitive performance and brain structure size. Other analyses, on other databases, should also consider the systematic presence of SMC in CH individuals, as well as the presence of symptoms related to awareness of changes and difficulties (anosognosia and/or anosodiaphoria). Alternatively, if our results do not show neuropsychiatric differences in CH-converted, this may suggest the existence of "subjective behavioral complaints" that would precede the objectification of a mild behavioral disorder, as described by Ismail et al. (2016, 2017), in analogy to the stages of cognitive decline model[31,228].

This study should be viewed in light of several limitations. First, in the AD conversion model, the duration of cognitive impairment was not available in the extracted data. Due to this limitation, it cannot be excluded that some MCI participants who converted to AD, had the longest duration of impairment. Another limitation of this study concerns the small proportion of CH individuals who convert to MCI[31,228], correspondingly, this small sample cannot be representative of this population limiting our understanding regarding potential factors involved in conversion to MCI. Finally, our model did not consider the socioeconomic aspect that may influence NPS, such as marital status, residential patterns, accompanied housemate, unemployment, or family income, as suggested by previous studies[229–231].

The generalizability of our results refers to the possibility of its implementation in a clinical setting and on an individual basis, in order to calculate the predictive value of the risk of cognitive decline

after 4 years, especially in individuals with such complaints. After the corresponding parameters are being quantified, the probability of conversion can be calculated using the equation: P(event) = $1/(1+e^{-[\beta1*X1+ \beta2*X2+ \beta3*X3+...+ \beta n*Xn+constant)}$. The regression tables (Table 2 and 4) provide the β coefficients of each significant variable in the model and the X values are the individual-specific values quantified using corresponding tests and MRI data. For example, the equation for conversion from MCI to AD after 4 years is P(AD) = $1/(1+e^{-[-0,071*X1+0,084*X2-0,300*X3-0,199*X4-2,800*X5-23741,592*X6-19389,102*X7+20,115]}$) where e = 2,71828 (the base of natural logarithm), X1 = Age, X2 = the FAQ score, X3 = the RAVLT 1st immediate recall score, X4 = the RAVLT 5th immediate recall score, X5 = the right inferior temporal gyrus thickness, X6 = the right hippocampal tail volume, X7 = the right amygdala accessory basal nucleus volume and 20,115 is the model's constant. A 70-year-old individual with MCI, a FAQ score of 10, RAVLT scores of 3 and 5, and structure values of 2.5, 0.0002, and 0.0001 would have a 60% probability of converting to AD after 4 years (Odds Ratio = 1.50). The data obtained from the calculation of each equation allows us to estimate, from the data of a given individual, the percentage risk of conversion of this individual.

Conclusion

Research on the preclinical stages of AD is frequent and focuses on different diagnostic criteria and risk factors. As far as we know, our study is one of the first to apply these types of models with MCI and CH individuals using both neuropsychiatric, cognitive and neuromorphological data. We proposed to distinguish MCI and CH participants who convert to AD and MCI, respectively, after 4 years of follow-up from the ADNI database. We were able to establish two predictive models to distinguish participants evolving to a more severe clinical stage. The conversion from MCI to AD was characterized by the presence of agitation, lower memory performance and smaller volumes of inferior temporal, hippocampal and amygdala brain structures, whereas the conversion from CH to MCI was characterized by lower performance on semantic evocation and smaller volumes of hippocampal and thalamic brain structures. From a clinical perspective, the construction of models with good psychometric characteristics would allow to estimate, for an individual evaluated in a clinical context, an objective probability of conversion and to anticipate cognitive and brain declines thanks to cognitive, family or social care and support.

Data Availability Statement

All data are available on the ADNI websites upon demand (http://adni.loni.usc.edu/data-samples/access-data/).

Acknowledgements

Funding

This work was supported by the doctoral research scholarship Centre de Recherche de l'Institut Universitaire de Gériatrie Montréal (CRIUGM)-Volet B in collaboration with NiEmoLab; a Faculty of Medicine of the Université de Montréal merit scholarship in collaboration with NiEmoLab; funding from the Parkinson Canada-Parkinson Quebec (2018-00355); IUGM Foundation; Fonds de Recherche du Québec Santé; Lemaire Foundation.

Use of ADNI data

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the

National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for NeuroImaging at the University of Southern California.

Disclosure statement

The authors report there are no competing interests to declare.

Tables

Table 3.1. Demographic, neuropsychiatric and neuropsychological characteristics for MCI and CH groups (non-converted and converted).

	MCI				CH			
	Non-converted	Converted	T/Chi²	P	Non-converted	Converted	T/Chi²	p
N	156	119			170	15		
Demographic (mean/sd)								
Age	75.07/7.75	74.54/7.52	0.572	0.568	75.41/4.92	74.00/5.28	1.06	0.291
Education	15.55/3.07	15.93/2.81	-1.060	0.290	16.15/2.81	16.07/2.84	0.114	0.909
Sex (% women)	39.1	35.3	0.418	0.518	48.8	40	0.430	0.512
MMSE	27.51/1.73	26.87/1.67	**3.125**	**0.002**	29.12/1.00	28.67/1.50	1.598	0.112
FAQ	2,72/3,83	5,75/5,22	**-5.329**	**0.000**	0,06/0,33	0,73/1,71	-1.512	0.153
NPS (%)								
Delusion	0	0.8	1.316	0.251	0	0	-	-
Hallucination	0	0.8	1.316	0.251	0.6	0	0.089	0.766
Agitation	12.8	26.9	**8.716**	**0.003**	3.5	0	0.547	0.459
Depression	14.7	21.8	2.327	0.127	4.7	0	0.738	0.390
Anxiety	16.0	21.0	1.127	0.288	3.5	6.7	0.373	0.542
Euphoria	3.2	3.4	0.005	0.942	0	0	-	-
Apathy	10.9	15.1	1.087	0.297	1.8	0	0.269	0.604
Disinhibition	5.1	9.2	1.778	0.182	0.6	0	0.089	0.766
Irritability	27.6	30.3	0.238	0.625	7.1	6.7	0.003	0.955
AMB	4.5	4.2	0.013	0.909	0.6	0	0.089	0.766
Nighttime behavior	12.2	13.4	0.097	0.755	9.4	20	1.677	0.195
Appetite changes	7.7	15.1	**3.838**	**0.050**	0.6	0	0.089	0.766
Cognitive Assess. (mean/sd)								
Clock drawing	4.43/0.76	4.13/1.05	**2.781**	**0.008**	4.71/0.59	4.60/0.74	0.650	0.516
Clock copy	4.76/0.49	4.61/0.69	1.924	0.056	4.89/0.35	4.67/0.82	1.043	0.314
RAVLT 1	4.62/1.64	3.76/1.26	**4.902**	**0.000**	5.18/1.61	4.73/1.03	1.047	0.296
RAVLT 2	6.10/2.06	5.00/1.48	**5.173**	**0.000**	7.72/1.97	6.60/1.18	**2.162**	**0.032**
RAVLT 3	7.24/2.32	5.90/1.53	**5.781**	**0.000**	9.44/2.32	8.53/2.59	1.429	0.155
RAVLT 4	7.77/2.54	6.27/1.54	**6.052**	**0.000**	10.54/2.38	9.33/2.61	1.860	0.065
RAVLT 5	8.47/2.67	6.64/2.00	**6.514**	**0.000**	11.18/2.24	10.53/2.62	1.061	0.290
RAVLT 6	4.79/3.58	2.55/2.08	**6.511**	**0.000**	8.39/3.44	7.07/2.63	1.456	0.147
RAVLT B	3.96/1.59	3.40/1.32	**3.103**	**0.002**	5.05/1.68	4.87/2.80	0.386	0.700
DS Forward	8.34/2.06	8.32/1.99	0.083	0.934	8.88/2.02	8.13/1.96	1.378	0.170
DS Backward	6.41/2.14	6.10/1.82	1.296	0.196	7.25/2.17	6.27/1.22	1.721	0.087
Animals	16.52/4.68	15.70/4.86	1.419	0.157	20.16/5.56	18.73/5.84	0.948	0.344
Vegetables	11.64/3.38	10.04/3.31	**3.922**	**0.000**	14.91/3.70	12.80/3.86	**2.114**	**0.036**
TMTA	40.72/17.02	48.76/26.19	**-2.912**	**0.004**	35.91/12.97	37.20/12.23	-0.370	0.712
TMTB	110.31/59.47	143.44/78.24	**-3.848**	**0.000**	86.12/43.96	91.20/26.92	-0.440	0.661
Symbol Digit	39.75/11.00	35.15/10.72	**3.473**	**0.001**	46.20/10.34	43.47/6.96	1.003	0.317
BNT	26.17/3.55	25.50/3.90	1.487	0.138	27.88/2.31	27.80/2.18	0.133	0.894
RAVLT Del.	3.90/3.70	1.55/2.30	**6.470**	**0.000**	7.73/3.62	6.07/3.67	1.703	0.090
RAVLT tot	10.63/3.32	8.58/3.83	**4.736**	**0.000**	12.98/2.44	12.40/2.10	0.886	0.377

Legend: sd = standard deviation, MMSE = MiniMental State Examination, FAQ = Functional Assessment Questionnaire, NPS = Neuropsychiatric Symptoms, RAVLT = Rey Auditory Verbal Learning Test (free recall 1 to 6, list B and delayed), DS = Digit Span, TMT = Trail Making Test, BNT = Boston Naming Test. **Bold values** = significant results.

Table 3.2. Binary Logistic Regression for the conversion from MCI to AD after 4 years.

Variables	β	Sig.	Exp(B)	95% Confidence Interval	
Age	-0,071	0,001	0,932	0,892	0,973
FAQ	0,084	0,012	1,088	1,019	1,162
Free recall 1 of RAVLT	-0,3	0,012	0,741	0,587	0,936
Free recall 5 of RAVLT	-0,199	0,007	0,82	0,709	0,948
Temporal inferior gyrus right	-2,8	0,001	0,061	0,011	0,34
Hippocampus tail right	-23741,592	0,009	0	0	0
Amygdala Accessory Basal nucleus right	-19389,102	0,006	0	0	0
Constante	20,115	0	5,44E+08		

Legend: β = Coefficient from each significant variable, Sig. = Significancy, FAQ = Functional Assessment Questionnaire

Table 3.3. Psychometric characteristics for regression model of the conversion from MCI to AD.

		Prediction		
		MCI	To AD	Correct Prediction
Observed	MCI	130	26	83.3(Spe.)
	To AD	32	87	73.1(Sens.)
Accuracy				78.9
Positive predictive value				76.99
Negative predictive value				80.25
Yule Q coefficient				0.86

Legend: Spe. = Specificity, Sens. = Sensitivity

Table 3.4. Variables significantly involved in predicting conversion from CH to MCI after 4 years.

Variables	β	Sig.	Exp(B)	95% Confidence Interval	
Age	-0,153	0,027	0,858	0,75	0,982
Semantic lexical evocation « vegetables »	-0,194	0,036	0,824	0,687	0,988
Hippocampus, subiculum body, right	-50786,249	0,011	0	0	0
Thalamus, pulvinar medial, left	-18793,242	0,001	0	0	0
Constante	30,892	0	2.608E+13		

Legend: β = Coefficient from each significant variable, Sig. = Significancy.

Table 3.5. Psychometric characteristics for regression model of the conversion from CH to MCI.

		Prediction		
		CH	To MCI	Correct Prediction
Observed	CH	169	1	99.4(Spe.)
	To MCI	14	1	6.7(Sens.)
Accuracy				91.9
Positive predictive value				50%
Negative predictive value				92.35
Yule Q coefficient				0.85

Legend: Spe. = Specificity, Sens. = Sensitivity

Supplementary Table

Supplementary Table 1 : Structural differences between MCI-non-converted vs MCI-converted.

Lobe	Structure	Left t	Left p	Right t	Right p
Frontal	superior gyrus	2,465	0,014	-	-
	superior sulcus	2,544	0,011	-	-
	middle gyrus	3,337	0,001	2,491	0,013
	middle sulcus	2,705	0,007	-	-
	inferior sulcus	3,806	0,000	1,963	0,051
	rectus gyrus	1,964	0,051	2,630	0,009
	precentral inferior part sulcus	2,319	0,021	2,041	0,042
	pole transverse gyrus and sulcus	3,764	0,000	3,517	0,001
	marginal gyrus and sulcus	2,760	0,006	3,173	0,002
	Inferior opercularis gyrus	3,049	0,003	2,511	0,013
	inferior triangularis gyrus	-	-	2,056	0,041
	inferior orbital gyrus	-	-	2,667	0,008
	orbital H shaped sulcus	1,987	0,048	-	-
	orbital medial olfactive sulcus	-	-	2,998	0,003
Occipital	superior transversal sulcus	3,024	0,003	-	-
	middle gyrus	3,470	0,001	2,268	0,024
	middle lunatus sulcus	2,075	0,039	-	-
	inferior gyrus and sulcus	2,087	0,038	-	-
	anterior sulcus	2,061	0,040	-	-
	calcarine sulcus	2,469	0,014	2,247	0,025
	occipito-temporal lateral sulcus	3,553	0,000	2,919	0,004
	occipito-temporal medial lingual sulcus	3,005	0,003	3,926	0,000
Cingulate	anterior gyrus and sulcus	2,003	0,046	-	-
	posterior dorsal gyrus	4,130	0,000	4,316	0,000
	posterior ventral gyrus	3,267	0,001	3,772	0,000
	subcallosal gyrus	2,810	0,005	2,646	0,009
	mid Posterior gyrus and sulcus	-	-	2,711	0,007
Insula	circular superior Sulcus	-	-	2,845	0,005
	circular inferior Sulcus	3,726	0,000	3,557	0,000
	circular anterior Sulcus	2,010	0,045	-	-
	long insular gyrus and central sulcus	4,136	0,000	3,681	0,000
	short gyrus	3,320	0,001	-	-
Parietal	superior gyrus	2,417	0,016	2,565	0,011
	inferior angular gyrus	4,439	0,000	3,807	0,000
	inferior supramar gyrus	4,561	0,000	2,880	0,004
	precuneus gyrus	4,092	0,000	3,807	0,000
	Jensen sulcus	3,535	0,000	2,933	0,004
	intraparietal sulcus	3,486	0,001	2,869	0,004
	parieto-occipital sulcus	3,026	0,003	2,613	0,009
	subparietal sulcus	2,664	0,008	3,506	0,001
Temporal	superior lateral gyrus	3,816	0,000	2,580	0,010
	superior planum polare gyrus	3,872	0,000	3,676	0,000
	superior planum temporale gyrus	3,427	0,001	2,832	0,005
	superior sulcus	4,647	0,000	4,287	0,000
	middle gyrus	4,677	0,000	5,275	0,000
	inferior gyrus	4,107	0,000	5,558	0,000
	inferior sulcus	4,527	0,000	5,873	0,000
	lateral fusiform gyrus	3,726	0,000	3,595	0,000
	medial parahippocampal gyrus	3,366	0,001	4,141	0,000
	pole	4,045	0,000	3,617	0,000
	lateral fissure posterior	-	-	3,116	0,002
	collateral transverse anterior sulcus	-	-	2,253	0,025
	collateral transverse posterior sulcus	-	-	2,759	0,006
Hippocampus	whole	5,708	0,000	5,815	0,000
	whole head	5,620	0,000	5,032	0,000
	whole body	5,137	0,000	5,659	0,000
	presubiculum head	4,870	0,000	4,649	0,000
	presubiculum body	2,910	0,004	3,787	0,000
	subiculum head	4,493	0,000	4,019	0,000
	subiculum body	4,262	0,000	5,168	0,000
	ca1 head	4,965	0,000	4,461	0,000
	ca1 body	3,083	0,002	3,600	0,000
	ca3 head	4,533	0,000	3,960	0,000
	ca3 body	4,544	0,000	4,800	0,000
	ca4 head	5,172	0,000	4,546	0,000
	ca4 body	4,498	0,000	5,053	0,000
	hata	4,450	0,000	4,097	0,000
	fimbria	4,243	0,000	3,284	0,001
	molecular Layer head	5,599	0,000	5,203	0,000
	molecular Layer body	5,122	0,000	6,025	0,000
	gcmldg head	5,271	0,000	4,713	0,000
	gcmldg body	4,654	0,000	5,019	0,000
	tail	4,303	0,000	5,562	0,000
Amygdala	Lateral nucleus	4,858	0,000	4,520	0,000
	Basal nucleus	5,445	0,000	5,435	0,000
	Accessory Basal nucleus	6,421	0,000	6,618	0,000
	Anterior amygdaloid area	4,823	0,000	3,891	0,000
	Central nucleus	6,772	0,000	5,876	0,000
	Medial nucleus	3,848	0,000	3,993	0,000
	Cortical nucleus	4,879	0,000	6,173	0,000
	Cortico-amygdaloid transition	4,346	0,000	4,399	0,000
	Paralaminar nucleus	3,107	0,002	3,653	0,000
	Whole	5,663	0,000	5,476	0,000
Thalamus	LD	2,241	0,026	2,493	0,013
	LGN	2,829	0,005	2,146	0,033
	MDl	2,332	0,020	-	-
	MVRe	2,227	0,027	2,520	0,012
	PuA	2,507	0,013	-	-
	Pul	2,539	0,012	2,010	0,045

Legend: gcmldg = granule cell layers of the dentate gyrus, CA = Cornu Ammonis, hata = Hippocampus amygdala transition area, LD = Laterodorsal, LGN = Lateral Geniculate Nucleus, MDl = Mediodorsal lateral, MVRe = Medial Ventral Reuniens, PuA = Pulvinar Anterior, Pul = Pulvinar Inferior.

Supplementary Table 2: Structural differences between CN-non-converted vs CN-converted.

Lobe	Structure	Left t	Left p	Right t	Right p
Cingulate	Posterior ventral gyrus	-	-	2.328	0.021
Frontal	inferior Orbital gyrus	-	-	2.027	0.044
Temporal	middle gyrus	-	-	1.973	0.050
	pole gyrus	-	-	2.001	0.047
Hippocampus	whole	-	-	2.032	0.044
	whole body	-	-	2.260	0.025
	presubiculum body	-	-	2.604	0.010
	subiculum head	2.349	0.020	-	-
	subiculum body	-	-	2.757	0.006
	ca1 body	2.167	0.032	-	-
	molecular layer body	-	-	2.472	0.014
	tail	2.039	0.043	2.287	0.023
Amygdala	anterior amygdaloid area	2.401	0.017	-	-
	corticoamygdaloid transition	-	-	2.109	0.036
Thalamus	whole	2.538	0.012	-	-
	central lateral	2.478	0.021	-	-
	paratenial	-	-	2.168	0.042
	pulvinar Interior	2.945	0.004	-	-
	pulvinar medial	3.364	0.001	-	-

Legend: t = statistical value from the Student T-test Model, Left = left hemisphere, right = right hemisphere, CA = Cornu Ammonis

Supplementary Table 3 (See below): Simple and interaction effects of group (MCI-converted vs MCI-non-converted) and NPS (Agitation and Appetite changes) on cognitive performance and brain structures from corrected ANCOVA model.

Legend: *p≤.05; **p≤.01; ***p≤.001; agi = agitation, app = appetite changes, F = statistical value from the ANCOVA Model, Left = left hemisphere, right = right hemisphere, CA = Cornu Ammonis, gcmldg = granule cell layers of the dentate gyrus.

		Simple effects			Interaction effects	
		Group	Agi	App	Group*Agi	Group*App
Domain	Variable	F-values				
Cognitive	Clock Drawing	1,4	1,4	0	0	0,8
	Free recall 1 RAVLT	19,7***	0,7	1,1	0,2	3,8
	Free recall 2 RAVLT	7,1**	1	3,4	0	0,1
	Free recall 3 RAVLT	9,2**	0,2	0,7	0,2	0,2
	Free recall 4 RAVLT	8,6**	0,3	0	0	0
	Free recall 5 RAVLT	9,4**	0,8	0,2	0,4	0
	Free recall 6 RAVLT	14,4***	0,3	0,1	0	2,9
	Free recall B RAVLT	11,3***	0,5	1,4	6,3*	1,6
	Semantic lexical evocation "Animals"	2,3	0,9	0,6	0,6	3
	Delayed free recall RAVLT	12,5***	1	0,9	0,4	3
	Total delayed recall RAVLT	10,2**	1	0	0	2,2
Frontal	rectus Gyrus Left	0,3	2,3	0,2	0,3	0,4
	rectus Gyrus Right	4,9*	0,1	0	2,2	1,1
	precentral Inferior part Sulcus Left	0,3	0,5	5,2*	8,3**	1
	precentral Inferior part Sulcus Right	0,3	1,4	0,8	5,2*	0,2
	Inferior Sulcus Left	2,6	5,3*	0,6	0,1	0,2
	Inferior Triangularis Gyrus Right	0	5,5*	1,1	0,8	0,3
Occipital	Superior transversal Sulcus Left	3,9*	8,7**	0,3	2,5	1,5
	middle Gyrus Left	4,1*	2,4	0,9	0,3	2,5
	middle Lunatus Sulcus Left	4,1*	4,2*	1,5	0,5	2,8
	temporal Lateral Sulcus Left	7,0**	0,5	0,6	0,5	0,8
	temporal Medial Lingual Sulcus Right	8,1**	1,7	4,2*	0,1	8,3**
	Inferior Gyrus and Sulcus Left	0,5	0,1	0	5,7*	0,1
Cingulate	subcallosal Gyrus Left	7,0**	3,6	0,1	4,1*	2,7
	subcallosal Gyrus Right	6,0*	1,3	1,6	1,9	2,6
Insula	circular Inferior Sulcus Left	3	0,6	0,1	1,8	2
Parietal	Superior Gyrus Left	6,2*	0,9	0,5	3,7	6,0*
	Superior Gyrus Right	4,8*	3,3	0	1,1	3,9*
	Inferior Angular Gyrus Left	8,6**	2,8	0	3,2	2,3
	Inferior Angular Gyrus Right	6,1*	4,3*	0,4	0,8	2,5
	Inferior Supramar Gyrus Left	7,4**	0	0,8	1,5	2,4
	Inferior Supramar Gyrus Right	2,4	6,0*	0,2	0,6	1,1
	intraParietal Sulcus Left	5,6*	0,3	1,5	4,8*	5,7*
	intraParietal Sulcus Right	2,4	1,4	0,1	0,8	2,6
	subparietal Sulcus Left	7,1**	4,2*	0,3	1,5	7,5**
	subparietal Sulcus Right	10,6***	1,3	2,7	0,5	6,8**
	parieto-occipital Sulcus Left	5,4*	1,6	0,4	4,1*	2,1
	parieto-occipital Sulcus Right	6,5*	3,2	2,3	0,4	9,7*
	precuneus Gyrus Left	8,9**	1,3	2	3	4,3*
	precuneus Gyrus Right	7,1**	5,7*	0	0,4	5,0*
Temporal	superior lateral Gyrus Left	4,7*	2,8	0	0	1,1
	superior lateral Gyrus Right	2,1	6,2*	0,1	2,8	0,9
	Superior sulcus Left	6,2*	2,2	0,4	0,4	1,2
	superior sulcus Right	3,5	1,1	0,1	1,3	0,6
	superior plan tempo Gyrus Right	3,7	0,7	2,1	0,5	1,4
	middle gyrus Left	4,0*	0,1	0	0,2	0,4
	middle gyrus Right	4,5*	1,9	0,4	4,0*	0,3
	lateral fissure Posterior Right	3,9*	1,7	0,6	1,7	2,6
	inferior gyrus Right	5,3*	0,3	1,2	2	0,4
	Inferior sulcus Left	3,7	0,3	1,6	1,1	0
	inferior sulcus Right	2,9	1,7	0,1	3,8	0
Hippocampus	whole left	6,6*	1,8	5,6*	0,1	2,3
	whole right	5,5*	4,8*	5,3*	0,1	0,5
	whole head left	5,3*	1,5	4,1*	0,3	1,9
	whole head right	2,7	4,9*	4,4*	0,1	0,3
	whole body left	7,0**	2,3	5,4*	0	2,5
	whole body right	7,4**	4,6*	4,5*	0	0,7
	presubiculum head left	4,4*	2,5	4,2*	1	1,1
	presubiculum head right	3	4,6*	2,7	1,5	0,8
	presubiculum body right	6,1*	1,6	0	0	1,9
	subiculum head left	5,1*	1,5	2,3	0,2	1,5
	subiculum body left	5,7*	2,3	4,2*	0	3,7
	subiculum body right	9,5**	4,9*	2,5	0	1,9
	ca1 head left	3,2	0,8	2,9	0,3	1,4
	ca1 head right	1,8	3,4	5,1*	0,1	0,1
	ca1 body right	0,8	0,8	5,4*	0	0
	ca3 head left	5,4*	1,8	3,3	0	3,7
	ca3 body left	3,8	2,2	8,5**	0	0,9
	ca3 body right	3,4	5,2*	6,7**	0	0,8
	ca4 head left	6,2*	2,1	3,7	0,6	3
	ca4 body right	4,9**	4,4*	6,2*	0	0
	ca4 body left	3,7	2,2	6,0*	0	1,3
	hata right	2,6	2,3	1,6	2,3	0
	fimbria left	3,2	0	0,7	0	0
	molecular Layer head left	5,2*	1	4,3*	0,4	1,6
	molecular Layer head right	2,9	4,2*	4,5*	0	0,1
	molecular Layer body left	7,8**	2,5	5,3*	0	2,7
	molecular Layer body right	8,4**	3,6	4,3*	0	0,6
	gcmldg head left	5,5*	1,3	3,8	0	1,8
	gcmldg body left	4,6*	2,3	6,0*	0	1,3
	gcmldg body right	4,5*	3,6	6,1*	0	0
	tail left	3,5	0,6	4,9*	0	1
	tail right	5,3*	1	4,0*	0	0,3
Amygdala	whole left	1,8	0,6	5,8*	0,1	0,2
	accessory basal nucleus left	4,3*	0,9	6,2*	0	0,6
	accessory basal nucleus right	5,0*	6,5*	3,5	0,2	0,1
	anterior amygdaloid area left	0	0	6,9**	0	0
	anterior amygdaloid area right	0	4,4*	6,1*	0	0
	basal nucleus right	1,7	5,4*	2,2	2,2	0,2
	central nucleus left	5,6*	0	0	0	0
	central nucleus right	3,6	4,5*	0	0	0
	corticoamygdaloid transition left	0,5	0	6,7**	0,9	0
	lateral nucleus left	1,3	0,4	5,2*	0	0,1
	paralaminar nucleus left	0	0	0	0	0

Supplementary table 4. Corrected ANCOVA model for differences between CN-non-converted vs CN-converted.

		Simple effect
Domain	Variable	F-Values
Cognitive	2nd recall of RAVLT	4,4*
	Digit Span Backward	2,5
	Semantic Lexical Evocation "Vegetables"	4,5*
Cingulate	posterior ventral gyrus right	5,0*
Frontal	inferior orbital gyrus right	3,9*
Temporal	middle gyrus right	5,2*
	pole gyrus right	4,5*
Hippocampus	whole right	7,0**
	body right	8,1**
	presubiculum body right	8,1**
	subiculum head left	8,3**
	subiculum body right	10,4**
	ca1 body left	5,8*
	molecular Layer body right	4,0*
	tail left	6,3*
	tail right	7,4**
Amygdala	anterior amygdaloid area left	7,8**
	corticoamygdaloid transition right	7,2**
Thalamus	whole left	5,8*
	central lateral left	2,0
	paratenial right	0,0
	pulvinar anterior left	8,9**
	pulvinar medial left	11,4***

Legend: *p≤.05; **p≤.01; ***p≤.001; F = statistical value from the ANCOVA Model, Left = left hemisphere, right = right hemisphere, CA = Cornu Ammonis

Transition

Cette troisième étude visait à prédire la conversion du TCL à la MA et du vieillissement sain au TCL en se basant sur des données neuropsychiatriques, neurostructurelles, cognitives et d'habiletés fonctionnelles rétrospectives. Les résultats montraient que les données neurostructurelles et cognitives étaient plus sensibles dans la prédiction de la conversion du TCL à la MA. L'implication de plus faibles habiletés fonctionnelles et non des SNP dans la conversion en MA suggérait que les SNP étaient en lien avec ces faibles habiletés plutôt que précurseurs de la conversion en MA. Cela soutient la question de l'origine des SNP : antérieurs aux troubles cognitifs, conséquence de ces derniers, ou encore conséquence des difficultés de la vie quotidienne.

L'étude suivante portera sur une problématique fréquemment questionnée mais encore peu étudiée. Comme il a pu être décrit, la dépression est fréquente dans la maladie d'Alzheimer. Pourtant, cette dépression ne remplit pas les critères du trouble dépressif majeur alors même que ce dernier peut s'accompagner de troubles mnésiques et de la concentration. En raison de ce flou, cette étude s'intéressera aux associations neuropsychiatriques et cognitives du trouble dépressif majeur dans différents échantillons : cognitivement sain, avec un TCL, ou ayant un diagnostic de MA.

Chapitre 4 - Neuropsychiatric and cognitive features of Major Depressive Disorder in aging

Caractéristiques neuropsychiatriques et cognitives du trouble dépressif majeur dans le vieillissement

Ronat Lucas[a,b], MSc, NACC Group[*], **Hanganu** Alexandru[a,c], PhD

[a]Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, Montréal, Québec, Canada

[b]Faculté de Médecine, Département de Médecine, Université de Montréal, Québec, Canada

[c]Faculté des Arts et des Sciences, Département de Psychologie, Université de Montréal, Québec, Canada

[*]The National Alzheimer's Coordinating Center

The authors have no conflicts of interest

Corresponding author:

Alexandru Hanganu, M7819, 4545 ch. Queen Mary, H3W 1W6, Montréal, QC

Phone: (514) 340-3540 #4897

Mail: alexandru.hanganu@umontreal.ca

Other Corresponding Author:

Lucas Ronat, M7820, 4545 ch. Queen Mary, H3W 1W6, Montréal, QC

ORCID : 0000-0003-1943-9833

Phone: +1 (438) 408-6806

Mail: lucas.ronat@umontreal.ca

Funding

L. Ronat reports having received a doctoral research scholarship from the IUGM Foundation and a merit scholarship from the Faculty of Medicine of the Université de Montréal. A. Hanganu has received funding from the IUGM Foundation, Parkinson Quebec, Parkinson Canada, FRQS, Lemaire Foundation.

Authors' contributions

L. Ronat defined the research project, the study design, oversaw data extraction, cleaning and analysis, and wrote the paper. A. Hanganu also designed the study and assisted with writing the article.

Abstract

Objectives: The diagnosis of Major Depressive Disorder (MDD) is based on the DSM-V criteria and is established by a clinician. This allows quantifying depression based on clinical criteria. As such, MDD differs from other types of depressions that are measured by subjective scales. Here, we evaluated the MDD risk factor on other neuropsychiatric symptoms (NPS) as well as MDD association with cognitive performance in Alzheimer's disease (AD), Mild Cognitive Impairment (MCI) and Healthy Controls (HC). Methods: Data of 208 patients with AD, 291 patients with MCI and 647 HC were extracted from the National Alzheimer's Coordinating Center database. All participants included in this study were assessed by a physician for the MDD criteria, underwent a NPS evaluation using the NeuroPsychiatric Inventory, and a comprehensive cognitive assessment. Participants were classified as with- and without MDD. We performed logistic regression and MANCOVA models respectively with NPS and cognitive performance as variables of interest and MDD as fixed factors within each group. The MANCOVA was controlled for the effects of age, sex, and education. Results: MDD increased the risk for psychotic, affective and behavioral NPS in MCI, as well as affective and behavioral NPS in HC and AD. Also, MCI with MDD had lower performance on selective attention and mental flexibility. Conclusions: MDD seems to increase the probability of a higher prevalence of NPS in all groups (HC, MCI and AD). Longitudinal data processing would help to understand the neuropsychiatric evolution of elderly subjects with MDD.

Keywords: Major Depressive Disorder, Cognitive Performance, Neuropsychiatric symptoms, Alzheimer's Disease

Résumé

Objectifs : Le diagnostic du trouble dépressif majeur (TDM) est basé sur les critères du DSM-V et est établi par un clinicien. Il permet de quantifier la dépression sur la base de critères cliniques. En tant que tel, le TDM diffère des autres types de dépressions quantifiées sur la base d'échelles subjectives. Ici, nous avons évalué le facteur de risque du TDM sur d'autres symptômes neuropsychiatriques (SNP) ainsi que l'association du TDM avec la performance cognitive dans la maladie d'Alzheimer (MA), les troubles cognitifs légers (TCL) et les contrôles sains (CS). Méthodes : Les données de 208 patients atteints de la MA, 291 patients atteints de TCL et 647 CS ont été extraites de la base de données du National Alzheimer's Coordinating Center. Chaque participant inclus a été évalué par un médecin selon les critères du TDM, a subi une évaluation des SNP à l'aide de l'inventaire neuropsychiatrique et une évaluation cognitive complète. Les participants ont été classés en deux catégories : avec et sans TDM. Nous avons effectué une régression logistique et un modèle d'analyse de covariance multivariée (MANCOVA) respectivement avec les SNP et les performances cognitives comme variables d'intérêt et le TDM comme facteur fixe au sein de chaque groupe. La MANCOVA a été contrôlée pour les effets de l'âge, du sexe et de l'éducation. Résultats : Le TDM a augmenté le risque de SNP psychotiques, affectifs et comportementaux dans le TCL, et de SNP affectifs/comportementaux chez les participants CS et MA. De plus, les personnes atteintes de TCL et de TDM avaient des performances inférieures en matière d'attention sélective et de flexibilité mentale par rapport aux TCL sans TDM. Conclusions : Le TDM semble augmenter la probabilité d'une prévalence plus élevée de NPS dans tous les groupes (CS, TCL et MA). Le traitement de données longitudinales permettrait de comprendre l'évolution neuropsychiatrique des sujets âgés avec un TDM.

Mots-clés: Trouble Dépressif Majeur, Performances cognitives, Symptômes neuropsychiatriques, Maladie d'Alzheimer

Introduction

Depression in the elderly has been associated with cognitive difficulties[232]. The connections between depression and Mild Cognitive Impairment (MCI) has been reported to be frequently co-morbid, and cognitive disorders occurring in the context of depression may not be remitted[233]. The persistence of cognitive impairment after depression is of a significant clinical concern, since it increases the risk of converting from MCI to Alzheimer's disease (AD)[234]. Some studies looked at depressive symptoms as risk factors for accelerated cognitive decline. Wilson et al (2002) reported that elderly participants with depressive symptoms and without AD at baseline, had a 19% increased risk of AD after seven years and the overall annual cognitive decline was increased by 24% in these participants[235]. In another prospective longitudinal study, Köhler et al. (2010) showed a robust relationship between depressive symptoms and subsequent cognitive decline[236]. Clinically meaningful depressive and persistently high depressive symptoms were associated with faster cognitive decline and increased the risk for development of future "Cognitive Impairment, No Dementia", especially with memory impairment. More recently, similar data were obtained by Oh et al (2020) from a large Korean cohort showing a threefold increased risk of dementia in non-demented, cognitively normal individuals with subsyndromal depression[237]. This risk was also increased in chronic or recurrent subsyndromal depression[237]. However, a longitudinal study of depressive symptoms before a diagnosis of dementia by Singh-Manoux et al., carried out over a 28-year follow-up, states that only depressive symptoms in late life but not midlife were associated with increased risk for dementia[238]. As such, the potential overlap between depression and age-related cognitive decline remains unclear.

The potential differences in results could be also due to different methods of quantifying depression. Some studies used specific clinical scales, but this is not in line with the clinical definition of depression, known as "major depressive disorder" (MDD) and which can be evoked from a psychiatric perspective[179]. MDD is defined by the DSM-V criteria and requires: (1) the presence of at least one of the two symptoms of (i) depressed mood and (ii) loss of interest or pleasure; (2) as well as at least five of the nine symptoms (first two and: (iii) weight or appetite loss or gain, (iv) insomnia or hypersomnia, (v) psychomotor agitation or retardation, (vi) fatigue, (vii) worthlessness, (viii) diminished ability to think or concentrate and (ix) suicidal ideation)[179].

MDD has been linked to various cognitive disorders, particularly memory and dysexecutive disorders, in both adults and the elderly. In the latter population, the severity of MDD has been linked to greater difficulties in initiation, as well as to greater instrumental activities of daily living impairment in individuals without dementia[239]. These findings were also confirmed by Gildengers et al. (2012) who describe dysexecutive impairments and slower processing speed in elderly patients with MDD compared to elder control participants[240]. Furthermore, the presence of cognitive impairments was not specific to acute phases of MDD but could be found in remittent phases[240]. Some of these impairments could then be irreversible precursors of mild cognitive impairment (MCI). Interestingly, MDD has been reported in 11.2-19.6% of MCI patients based on DSM-V criteria[241,242], in 11.5% of mild AD, 10% of moderate AD and 4.5% of severe AD[243]. However, other studies looking at neuropsychiatric symptoms (NPS) of depression (without identifying a full diagnosis of MDD) have also been able to show associations with poorer cognitive performance in individuals and an increased risk of decline[235,236,238].

Although the increased risk of dementia in the presence of NPS has already been reported[12,33,36], the data showing comorbidities between MDD and other NPS are scarce. Recent factorial models, demonstrated in the review and meta-analysis by Liew (2019), showed that depression was consistently associated with anxiety and often associated with apathy[244]. Other studies showed that depression is frequently comorbid with anxiety, and more so in the elderly than in the young[245,246]. Depression was also shown to be associated with apathy as well cognitive changes in the form of poorer episodic memory and diminished processing speed[247]. In patients with dementia, depression has been associated with various NPS factors such as hallucinations and anxiety[248]. Nevertheless, previous studies investigating the associations between depression, NPS and cognitive performance used clinical scales for depressive symptomatology, and, to our knowledge, the potential associations with the MDD diagnosis have not been studied yet.

Considering the affective (anxiety, apathy) and cognitive (memory and executive functions) associations of MDD in aging and the possible associations with pathological cognitive decline (MCI and AD), as well as the reduced prevalence of MDD in the most declining population, the aim of this study is to determine i) the probability of the presence of other NPS based on a

MDD diagnosis; ii) associations between MDD and cognitive performance at different clinical stages (Healthy Control [HC], MCI and AD with MDD compared to those without).

Methods

Participants

Data used in the preparation of this article were obtained from the NACC database (specifically NACC UDSv1-2). The NACC database is a large compilation of longitudinal data of participants that are HC as well as patients with MCI, AD and other neurodegenerative disorders. Each participant benefited from a neuropsychiatric assessment via the Neuropsychiatric Inventory and a comprehensive cognitive examination. Exclusion criteria were: (i) incomplete assessments, (ii) incomplete neuropsychiatric and cognitive assessments, (iii) presence of psychiatric history other than MDD (schizophrenia, bipolar disorder, substance abuse, post-traumatic stress, obsessive-compulsive disorder), (iv) presence of neurological history (stroke, head injury, brain tumor, anoxia, epilepsy, alcohol dependence and Korsakoff, neurodevelopmental disorder), (v) prematurity, (vi) diagnostic criteria in favor of other neurodegenerative or neurological etiology (Parkinson's disease, frontotemporal degeneration, progressive supranuclear paralysis, corticobasal degeneration, Lewy body dementia, amyotrophic lateral sclerosis, multiple sclerosis, multi-system atrophy, vascular dementia), (vii) presence of substance abuse. After the exclusion, the final sample for analyses consisted of 647 HC, 291 patients with MCI and 208 patients with AD. In the NACC database, patients with AD met the NINCDS/ADRDA criteria for probable or possible AD. Patients with MCI presented a diminished cognitive performance in at least one cognitive domain.

Psychiatric conditions (such as diagnosis and treatment by a physician) are collected at the initial NACC data collection visit. The patients are considered with MDD if the diagnosis of MDD as described by the DSM criteria was attested by a physician in the previous two years. As previously mentioned, the diagnosis of MDD requires a distinct change of mood, often characterized by sadness and anhedonia accompanied by at least several psychophysiological

changes, such as disturbances in sleep, appetite, or sexual desire, cognitive disorders, suicidal thoughts, weak self-esteem, and slowing of speech and action. These changes must last a minimum of 2 weeks and interfere considerably with work and family relations. Each clinical group (HC, MCI, AD) was further divided in two groups based on the presence of MDD, resulting in six final groups: HC-no-MDD, HC+MDD, MCI-no-MDD, MCI+MDD, AD-no-MDD and AD+MDD (Table 1). The sample with MDD was limited to late-life MDD. Previous diagnoses and previously treated MDD were excluded.

This study was approved by the Comité d'éthique de la recherche vieillissement-neuroimagerie CER VN 19-20-06. Ethics committee approval and individual patient consents were received by the NACC databases (https://naccdata.org/data-collection/forms-documentation/uds-3).

Neuropsychiatric and Cognitive Assessments

The NPS were quantified based on the Neuropsychiatric Inventory; version evaluated by participants' relatives, that was collected during the initial visit. We extracted the values of "presence" / "absence" of 12 NPS: delusions, hallucinations, agitation/aggressiveness, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviors, sleep disorders and eating disorders.

The cognitive assessment included the following tests present in both datasets: (1) global cognitive efficiency (MMSE), (2) auditory-verbal memory (logical memory test from Wechsler Memory Scale), (3) focused attention (Trail Making Test A), (4) processing speed (WAIS Coding), (5) mental flexibility (Trail Making Test B), (6) working memory (digit span), (7) semantic verbal fluency (animal and vegetable) and (8) visual confrontation naming (Boston Naming Test).

Statistical analysis

Demographic data analyses included: (1) between groups distribution using the student t-test for age, years of education, MMSE score, and the Chi-square test for sex prevalence (Table

1) as well as (2) analysis of prevalence of NPS among subgroups as well inter-group differences (Table 2).

To determine the association of MDD with the other NPS probability in HC, MCI and AD, we performed binary logistic regression models for each NPS as dependent variables and the presence/absence of MDD as the independent variable.

In a second step, cognitive performance was compared between HC, MCI and AD patients with MDD versus those without MDD using a MANCOVA model with age, sex, and education as covariables (because the +MDD subgroups were younger). Interpretations were made with an alpha threshold of 0.05, and a Bonferroni correction was made for multiple comparisons.

Results

Demographic, neuropsychiatric and cognitive performance data (Tables 1, 2, 3) showed that the years of education, sex distributions and MMSE score were similar between subgroups within each clinical group. For age, the +MDD subgroups were younger than the no-MDD within each clinical group (Table 1).

Prevalence analysis showed that within the two groups MCI and AD, those with MDD exhibited anxiety, apathy, disinhibition, irritability, disturbed nighttime behavior, and appetite changes more frequently than those without MDD. Furthermore, MCI+MDD participants had more delusions and agitation than MCI-no-MDD. Within the group HC, those with MDD exhibited more frequently anxiety, apathy, disinhibition, irritability, nighttime behaviors and appetite changes (Table 2).

Neuropsychiatric associations with MDD

The models of association between NPS and MDD are reported in Table 3. In the HC group, the presence of MDD was positively and significantly involved in the probability equations for

anxiety, disinhibition, irritability, nighttime behaviors, and appetite changes. However, MDD alone does not appear to improve the model sensitivity (Specificity = 100%, sensitivity = 0%).

In the MCI group, the MDD was positively and significantly involved in the probability equations for delusions, agitation, anxiety, apathy, disinhibition, irritability, nighttime behaviors, and appetite changes. Thus, the presence of MDD increased the likelihood of experiencing these NPS. However, MDD alone does not appear to improve the model sensitivity in MCI (Specificity = 100%, sensitivity = 0%).

In the AD group, the MDD was positively and significantly involved in the probability equations for anxiety, euphoria, apathy, disinhibition, irritability, nocturnal behaviors, and appetite changes. Additionally, MDD did improve the model sensitivity for apathy only in AD group (specificity = 65.4%, sensitivity = 69.4%).

Cognitive association with MDD

After controlling for covariates, the MANCOVA model showed no cognitive associations with MDD in HC participants: mean performance was similar between HC+MDD and HC-no-MDD.

Among participants with MCI, MCI+MDD performed significantly worse on the Trail Making Test A and B (TMTA and TMTB), with longer completion times than MCI-no-MDD, reflecting poorer performance in focused attention and mental flexibility respectively.

Finally, among participants with AD, AD+MDD performed better on the digit span backward task (DSB), reflecting a better auditory-verbal working memory compared to AD-no-MDD patients (Table 4).

Discussion

When considering 2 levels of cognitive decline: MCI and AD, the regression models and analysis of covariance performed in our study showed 1) a role of MDD in increasing the probability of NPS and 2) a significant impact of MDD on executive performances. These results

remained significant even when the MANCOVA model included that confounding factors of age, sex, and years of education. The presence of MDD is associated with a higher prevalence of delusions and agitation in the MCI group and more prevalence of anxiety, apathy, disinhibition, irritability, disturbed nighttime behaviors and appetite disturbance in the MCI and AD groups. Moreover, logistic regression models confirm these associations, MDD being a significant involvement in determining the presence of these NPS, implying that a patient with MDD had a higher probability of having an additional NPS. In HC participants, MDD had only NPS association, featured by higher prevalence of anxiety, disinhibition, irritability, nighttime behaviors and appetite changes. Finally, the fact that MDD and some NPS are associated in all groups (including HC) seems to indicate that these symptoms are part of a global picture, such that having one NPS enhances the probability of having others, even in HC individuals.

These relationships might suggest a likely mood lability in MCI and AD patients, as mood can shift from apathy to aggressivity or from depression to euphoria in these patients. Previous studies outlined this link by describing that emotional lability can be frequent in AD patients, as well as the emergence of late onset "bipolar disorder" type syndromes with manic episodes[249]. Moreover, the emergence of these disorders has been described as a risk factor in the development of dementia[250]. Interestingly, previous studies also demonstrated an association between depression and disinhibition in MCI and AD, though it was less frequently reported[251].

The significant association between MDD and agitation, depicted by our model, is in line with previous literature. Agitation is commonly described in MCI and AD and appeared to be associated with most other neuropsychiatric and behavioral disorders, including depression, even in MCI[251–253]. Agitation has been shown to be an expression of anxiety in AD patients[254]. In contrast, depression and apathy appeared to be more closely associated with the incidence of agitation and the agitation composite score (which includes anxiety, agitation, irritability, disinhibition, and aberrant motor behavior) as reported by Liu et. al. 2020[255].

Our study showed no relation between MDD and hallucinations, whereas several previous studies reported this association in AD, specifically with respect to visual, auditory, and olfactory hallucinations[256–258]. Thus, it could be that the occurrence of hallucinations is not directly due to

depression but mediated by it. These hallucinations may also be accentuated by social isolation, loneliness and sensory deprivation[259–261]. On the other hand, behaviors of euphoria or excessive joviality have also been described in the context of late bipolarity[249].

Overall, our results show that patients with MDD had more frontal-type symptoms (such as disinhibition, agitation or irritability) and no aberrant motor behaviors. Even if previous literature described motor behaviors in relation to frontal-type symptoms, our study shows a potential distinct impact of MDD on this NPS[251]. However, these behaviors are poorly studied and do not seem to have direct links with depression[262]. According to Martin & Velayudhan's (2020) literature review on NPS in MCI, some symptoms that are less frequent, or even as frequent as in the general population, would not present a higher risk factor for developing a dementia state or accelerated cognitive decline compared to people without these NPS, which include: disinhibition, euphoria, appetite/eating disorders, and aberrant motor behavior[20]. Indeed, a recent study looked at clusters of NPS in MCI and their comparative risks of dementia and found that frontal/hyperactivity-like symptoms, such as euphoria, disinhibition, and aberrant motor behaviors would not present an increased risk for patients to develop dementia, and that these symptoms would be a consequence of other symptoms such as psychotic or affective symptoms[244].

Our results also showed that the MCI+MDD group was characterized by poorer performance on selective attention and mental flexibility in comparison to the MCI-no-MDD group while the AD+MDD was characterized by better auditory-verbal working memory performance. This would imply that MDD potentiates reductions in cognitive performance in MCI but not in AD. Despite this finding being too challenging to explain at this stage, some studies have shown a protective role of certain antidepressants against cognitive decline (dementia or MCI)[263–265]. Thus, treatment of MDD may provide compensatory protection from cognitive decline. However, these results are not systematically confirmed and only include certain treatments, such as tricyclic antidepressants or lithium, with other antidepressants tending to increase the risk of dementia (added to the accentuated risk due to depression)[266].

Executive dysfunction has been described in AD and associated with some NPS such as depression[257]. It has been suggested that depression is a risk factor for dysexecutive disorders in AD. However, these results are not in line with our results and other studies showing an impact of depression on executive function in MCI but not in AD[267]. It seems that in AD patients, severe depressive symptoms may play an important role in cognitive impairment, while less severe depressive symptoms may have limited effects[267]. The diagnosis of MDD does not necessarily imply a high severity of symptoms, as there are different levels of severity in MDD, and this parameter was not estimated in our study. Other studies have linked depression with dysexecutive disorders as well as the severity of depression as a mediator of the functional impact of executive disorders[131,268,269]. Here, a limitation could be that the reduction of executive functions in MCI was not totally explained by the presence of depression due to subtypes of MCI not considered in this study. Indeed, some subtypes can show more severe dysexecutive disorders without high prevalence of depression while other subtypes show higher prevalence of depression with less cognitive impairment[270] Further investigations are required to consider other impact factors such as the duration of depressive symptoms or their frequency.

In connection with the debate about depression as a risk factor or prodromal sign of AD and dementia, Köhler et al (2010) recalled that there is evidence that depression may accompany pre-clinical AD, or precede the onset of AD by several years, in the sense that past occurrences of depressive episodes increase the risk of subsequent AD[236]. Thus, depressive symptoms in the broad sense may have this dual role of risk factor and consequence of AD.

Our study should be viewed in light of some limitations: (1) In the analyses, the presence or absence of treatments for MDD was not considered; (2) the cross-sectional design does not allow to assess the risk of cognitive decline or NPS appearance in the presence of late MDD. The inclusion of longitudinal NACC data would contribute to the study of the evolutionary impact of MDD through the different groups.

In conclusion, our study shows associations between MDD and a higher prevalence of NPS, while its relationship with cognitive performance was weak. It is important that future studies pay more attention to the characteristics of the processes that are broadly referred as

"depression," which may both involve a clinical picture of a mental disorder or more isolated symptoms that occur in aging.

DISCLOSURE/CONFLICT OF INTEREST

The authors have no conflict of interest to report.

ACKNOWLEDGEMENTS

The authors are grateful to Adriana Cannizzaro, master's student in psychology at the University of Montreal, for editing this manuscript.

Use of NACC data

The NACC database is funded by NIA/NIH Grant U01 AG016976. NACC data are contributed by the NIA-funded ADCs: P30 AG019610 (PI Eric Reiman, MD), P30 AG013846 (PI Neil Kowall, MD), P50 AG008702 (PI Scott Small, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P50 AG047266 (PI Todd Golde, MD, PhD), P30 AG010133 (PI Andrew Saykin, PsyD), P50 AG005146 (PI Marilyn Albert, PhD), P50 AG005134 (PI Bradley Hyman, MD, PhD), P50 AG016574 (PI Ronald Petersen, MD, PhD), P50 AG005138 (PI Mary Sano, PhD), P30 AG008051 (PI Thomas Wisniewski, MD), P30 AG013854 (PI Robert Vassar, PhD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG010161 (PI David Bennett, MD), P50 AG047366 (PI Victor Henderson, MD, MS), P30 AG010129 (PI Charles DeCarli, MD), P50 AG016573 (PI Frank LaFerla, PhD), P50 AG005131 (PI James Brewer, MD, PhD), P50 AG023501 (PI Bruce Miller, MD), P30 AG035982 (PI Russell Swerdlow, MD), P30 AG028383 (PI Linda Van Eldik, PhD), P30 AG053760 (PI Henry Paulson, MD, PhD), P30 AG010124 (PI John Trojanowski, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005142 (PI Helena Chui, MD), P30 AG012300 (PI Roger Rosenberg, MD), P30 AG049638 (PI Suzanne Craft, PhD), P50 AG005136 (PI Thomas Grabowski, MD), P50 AG033514 (PI Sanjay Asthana, MD, FRCP), P50 AG005681 (PI John Morris, MD), P50 AG047270 (PI Stephen Strittmatter, MD, PhD).

All data are available on the NACC website upon demand (https://naccdata.org/requesting-data/submit-data-request).

Tables

Table 4.1: Demographic comparisons between depressive status subgroups for each clinical status.

	HC -no-MDD	HC +MDD	p	MCI-no-MDD	MCI+MDD	p	AD-no-MDD	AD+MDD	p
N	509	138		175	116		111	97	
Age	73.73	70.98	0.002	76.69	74.39	0.020	77.10	72.42	<0.001
Edu	15.94	16.33	0.131	15.39	15.64	0.507	15.79	15.28	0.240
MMSE	29.07	29.04	0.788	27.02	27.25	0.399	23.57	23.82	0.586
Women	66.4	70.3	0.415	46.9	56.0	0.151	46.8	53.6	0.404

Legend: HC = Healthy Control; MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease; MDD = Major Depressive Disorder; N = group size; Age = age mean; p = p-value; Edu = education mean; MMSE = Mini-Mental State Examination score mean; Women = percentage of women in each group.

Table 4.2: Neuropsychiatric Symptoms prevalence (%) comparisons between depressive status subgroup for each clinical status.

	HC-no-MDD	HC +MDD	p	MCI-no-MDD	MCI+MDD	p	AD-no-MDD	AD+MDD	p
N	509	138		175	116		111	97	
Del	-	-	-	1.1	6.0	0.032	10.8	15.5	0.409
Hal	-	-	-	-	-	-	4.5	5.2	1.000
Agi	1.6	2.2	0.709	9.1	19.8	0.013	20.7	24.7	0.510
Dep	0	28.3	<0.001	0	52.6	<0.001	0	59.8	<0.001
Anx	2.4	16.7	<0.001	10.3	37.9	<0.001	20.7	45.4	<0.001
Eup	0	0.7	0.213	0.6	0	1.000	0.9	6.2	0.052
Apa	0	7.2	<0.001	8.0	24.1	<0.001	19.8	51.5	<0.001
Dis	0.2	3.6	0.002	4.6	11.2	0.038	10.8	25.8	0.006
Irr	3.9	9.4	0.015	14.9	28.4	0.007	20.7	36.1	0.020
Mot	0.4	0	1.000	2.3	3.4	0.717	11.7	19.6	0.127
Nit	2.8	14.5	<0.001	10.9	25.0	0.002	13.5	34.0	0.001
App	0.6	3.6	0.013	5.1	19.0	<0.001	10.8	22.7	0.024

Legend: HC = Healthy Control; MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease; MDD = Major Depressive Disorder; N = group size; Del = Delusions; Hal = Hallucinations; Agi = Agitation; Dep = Depression; Anx = Anxiety; Eup = Euphoria; Apa = Apathy; Dis = Disinhibition; Irr = Irritability; Mot = Aberrant Motor Behaviors; Nit = Nighttime behaviors; App = Appetite changes; p = p-value.

Table 4.3. Probability models of NPS based on MDD in HC, MCI and AD.

	HC				MCI				AD			
NPS	**β**	**p**	**OR**	**95%CI**	**β**	**p**	**OR**	**95%CI**	**β**	**p**	**OR**	**95%CI**
Del	-	-	-	-	1.715	0.035	5.555	1.133; 27.231	-	-	-	-
Hal	-	-	-	-	-	-			-	-	-	-
Agi	-	-	-	-	0.899	0.010	2.458	1.236; 4.887	-	-	-	-
Dep	20.271	0.991	NS	NS	21.306	0.994	NS	NS	21.600	0.995	NS	NS
Anx	2.114	<0.001	8.283	4.005; 17.134	1.673	<0.001	5.330	2.881; 9.862	1.156	<0.001	3.176	1.728; 5.838
Eup	-	-	-	-	-	-	-	-	1.981	0.069	7.252	0.857; 61.35
Apa	18.653	0.992	NS	NS	1.297	<0.001	3.659	1.831; 7.311	1.459	<0.001	4.304	2.330; 7.948
Dis	2.950	0.007	19.098	2.212; 164.9	0.969	0.038	2.635	1.056; 6.574	1.052	0.006	2.865	1.350; 6.078
Irr	0.933	0.012	2.543	1.231; 5.252	0.824	0.005	2.278	1.276; 4.069	0.770	0.015	2.160	1.164; 4.009
Mot	-	-	-	-	-	-	-	-	-	-	-	-
Nit	1.791	<0.001	5.993	2.941; 12.21	1.007	0.002	2.737	1.450; 5.165	1.194	0.001	3.300	1.659; 6.562
App	1.847	0.012	6.341	1.496; 26.87	1.463	<0.001	4.317	1.909; 9.760	0.884	0.024	2.420	1.126; 5.199

Legend: HC = Healthy Control; MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease; NPS = Neuropsychiatric Symptoms; **β** = coefficient of regression models. A positive coefficient indicates that presence of MDD increase the probability of NPS; p = p-value; OR = Odd Ratio; Del = Delusions; Hal = Hallucinations; Agi = Agitation; Dep = Depression; Anx = Anxiety; Eup = Euphoria; Apa = Apathy; Dis = Disinhibition; Irr = Irritability; Mot = Aberrant Motor Behaviors; Nit = Nighttime behaviors; App = Appetite changes; empty values = prevalence of NPS is insufficient for analysis or the independent factor does not significantly change the model based on the constant alone; NS = not significant.

Table 4.4. Comparisons of cognitive performance means between depressive status subgroups for each clinical status (Controlling for age, sex, and education as covariables).

	HC			MCI			AD		
Variable	Difference MDD – no-MDD	F	p	Difference MDD – no-MDD	F	p	Difference MDD – no-MDD	F	p
LM	-0.025	0.005	0.945	-0.056	0.011	0.916	-0.053	0.010	0.919
LMD	-0.066	0.027	0.868	-0.765	1.898	0.169	0.042	0.007	0.934
DSF	0.037	0.038	0.846	0.275	1.079	0.300	0.509	2.926	0.089
DSB	0.129	0.381	0.537	0.427	3.076	0.081	0.756	6.973	0.009
Ani	-0.165	0.109	0.742	0.095	0.026	0.873	-0.148	0.041	0.839
Veg	-0.450	1.480	0.224	0.177	0.162	0.688	0.828	2.916	0.089
TMTA	0.147	0.019	0.890	5.824	7.373	0.007	5.375	1.345	0.247
TMTB	3.621	1.036	0.309	19.285	5.252	0.023	13.787	1.268	0.261
Code	-0.162	0.027	0.869	-2.276	3.744	0.054	-2.453	1.700	0.194
BNT	-0.283	1.033	0.310	0.002	<0.001	0.996	0.967	1.234	0.268

Legend: HC = Healthy Control; MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease; MDD = Major Depressive Disorder; F = ANCOVA statistical value; LM = Logical Memory immediate recall; LMD = Logical Memory Delayed recall; DSF/DSB = Digit Span Forward/Backward; Ani = Animal verbal fluency; Veg = Vegetables verbal fluency; TMTA = Trail Making Test version A; TMTB = Trail Making Test version B; Code = WAIS code subtest; BNT = Boston Naming Test; p = p-value.

Transition

Cette quatrième étude montrait que dans tous les groupes (sains, TCL, MA), les SNP étaient plus fréquents chez les participants présentant un trouble dépressif majeur, alors que les performances cognitives étaient plus faibles uniquement chez les individus ayant un TCL et un trouble dépressif majeur par rapport à ceux sans (notamment dans les performances d'attention focalisée et de flexibilité mentale). Cette réduction des performances ne s'observait pas dans le groupe MA, suggérant que la présence de trouble dépressif a un impact différent dans cette population (pas de difficultés cognitives sur-ajoutées aux troubles déjà générés par la maladie par exemple).

L'étude suivante sort un peu de certains sentiers battus : s'inspirant de facteurs de personnalité révisés du *Temperament and Character Inventory*, démontrés comme étant associés à des risques accru de troubles mentaux, ce travail s'intéresse aux relations transversales et longitudinales entre ces facteurs de personnalité et : 1) le développement de SNP dans le vieillissement ; 2) les performances cognitives et ; 3) les volumes et la diffusion du cerveau. Les différentes analyses s'intéressent à la fois aux individus âgés sains et à ceux développant un état de démence due à la MA.

Chapitre 5 - Revised Temperament and Character Inventory personality factors' associations with neuropsychiatric symptoms and aging-related cognitive decline across 25 years (In Prep)

Lucas Ronat[a,b,c,d], Michael Rönnlund[e], Alexandru Hanganu[a,f], Sara Pudas[c,d]

Author's affiliation:

[a]Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, Neuroimaging of Emotions Lab, Montreal, Quebec, Canada

[b]Faculty of Medicine, Department of Medicine, University of Montreal, Montreal, Quebec, Canada

[c]Department of Integrative Medical Biology, Umeå University, Umeå, Sweden

[d]Umeå Center for Functional Brain Imaging, Umeå University, Umeå, Sweden

[e]Department of Psychology, Development across the lifespan Research group, Umeå University, Umeå, Sweden

[f]Faculty of Arts and Sciences, Department of Psychology, University of Montreal, Montreal, Quebec, Canada

Corresponding author:

Sara Pudas, Research fellow at Department of Integrative Medical Biology (IMB)

Johan Bures väg 12, Biologihuset

Umeå universitet, 901 87 Umeå

sara.pudas@umu.se

+46 90 786 56 21

Abstract

Various personality and neuropsychiatric factors have been identified as additional risks development of cognitive disorders due to Alzheimer's disease (AD) for instance neuroticism or depression and anxiety. The objective of this study is to understand the relationships between revised personality factors from the Temperament and Character Inventory [271] previously shown to be predictive of/associated with mental disorders [272] and the neuropsychiatric, cognitive and brain trajectories of healthy participants from the population-based prospective BETULA study. Mixed-effect linear regression analyses are reported for the full sample, as well as a healthy subsample not converting to AD-dementia during longitudinal follow-up, and complemented by Cox proportional regression models to determine personality risk factors for conversion to clinical AD. The results showed that the revised Closeness to Experience (CE: avoidance of new stimuli, high anxiety, pessimistic anticipation, low reward seeking) and Tendence to Liability factors (TL:) were associated with more depression (both), stress (CE) and sleep disturbance (TL) as well as greater cognitive declines in memory, vocabulary and verbal fluency. Adjusted results showed negative associations between the CE factor and cingulate-cingulum network fractional anisotropy. Brain volumes analyses did not show significant associations with personality factors when adjusted. In terms of the risk of conversion to AD, it seems that the risk is mainly explained by higher age and APOE-ε4 status of individuals. Further work on the interactions between these factors and personality would help to understand the added risk of personality in older individuals and/or APOE-ε4 carriers, or the protective role of certain factors. The results nevertheless show a role for personality traits related to psychiatric symptoms as predictors of accelerated cognitive decline, whether or not it is underpinned by the presence of neurodegenerative disease, and further emphasize the importance of personality in cognitive and cerebral aging, and thus to adopt an integrative vision (biopsychosocial) of normal and pathological neurocognitive decline.

Keywords: personality, cognitive decline, neuropsychiatric symptoms, Alzheimer's dementia, MRI, longitudinal study

Introduction

Personality, aging and dementia

Two of the major causes of disability in aging are neurodegenerative diseases and cognitive decline. Alzheimer's disease (AD) is considered to be the most common cause of these symptoms and has been the subject of numerous studies that have made it possible to increase understanding of the physiopathological processes, as well as the underlying biological and psychological contributors. Through these studies, many have been able to demonstrate relationships between the personality traits of individuals and the risk of developing cognitive disorders. According to two meta-analyses by Low et al (2013) and Terracciano et al., (2014), the trait of neuroticism (tendency to experience negative and stressful life events) increases the risk of developing Alzheimer's type dementia or mild cognitive impairment, whereas the traits of conscientiousness (ability to control impulses and engage in goal-directed behaviors) and openness (tendency to try new things and engage in imaginative and intellectual activities) are rather protective factors [273,274]. More recently, these data were substantiated both regarding the risk of dementia (neuroticism at risk, conscientiousness protective), cognitive impairment in non-demented individuals, and conversion from such cognitive impairment to dementia (additional risk in individuals with low conscientiousness) [275].

In individuals without dementia, neuroticism may also have been associated with a higher risk of cognitive impairment, faster decline in cognitive, memory, and executive functions [276,277]. The risk may even be heightened in individuals who also have a high trait extraversion (tendency to interact with the environment, especially socially) (Crowe et al., 2006). Conversely, conscientiousness and openness tend to reduce cognitive decline, even in individuals carrying the *APOE*-ε4 allele, the major genetic risk factor for AD (Caselli et al., 2016).

At the same time, associations between brain structure and personality traits have also been shown during aging. Zufferey et al. (2017) showed smaller medial temporal lobe regions, a region implicated in both AD and age-related cognitive decline [164,278] in individuals with higher neuroticism, regardless of whether they had mild cognitive impairment or not [279]. Interestingly, conscientiousness was negatively associated with total cortical volume in both cross-sectional and longitudinal estimates, as well as with accelerated decline in right medial prefrontal volume, whereas medial temporal regions were better preserved in individuals with AD with high openness [280,281]. Similarly, inferior parietal and right dorsolateral regions were better preserved in healthy individuals with high openness [282].

Personality and neuropsychiatric symptoms

Several studies have been able to demonstrate associations between personality traits and neuropsychiatric consequences of various medical conditions [283–286]. However, few have focused on these relationships in normal and pathological aging. Instead, neuropsychiatric symptoms are considered personality changes [287], but their relationship to personality traits prior to their onset has been little studied. In the probable AD, premorbid neuroticism was correlated with anxiety and higher Neuropsychiatric Inventory total scores. Conversely, premorbid agreeableness was negatively correlated with symptoms of agitation and irritability [288]. Other data positively associated neuroticism with agitation, anxiety, apathy, and irritability, and negatively associated openness with depression, and apathy, and extraversion with agitation and irritability [289]. Finally, in MCI, neuroticism was positively associated with the total NPI score while openness was negatively associated (Rubio et al., 2013). These studies were all based on McCrae and Costa's 5-factor model of personality [290].

Neuropsychiatry and cognitive decline in aging

In addition to personality factors, neuropsychiatric symptoms (NPS) have also been identified as additional risks for accelerated cognitive decline and development of dementia. They can be described as psychological and behavioral manifestations marked by a change with the individual's previous functioning. They are common in AD, whether it is agitation, irritability,

anxiety, depression, apathy, or disturbances in nocturnal behavior (Zhao et al., 2016). These symptoms have been shown to be a risk factors for AD dementia in non-demented individuals with and without cognitive impairment, as well as in individuals with clinically diagnosed mild cognitive impairment, or no cognitive impairment (Acosta et al., 2018; Forrester et al., 2016; Liew, 2019; Peters et al., 2013). Similarly, depression and anxiety have been identified as risk factors for the development of mild cognitive impairment in cognitively healthy individuals after a 6-year follow-up period (Burhanullah et al., 2020).

TCI and mental illness

For the most part, previous personality studies, especially longitudinal ones, have been based on personality assessments from Costa and McCrae's 5-factor model: the BIG-FIVE (Costa Jr. & McCrae, 2008). However, few studies have been based on the temperament and character inventory (TCI) from Cloninger's psychobiosocial theory of personality (Cloninger et al., 1993). Different studies were interested by the correspondences between these two personality assessments and have shown similar correlations between the BIG-FIVE factors and the temperaments and characters from the TCI[291,292]. In particular, neuroticism was positively correlated with harm avoidance, and negatively correlated with self-directedness. The extraversion was negatively correlated with the harm avoidance and positively with the novelty seeking, persistence and self-transcendence. Openness was positively correlated with cooperativeness. Conscientiousness was negatively correlated with the novelty seeking and positively with persistence and self-directedness. Finally, agreeableness was positively correlated with reward dependency, cooperativeness and self-transcendence. The main correlations between indices are summarized in the table below.

Table 5.1 : Correlations between TCI and BIG-FIVE factors.

TCI/BIG-FIVE	Neuroticism	Extraversion	Openness	Conscientiousness	Agreeableness
HA	0.55	-0.6			
NS		0.32		-0.4	

P		0.58	0.54	
RD				0.56
SD	-0.48		0.4	
C		0.26		0.61
ST		0.12		0.23

Legend: HA = Harm Avoidance; NS = Novelty Seeking; P = Persistence; RD = Reward Dependency; SD = Self-Directedness; C = Cooperativeness; ST = Self-Transcendence.

The TCI distinguishes 4 temperament factors: novelty seeking, danger avoidance, reward dependence and perseverance; and 3-character factors: determination, cooperation and transcendence. Of these factors, some have been associated with a greater risk of mental disorders and psychiatric symptoms, both in students, adults, and older adults (Izci et al., 2014; Margetić et al., 2011; Matsudaira & Kitamura, 2006; Norberg et al., 2015). Specifically in the elderly, low transcendence was associated with lower social contacts, greater loneliness, and more negative life events, whereas high transcendence, danger avoidance, and novelty seeking factors were associated with a greater tendency for agoraphobia panic attacks (Izci et al., 2014; Norberg et al., 2015). To the best of our knowledge, work on the relationship between cognitive and cerebral aging and personality traits has been based exclusively on the 5-factor model. However, significant correlations between these 5 factors and Cloninger's TCI factors have been demonstrated. In particular, neuroticism is positively correlated with harm-avoidance and negatively correlated with self-determination, extraversion is negatively correlated with harm-avoidance and positively with novelty seeking, persistence, and self-transcendence, openness is positively correlated with cooperativeness, conscientiousness is negatively correlated with novelty seeking and positively with persistence and self-determination, and agreeableness is positively correlated with reward dependence, cooperativeness and self-transcendence [291,292]. These relations suggest that associations between TCI and cognitive and brain aging may be expected.

More recently, a work of correlational analyses based on TCI items focused on those associated with increased risk for mental disorders (Dell'Orco et al., 2018). The authors then identified and validated four new factors: optimism (OTT: optimism about the future, high confidence in one's own resources and determination), closeness to experience (CE: avoidance of new stimuli, high anxiety, pessimistic anticipation, low reward seeking), tendency to liability (TL: feeling of inability to change their own reality, low autonomy, low sense of the value of their existence), and fantasy of superiority (FS: narcissistic fantasy of being more intelligent, attractive and strong than others, fear of the passage of time and the weakening of the body). Analyses of the factors demonstrated good internal consistencies within them as well as significance in terms of predicting mental disorders: OTT being a protective factor, while the other three factors were factors for higher risk of mental disorders (Dell'Orco et al., 2018).

Objectives and hypothesis

Because of the established links between personality traits and NPS, and their relationships to age-related neurocognitive declines, the objectives of this study was to understand the longitudinal and cross-sectional relationships between the mental disorders-related personality factors from the Dell'Orco et al. (2018) Revised TCI and NPS (as a validation step for these personality factors as risk factors for NPS in aging), cognitive performance, and brain gray and white matter structures in a population-based sample from the in the BETULA study, developing Alzheimer's-like dementia or not. A secondary objective is to estimate the risk of AD dementia underpinned by the personality factors of the TCI-R.

Depending on the internal consistency of each personality factor (only acceptable ones will be retained for analysis), it is expected that participants with higher CE, TL, and FS factors would have higher NPS of increasing severity during follow-up, whereas participants with higher OTT would be more preserved against NPS. Cognitively, CE, TL and FS factors are expected to be associated with poorer and more rapidly declining cognitive performance, especially memory and executive function (verbal fluency tests). On the contrary, OTT would be associated with lower NPS and better cognitive preservation. The imaging analyses will focus on regions and networks known to be associated with personality and involving frontal, temporal and cingulate structures.

It is expected that higher CE, TL and FS factors would be associated with greater volume and diffusion reductions over time, while the OTT factor would be associated with better structural integrity.

Methods

Betula database

Participants in the Betula study, recruited from the city of Umeå on the northeast coast of Sweden and its surroundings, were randomly sampled from the population register, stratified by age and sex. The age cohorts were divided into 5-year intervals (25, 30, 35, ... 80, 85, 95 years) and the number of men and women selected for inclusion was proportional to the male-to-female ratio in each age cohort of the general population. Participants with dementia, non-native speakers of Swedish, severe hearing or visual impairment, or congenital or acquired intellectual disability were excluded and replaced by another individual from the population registry of the same age and sex. The recruitment procedure has been described in detail (Nilsson et al., 2004; Nilsson et al., 1997). The first wave of data collection started in 1988 and in total six main waves (W1-W6) of data collection have been conducted, with the sixth wave completed in 2014. In addition, a seventh wave of testing (W7) was conducted in 2017 for participants returning for a third follow-up neuroimaging (MRI/FMRI) and a limited set of health and cognitive assessments.

In the Betula study, the same diagnostic criteria were applied throughout the study period (1988 - 2017). Sufficient information was obtained to apply systems based on clinical criteria, namely the core criteria of the DSM-IV classification for dementia (American Psychiatric Association, 1998). Participants diagnosed with AD had an insidious onset and progressive cognitive decline and other symptoms typically attributable to clinical AD. Disease onset was defined as the year when clinical symptoms became severe enough to interfere with social functioning and instrumental activities of daily living, i.e., when the basic criteria for dementia were met (McKhann et al., 2011).

Inclusion and exclusion criteria

For analysis, only participants who were cognitively healthy or developing dementia of the Alzheimer type were included. Participants with a neurological or cognitive impairment history, or developing another dementia condition (vascular, Lewy body, Parkinson, mixed, other) were excluded. Similarly, participants with missing genetic (APOE status: carriers or noncarriers of at least one ε4 allele), personality (TCI), cognitive, neuropsychiatric, or imaging data were respectively excluded for each analysis group. For the neuropsychiatric and cognitive models, the continuous data were standardized into z-scores according to the formula: *(subject residuals – baseline group mean) / baseline group SD*. Outliers beyond +/- 3SD from the mean were excluded. For the neuroimaging models, the residuals of each structure for each participant were extracted using regressions using structures as dependent variables and time, baseline age (continuous and quadratic), estimated total intracranial volume (for hippocampi). Residuals were standardized to z-scores according to the formula: *(subject residuals - baseline group mean) / baseline group SD*. Outliers beyond +/- 3SD of the mean were excluded. After exclusion, the raw continuous data were converted to z-scores and used for mixed-effects linear regressions.

The information for each subsample is summarized in the table below. There may be small differences in sample sizes between the different analyses (whole sample, HC sample) and the data reported in the demographic tables, this is due to the processes of standardization and exclusion of outliers by the z-scores which do not exclude exactly the same number of participants depending on the sample considered.

Table 5.2. Samples features for every analysis group.

Analysis	Samples	N at baseline	Observations	Study waves	Mean follow-up (Min-Max)
Neuropsychiatric	Full sample (CES-D)	1166	3174	3 to 6	8.5 years (0-15)

	Full sample (PHQ-9)	657	1071	5 to 6	3 years (0-5)
	Full sample (PSQ)	948	2058	4 to 6	6 years (0-10)
Sleep (KSQ)	Full sample	445	625	5 to 6	2 years (0-5)
Cognitive	Full sample	1286	4848	1 to 6	14 years (0-25)
	HC Only	1145	4413	1 to 6	14.5 years (0-25)
Structural MRI	Full sample	235	414	5 to 7	4 years (0-10)
	HC Only	216	411	5 to 7	4.5 years (0-10)
DTI	Full sample	228	436	5 to 7	4.5 years (0-10)
	HC Only	211	410	5 to 7	4.5 years (0-10)

Legend : Full sample = Participants with or without conversion to dementia at follow-up, HC = Healthy controls without conversion to dementia at follow-up, CES-D = Center for Epidemiological Study – Depression scale, PHQ-9 = Patient Health Questionnaire 9 items, PSQ = Perceived Stress Questionnaire, KSQ = Karolinska Sleep Questionnaire, baseline = refers to the wave where the first evaluations of the model were performed (5th for retained neuropsychiatric data and imagery, 1st for cognitive data).

Personality data

Considering the relative stability of personality across development and aging, the first time of personality measurement for each participant was kept as a single personality measure (Wave 2 or 3) (Brändström et al., 2008).

The personality factors used were derived from the new factors determined by the analyses of Dell'Orco et al. (2018). The dimension "Optimism" (OTT) describes subjects who are clearly optimistic about the future, have high confidence in their own resources, and are determined to act. The "Closeness to Experience" (CE) dimension describes subjects who avoid novel stimuli, have marked anxiety, pessimistic anticipatory tendency, and habitual behaviors and reflexivity, low reward seeking, and refusal of unusual activities. The dimension "Tendency to Liability" (TL) describes subjects who represent themselves as unable to change their own reality, which is basically not very autonomous and with a low sense of the value of their existence. The dimension " Fantasy of Superiority " (FS) describes subjects who narcissistically fantasize about being smarter, more attractive and stronger than anyone else and who fear the passage of time and the weakening of the body.

For verification purposes, the internal consistency of the factors in our sample as well as the correlation between measurement times 2 and 3 (W2-W3) were tested. The data indicate that two of the factors have acceptable internal consistency (CE and TL), or questionable internal consistency (OTT and FS). The data are summarized in the table below.

Table 5.3. Internal consistency and correlation between TCI-R factors in whole sample

TCI factor	Cronbach's α	OTT	CE	TL	FS
OTT	0.61	$r_{w2\text{-}w3} = 0.62$			
CE	0.78	$r_{w2\text{-}w2} = -0.31$	$r_{w2\text{-}w3} = 0.67$		

TL	0.76	$r_{w2\text{-}w2} = -0.20$ $r_{w2\text{-}w2} = 0.62$ $r_{w2\text{-}w3} = 0.67$
FS	0.67	$r_{w2\text{-}w2} = 0.02$ $r_{w2\text{-}w2} = 0.40$ $r_{w2\text{-}w2} = 0.44$ $r_{w2\text{-}w3} = 0.69$

Legend : OTT = Optimism, CE = Closeness to Experience, TL = Tendence to Liability, FS = Fantasy of Superiority. Cronbach's Interpretation : >0,70 is acceptable, >0,60 is questionable (Gliem & Gliem, 2003). r = Pearson's correlation coefficient, $r_{w2\text{-}w3}$ = correlation between assessments from waves 2 and 3, $r_{w2\text{-}w2}$ = correlation between assessments from wave 2. Every coefficient is significant at $p < 0.001$ except for OTT*FS correlation ($p = 0.591$).

Neuropsychiatric data

Neuropsychiatric data were extracted from waves 3 to 6 depending on the questionnaire used and consisted of assessments of depression, stress, and sleep.

Depression was assessed by the Patient Health Questionnaire-9 (PHQ-9) [293]. This is a self-report consisting of 9 questions designed to screen for the presence and severity of depression in adult patients. Each question assesses the frequency of problems experienced by individuals in the past two weeks. This frequency is rated from 0 to 3 (0: not at all, 1: a few days, 2: at least half the days, 3: almost every day).

Depression was also assessed by the Center for Epidemiologic Studies-Depression scale (CES-D) [294]. This is a self-report consisting of 20 questions designed to screen for the presence and severity of depression in adult patients. Each question assesses the frequency of affect experienced by individuals during the past week. This frequency is rated from 0 to 3 (0: never/very rarely, 1: occasionally, 2: often, 3: frequently/permanently). Four of the 20 items are reversed.

Stress was assessed using the Perceived Stress Questionnaire [295]. It was designed as an instrument to assess stressful life events and circumstances that tend to trigger or exacerbate symptoms of illness. This 30-item questionnaire is a self-report of the frequency of stressful feelings and

experiences rated from 1 to 4 (1: never/very rarely, 2: occasionally, 3: often, 4: frequently/always). Eight of the 30 items are reversed.

Sleep was assessed using the Karolinska Sleep Questionnaire [296]. In addition to assessing the sleep characteristics of individuals (need, sufficiency, quality, schedule...), the questionnaire has 4 subscales: sleep apnea consisting of 3 items, sleepiness consisting of 5 items, sleep quality consisting of 4 items, and non-restorative sleep consisting of 3 items. Each item focuses on the frequency of experiences based on the last 3 months and is scored from 0 to 5 (0: never, 1: rarely, 2: sometimes, 3: often, 4: most of the time, 5: always). The sum of the scores was also used as the total score of the questionnaire.

Neuropsychological data

The cognitive battery used in this study includes a composite episodic memory score (including free recall, cueing and recognition tasks for different types of material: words, sentences, actions and faces), vocabulary from the SBR [297] and block design task from the WAIS, and a composite verbal fluency score calculated on the basis of the average of the z-scores on the different fluency tests (words starting with letter A, 5-letter and starting with letter M, occupations starting with letter B, 5-letter animals starting with letter S).

MRI and DTI data

MRI acquisition was performed on the same General Electric 3 T scanner equipped with a 32-channel head coil at all time-points. At W5, the scanning session comprised a high-resolution anatomical T1-image, a T2 image, and a DTI sequence with 3 repetitions of 32 independent directions. Acquisitions were based on participants in cohorts 1, 3, and 6 with complete health and cognitive data at visit 5, without contraindications to MRI, severe neurological disorders, or motor/visuospatial deficits. Participants were selected via stratification by age and sex.

Thus, the total sample consisted of N = 376 (52% female, age-range = 25-80 years) at visit 5, N = 231 at visit 6 and N = 103 at visit 7.

For the image analysis, we used the Freesurfer v. 6.0 (Martinos Center for Biomedical Imaging, Charlestown, MA, USA) where regional cortical thicknesses and volumetric measures were estimated [159,298]. The software is well documented and available for download online (http://surfer.nmr.mgh.harvard.edu/). To adjust the subcortical volumes to the intracranial volume we performed simple regressions between each nucleus and the intracranial volume, and then calculated an adjusted volume according to the formula volume(adjusted) = volume(observed) - a(eTIV[observed] - eTIV[mean]), where a is the simple regression coefficient between each nucleus and the intracranial volume (Jack et al., 2015; Whelan et al., 2019).

Diffusion-weighted data were preprocessed using the University of Oxford's Center for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) package (http://www.fmrib.ox.ac.uk/fsl). Images were acquired with a spin-echo-planar T2-weighted sequence as follows: 64 slices, TR = 8,000 ms, TE = 84.4 ms, flip angle = 90°, FOV = 250 × 250 mm, b = 1000 s/mm2, 32 independent directions, and six b = 0 images. Three sequence repetitions were acquired at W5 and W6, whereas W7 only included one repetition. To allow for consistency between waves, only the first repetition at each wave was used. Head movement was minimized using cushions inside the head coil for all imaging sequences. Each imaging occasion followed identical experimental designs and procedures, i.e., the same scanner, acquisition times, and head coil were used at each data collection wave. More details are available in previous studies using Betula imaging data (Avelar-Pereira et al., 2020 ; Pedersen et al., 2021).

As structural variables of interest, cortical and white matter, total and lobar (frontal, cingular, insula, temporal), and bilateral hippocampal volumes were extracted. The table below describes the structures used in the calculation of total lobar volumes.

Table 5.4. Details of the structures included in the calculation of lobar volumes.

Lobes	Structures

Frontal	Frontal pole, paracentral gyrus, pars opercularis / triangularis / orbitalis gyri, caudal / rostral middle gyri, superior gyrus, lateral / medial orbitofrontal gyri, precentral gyrus
Temporal	Superior temporal sulcus, entorhinal gyrus, fusiform gyrus, inferior / middle / superior temporal gyri, parahippocampal gyrus, temporal pole, temporal transverse
Cingulate	Caudal / rostral anterior, posterior, isthmus

Similarly, diffusion variables of interest, based on the fractional anisotropy of white matter networks, involved the fornix, cingulate cingulum, cingulum-hippocampal networks, and the uncinate tracts. These networks were selected because of the relationship between their structures and personality factors by both structural MRI and DTI studies [279–282,299–311].

Genotyping

Genotyping for the Apolipoprotein E (*APOE*) gene (ε2, ε3, ε4 alleles) was performed by polymerase chain reaction, and was available in 2 990 participants from the whole cohorts S1-S3 and S5 (see e.g., [312]).

Statistical analysis

Statistical analyses were performed on the open source web application Jupyter Notebook (version 6.3.0) using scripts written in Python language (version 3.9.5).

First, correlations were established using Pearson's tests to describe associations between the personality factors. In case of significant correlations, the regression models considered each personality factor independently. These correlations were performed with the scipy.stats.pearsonr function.

In a second step, linear mixed-effects regression models are used to test the main and time-interaction effects of personality factors with acceptable internal consistency on neuropsychiatric

symptoms. Ces modèles sont une étape de validation des traits de personnalité comme associations avec les NPS. For each model, age at baseline, quadratic age at baseline, time (years from the baseline), sex *APOE* status, interaction between time and *APOE* status, personality factors, and interaction between time and personality factors are considered fixed factors (time, personality factors, and their interaction as factors of interest, the others as covariates).

In a last step, linear mixed-effects regression models are used to test the main and time-interaction effects of validated personality factors on cognitive performance, and brain structures/diffusivity. For each model, age at baseline, quadratic age at baseline, time (years from the baseline), sex, years of education, *APOE* status, interaction between time and *APOE* status, personality factors, and interaction between time and personality factors are considered fixed factors (time, personality factors, and interaction as factors of interest, the others as covariates). Individual participants are considered as random factors. All models included random effects for intercepts and slopes. These models were generated with the statsmodel package and the functions statsmodel.api and statsmodel.formula.api.mixedlm. Despite data cleaning steps to normalize the distributions, they did not meet the residuals normality criterion for linear mixed models. However, recent work has demonstrated the robustness of these models even when this application condition was violated [313].

Each regression model is estimated according to the form:

*Dependent variables ~ age + age² + sex + APOE + education + time + ApoE*Time + Personality + Personality*time + random intercept + random slope.*

With neuropsychiatric symptoms, cognitive performance, and brain structures as dependent variables. In order to enhance convergence of the model matrices, "lbfgs" or "powell" data fitting methods were applied.

A Cox proportional hazards regression was used to predict the risk of Alzheimer's type dementia based on demographics, APOE status, and revised personality factors. Dementia diagnosis was treated as the failure event. Years from the baseline (first measure wave) were used as the time scale. The last available visit was used for censoring participants not developing dementia,

whereas the conversion visit was used for participants developing dementia. Finally, age, sex, years of education, *APOE* status (*APOE*-ε4 carriers or not), and scores on the revised TCI personality factors (CE, TL) were used as covariates. This type of model was performed using the lifelines.CoxPHFitter package.

For cognitive and cerebral models, a False Discovery Rate correction was applied by considering the number of dependent variables (4 for cognitive, 15 for brain volumes, 7 for fractional anisotropy), the number of fixed interest factors (3 per model: main effect of time, main effect of personality factor and its interaction with time), and the number of personality factors (2) as repetition factors. The corrections were applied using the package statsmodel, and the function stats.multitest.fdrcorrection with: a Benjamini/Hochberg method and a Family-wise error rate of 0.05. The results tables display the adjusted p-values (p-adj), which are significant if they are less than 0.05.

Results

Demographic characteristics

The main sample selected included 1149 healthy participants at baseline not converting to AD dementia during follow-up and 137 participants converting during follow-up. These two subgroups differed in age, years of education, MMSE score, sex and *APOE* status distribution. These descriptive data are summarized in the table below.

Table 5.5. Demographic characteristics of the total sample retained at baseline

	HC	AD	Statistic T/Chi²	p-value
N	1149	137	-	-
Age m(sd)	48.13 (8.30)	56.84 (5.33)	-4.49	< 0.001
Education m(sd)	12.23 (3.85)	8.89 (3.46)	3.65	< 0.001

MMSE m(sd)	27.98 (1.65)	27.42 (1.87)	1.39	0.166
Women %	50.46	84.21	6.69	0.010
APOE-ε4 %	25	52.63	5.41	0.02

Legend: HC = participant who not converted in any dementia type; AD = participants who converted in AD dementia type during the follow-up.

The subsample for MRI analysis included 216 healthy participants at baseline not converting to AD dementia during follow-up and 19 participants converting during follow-up. The descriptive data are summarized in the table below.

Table 5.6. Demographic characteristics of the MRI subsample retained at baseline

	HC	AD	Statistic T/Chi²	p-value
N	216	19	-	-
Age m(sd)	48.13 (13.55)	66.93 (9.16)	-9.33	< 0.001
Education m(sd)	10.47 (3.92)	8.00 (2.81)	7.17	< 0.001
MMSE m(sd)	27.97 (1.66)	27.40 (2.00)	3.67	< 0.001
Women %	51.52	75.91	28.35	< 0.001
APOE-ε4 %	27.50	54.74	41.65	< 0.001

Legend: HC = participant who not converted in any dementia type; AD = participants who converted in AD dementia type during the follow-up.

Neuropsychiatric trajectories related to TCI new factors

Controlling for age, sex, and *APOE* status, CE showed positive cross-sectional association with CES-D (depression), and positive longitudinal association with PSQ (stress). TL showed also a positive

cross-sectional association with CES-D, PSQ, and KSQ, and a positive longitudinal association with PHQ-9 score (Depression). Thus, the higher the CE and TL, the higher the depression, stress and sleep disturbances, and the higher the longitudinal progression of depression and stress (depression assessed with CES-D, with PHQ-9, stress and sleep were measured respectively 10.01 +/- 5.60, 16.43 +/- 2.98, 13.27 +/- 4.29 and 16.53 +/- 2.97 years after the personality). The neuropsychiatric and sleep results are presented in Table 5.7.

Table 5.7. Relationships between time, personality factors and their interactions on neuropsychiatric symptoms.

Dependant	Fixed factors	Coef.	Std.Err.	P>|z|	[0.025	0.975]
CES-D	Time	0.001	0.003	0.835	-0.005	0.006
	CE	0.249	0.040	**<.001*** **	0.171	0.328
	Time*CE	0.003	0.003	0.298	-0.003	0.008
	Time	0.001	0.003	0.859	-0.005	0.006
	TL	0.237	0.042	**<.001*** **	0.155	0.320
	Time*TL	0.003	0.003	0.235	-0.002	0.009
PHQ-9	Time	0.010	0.008	0.187	-0.005	0.026
	CE	-0.038	0.140	0.787	-0.312	0.236
	Time*CE	0.014	0.007	*0.055†*	-0.000	0.028
	Time	0.010	0.008	0.221	-0.006	0.025
	TL	-0.062	0.149	0.678	-0.354	0.230
	Time*TL	0.016	0.008	**0.042***	0.001	0.031
PSQ	Time	-0.028	0.004	**<.001*** **	-0.037	-0.020
	CE	0.073	0.068	0.281	-0.060	0.207
	Time*CE	0.012	0.004	**0.002****	0.004	0.020
	Time	-0.029	0.004	**<.001*** **	-0.037	-0.021
	TL	0.145	0.070	**0.038***	0.008	0.283
	Time*TL	0.006	0.004	0.141	-0.002	0.014
KSQ	Time	-0.006	0.011	0.552	-0.028	0.015
	CE	0.159	0.210	0.448	-0.252	0.570
	Time*CE	0.002	0.011	0.868	-0.019	0.023
	Time	-0.010	0.011	0.378	-0.031	0.012
	TL	0.497	0.220	**0.024***	0.066	0.928
	Time*TL	-0.018	0.011	0.102	-0.040	0.004

Legend: CES-D = Center for Epidemiologic Studies-Depression scale; PSQ = Perceived Stress Questionnaire; PHQ-9 = Patient Health Questionnaire-9 items; KSQ = Karolinska Sleep Questionnaire; CE = Closeness to Experience; TL = Tendence to Liability. Models are adjusted for age, sex, and APOE status of participants. †p<.10; *p<.05; **p<.01; ***p<.001

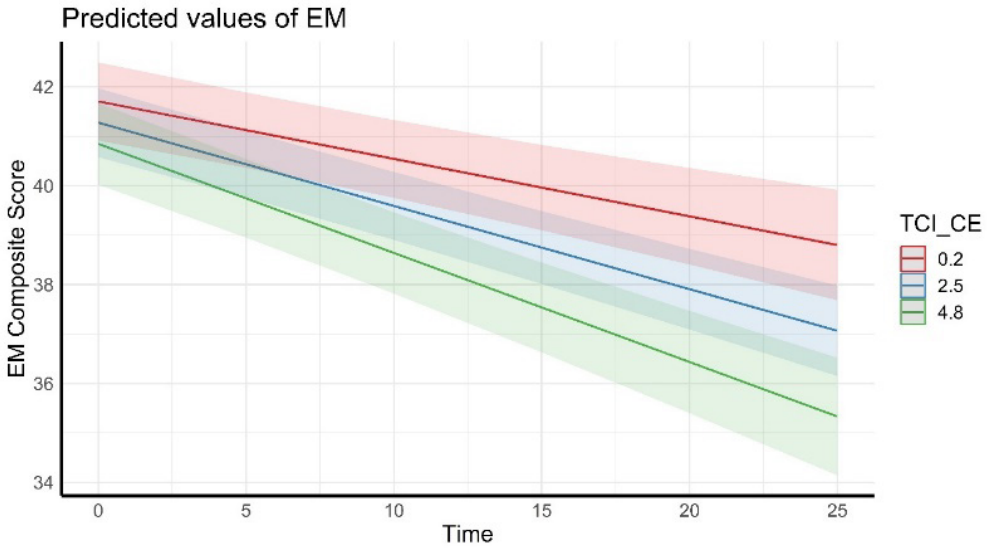
Cognitive trajectories related to TCI new factors

Controlling for age, sex, education, APOE status, and adjusting the models with an FDR correction, both CE and TL personality factors showed significant effects on cognitive cross-sectional and longitudinal outcomes.

The unadjusted and adjusted cognitive outcomes are summarized in Table 5.8. We report results for the full samples, as well as a healthy subset of non-AD converting participants, in order to determine whether potential personality-related effects on cognitive performance are driven by pre-clinical AD-related declines.

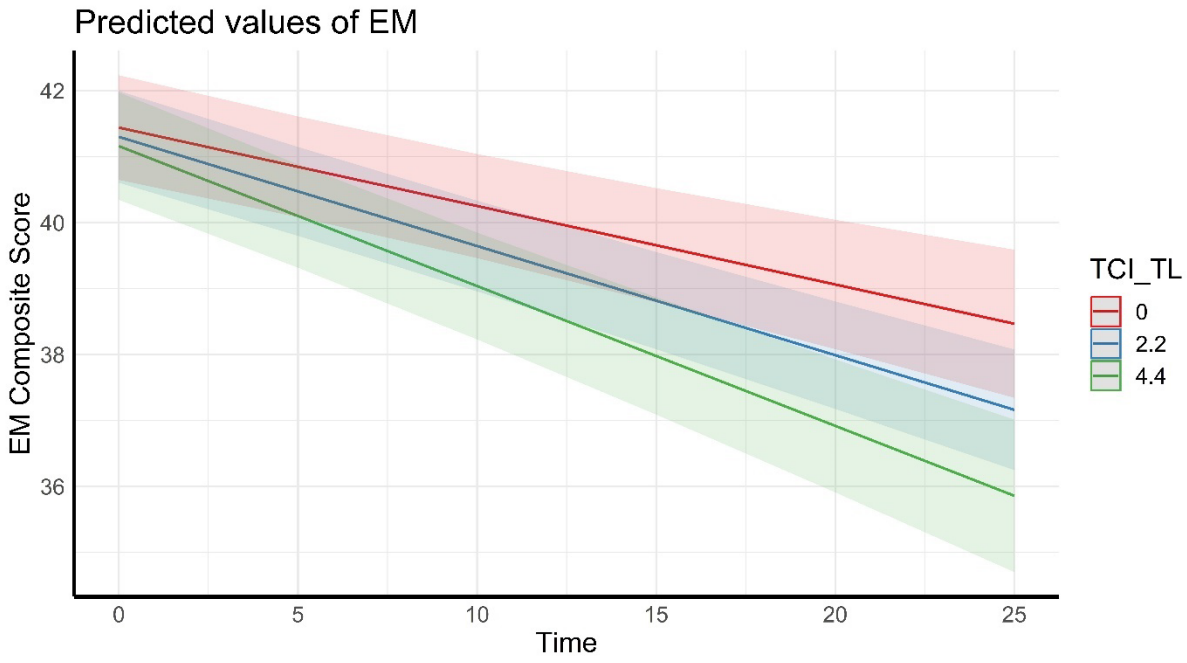
In the full sample, the analyses show that episodic memory performance decreases over time and decreases the more the personality factors CE and TL are high (longitudinal main and interaction effects – Figures 5.1 and 5.2). It was in line with our hypotheses.

Figure 5.1. Interaction effects of Closeness to Experience and Time on Episodic memory composite score in full sample.



Legend: EM = Episodic Memory, TCI_CE = Closeness to Experience score assessed with Temperament and Character Inventory.

Figure 5.2. Interaction effects of Tendence to Liability and Time on Episodic memory composite score in full sample



Legend: EM = Episodic Memory, TCI_TL = Tendence to Liability score assessed with Temperament and Character Inventory.

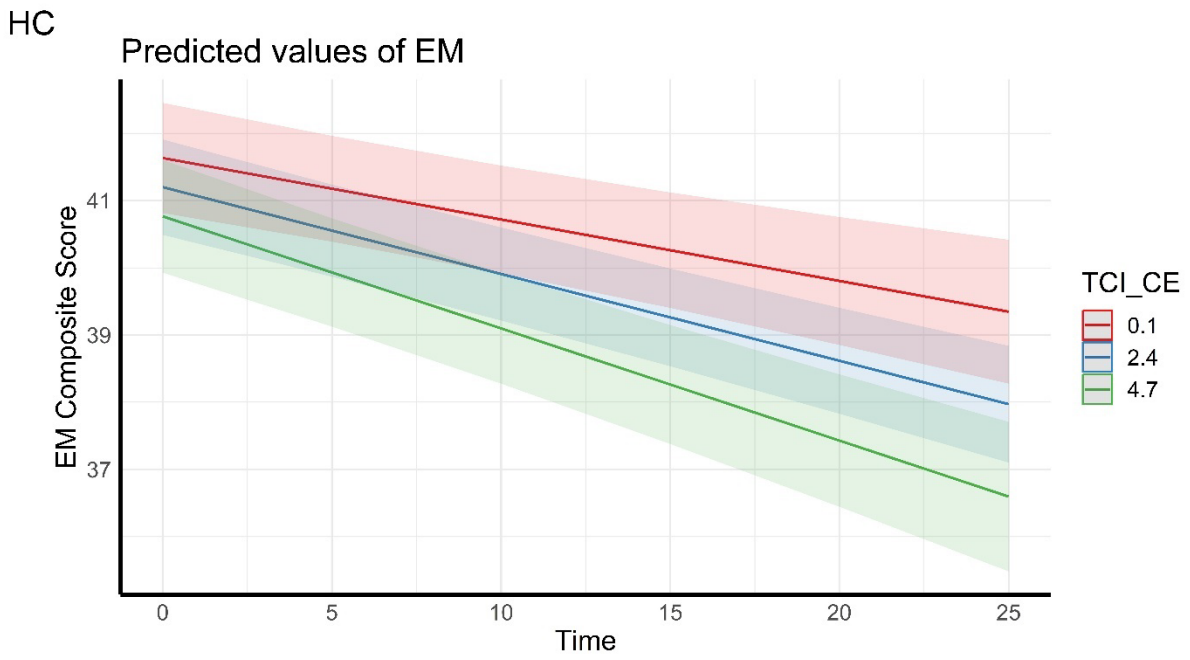
Concerning vocabulary performance, higher CE and TL factors are associated with lower performance (cross-sectional main effects), performance decreases over time and the higher the CE and TL factors are (longitudinal main and interaction effects). It was an unexpected result and therefore not in line with our assumptions. Moreover, it was unexpected to observe a negative effect of time on performance due to the relative stability of crystallized abilities in aging.

Regarding block design task, higher CE and TL factors are associated with lower performance (cross-sectional main effects), and performance decreases over time (longitudinal main and interaction effects). No longitudinal interaction effects between time and personality factors on performance were observed. We did not expect any longitudinal effects of personality on this cognitive performance.

Concerning fluency performance, higher CE factor is associated with lower performance (cross-sectional main effects), performance decreases over time and the higher the CE and TL factors are (longitudinal main and interaction effects). It was in line with our hypotheses.

In the HC subsample, the analyses show that episodic memory performance decreases over time and decreases the more the personality factor CE is high (longitudinal main and interaction effects – Figure 5.3). It was in line with our hypotheses.

Figure 5.3. Interaction effects of Closeness to Experience and Time on Episodic memory composite score in HC subsample.



Legend: EM = Episodic Memory, TCI_CE = Closeness to Experience score assessed with Temperament and Character Inventory.

Concerning vocabulary performance, higher CE and TL factors are associated with lower performance (cross-sectional main effects), performance decreases over time (longitudinal main effect). No longitudinal interaction effects between time and personality factors on performance were observed. We did not expect any longitudinal effects of personality on this cognitive performance.

Regarding block design task, higher CE factor is associated with lower performance (cross-sectional main effect), and performance decreases over time (longitudinal main and interaction effects). No longitudinal interaction effects between time and personality factors on performance

were observed. We did not expect any longitudinal effects of personality on this cognitive performance.

Concerning fluency performance, higher CE factor is associated with lower performance (cross-sectional main effects), and performance decreases over time (longitudinal main and interaction effects). No longitudinal interaction effects between time and personality factors on performance were observed. It was an unexpected result and therefore not in line with our assumptions.

Table 5.8. Relationships between time, personality factors and their interactions on cognitive performance.

		Full Sample						HC Sample					
Dependant	Fixed factors	Coef.	Std.Err.	P>|z|	[0.025	0.975]	p fdr	Coef.	Std.Err.	P>|z|	[0.025	0.975]	p fdr
Memory	Time	-0.017	0.002	**<.001*** **	-0.020	-0.014	**<.001*** **	-0.013	0.001	**<.001*** **	-0.016	-0.010	**<.001*** **
	CE	-0.044	0.024	*0.059†*	-0.091	0.002	*0.070†*	-0.048	0.025	*0.054†*	-0.096	0.001	*0.093†*
	Time*CE	-0.006	0.002	**<.001*** **	-0.009	-0.003	**0.002****	-0.004	0.002	**0.006****	-0.007	-0.001	**0.022***
	Time	-0.017	0.002	**<.001*** **	-0.020	-0.013	**<.001*** **	-0.013	0.001	**<.001*** **	-0.016	-0.010	**<.001*** **
	TL	-0.013	0.023	0.573	-0.059	0.033	0.573	-0.036	0.025	0.148	-0.084	0.013	0.170
	Time*TL	-0.005	0.002	**0.001****	-0.008	-0.002	**0.004****	-0.003	0.002	*0.071†*	-0.006	0.000	0.107
Vocabulary	Time	-0.004	0.001	**0.003****	-0.006	-0.001	**0.007****	-0.003	0.001	**0.013***	-0.005	-0.001	**0.034***
	CE	-0.063	0.023	**0.007****	-0.109	-0.017	**0.013***	-0.058	0.024	**0.018***	-0.105	-0.010	**0.036***
	Time*CE	-0.003	0.001	**0.012***	-0.005	-0.001	**0.018***	-0.002	0.001	*0.062†*	-0.005	0.000	*0.099†*
	Time	-0.003	0.001	**0.003****	-0.006	-0.001	**0.008****	-0.003	0.001	**0.017***	-0.005	-0.000	**0.036***
	TL	-0.063	0.023	**0.006****	-0.108	-0.018	**0.013***	-0.075	0.024	**0.002****	-0.123	-0.027	**0.010***
	Time*TL	-0.003	0.001	**0.012***	-0.005	-0.001	**0.018***	-0.002	0.001	*0.089†*	-0.004	0.000	0.118
Block design	Time	-0.028	0.001	**<.001*** **	-0.030	-0.025	**<.001*** **	-0.027	0.001	**<.001*** **	-0.029	-0.024	**<.001*** **
	CE	-0.066	0.025	**0.008****	-0.114	-0.018	**0.013***	-0.055	0.026	**0.038***	-0.107	-0.003	*0.071†*
	Time*CE	-0.001	0.001	0.307	-0.004	0.001	0.334	-0.001	0.001	0.307	-0.004	0.001	0.320
	Time	-0.028	0.001	**<.001*** **	-0.030	-0.025	**<.001*** **	-0.027	0.001	**<.001*** **	-0.029	-0.024	**<.001*** **
	TL	-0.055	0.025	**0.024***	-0.104	-0.007	**0.032***	-0.046	0.026	*0.084†*	-0.098	0.006	0.118
	Time*TL	-0.002	0.001	0.172	-0.004	0.001	0.197	-0.002	0.001	0.227	-0.004	0.001	0.247
Fluency	Time	-0.005	0.001	**<.001*** **	-0.007	-0.002	**<.001*** **	-0.003	0.001	**0.009****	-0.006	-0.001	**0.028***
	CE	-0.057	0.021	**0.006****	-0.098	-0.017	**0.013***	-0.053	0.022	**0.016***	-0.096	-0.010	**0.036***
	Time*CE	-0.003	0.001	**0.033***	-0.005	-0.000	**0.041***	-0.002	0.001	0.121	-0.005	0.001	0.153
	Time	-0.005	0.001	**<.001*** **	-0.007	-0.002	**<.001*** **	-0.003	0.001	**0.006****	-0.006	-0.001	**0.022***
	TL	-0.014	0.021	0.504	-0.054	0.027	0.526	-0.015	0.023	0.515	-0.060	0.030	0.515
	Time*TL	-0.003	0.001	**0.014***	-0.006	-0.001	**0.019***	-0.002	0.001	0.139	-0.004	0.001	0.167

Legend: Mem = Episodic Memory; Voc = Vocabulary; Bloc = Bloc Design; Flu = Verbal Fluency; CE = Closeness to Experience; TL = Tendence to Liability. Models are adjusted for age, sex, education, and *APOE* status of participants. †p<.10; *p<.05; **p<.01; ***p<.001

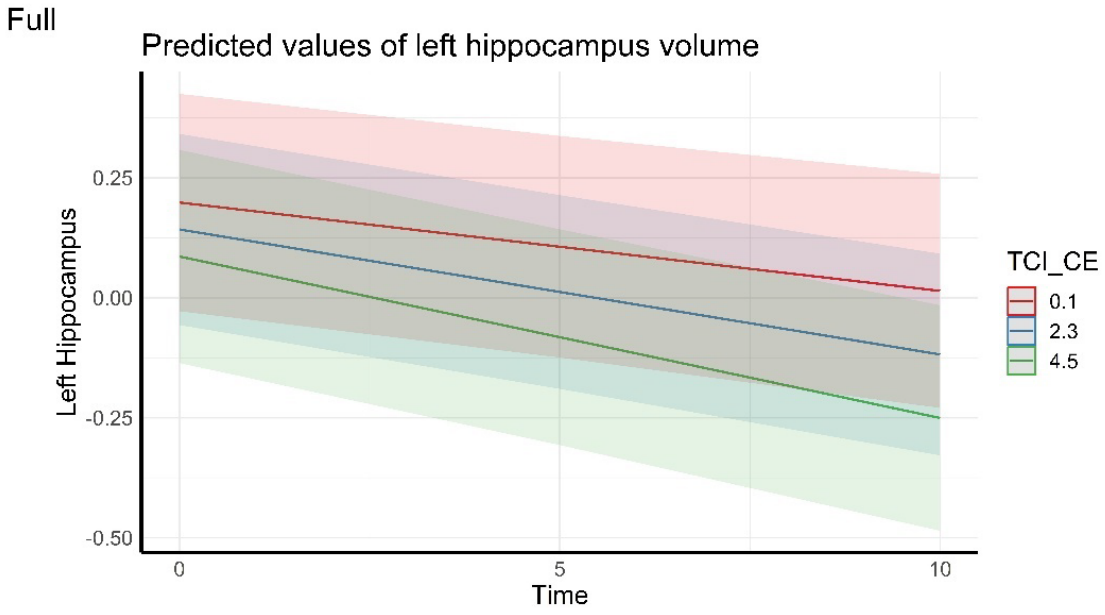
Brain trajectories related to TCI new factors

Controlling for age, sex, education, APOE status, and adjusting the models with an FDR correction, only CE personality factors showed significant cross-sectional effects on brain.

The unadjusted and adjusted neuroimaging outcomes are summarized in Tables 5.9 (Grey matter volumes), 5.10 (White matter volumes) and 5.11 (White matter tracts).

In the full sample, regarding the cortical and hippocampal volumes using MRI, main effects of time on all structures (cortical and white matter volumes) are observed: volumes decrease over time. The left hippocampal volume decreased more over time as the CE score increased (interaction effect – Figure 5.4). The interaction effects on right hippocampus and right temporal volume did not survive FDR corrections. No cross-sectional effects with personality factors on brain volumes were observed.

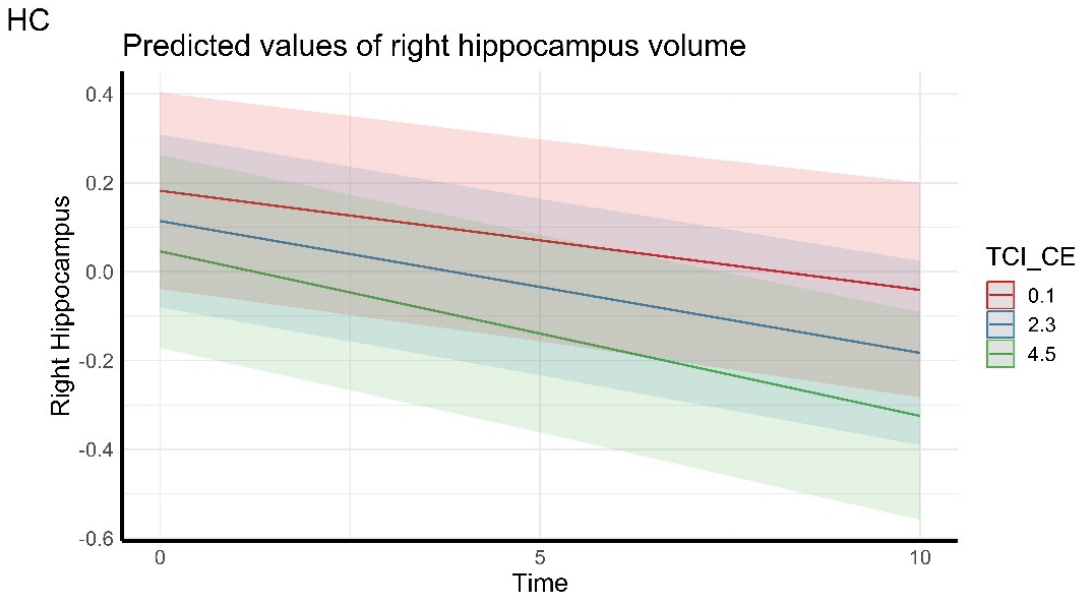
Figure 5.4. Longitudinal effect of time on left hippocampal volume in Full subsample.



Legend: TCI_CE = Closeness to Experience score assessed with Temperament and Character Inventory.

In the HC subsample, regarding the cortical and hippocampal volumes, main effects of time on all structures (cortical and white matter volumes) are observed: volumes decrease over time. The right hippocampal volume decreased more over time as the CE score increased (Figure 5.5), whereas the right temporal volume decrease less over time as the CE and TL scores were higher (interaction effects). The interaction effects on left hippocampus volume did not survive FDR corrections. No cross-sectional effects with personality factors on brain volumes were observed.

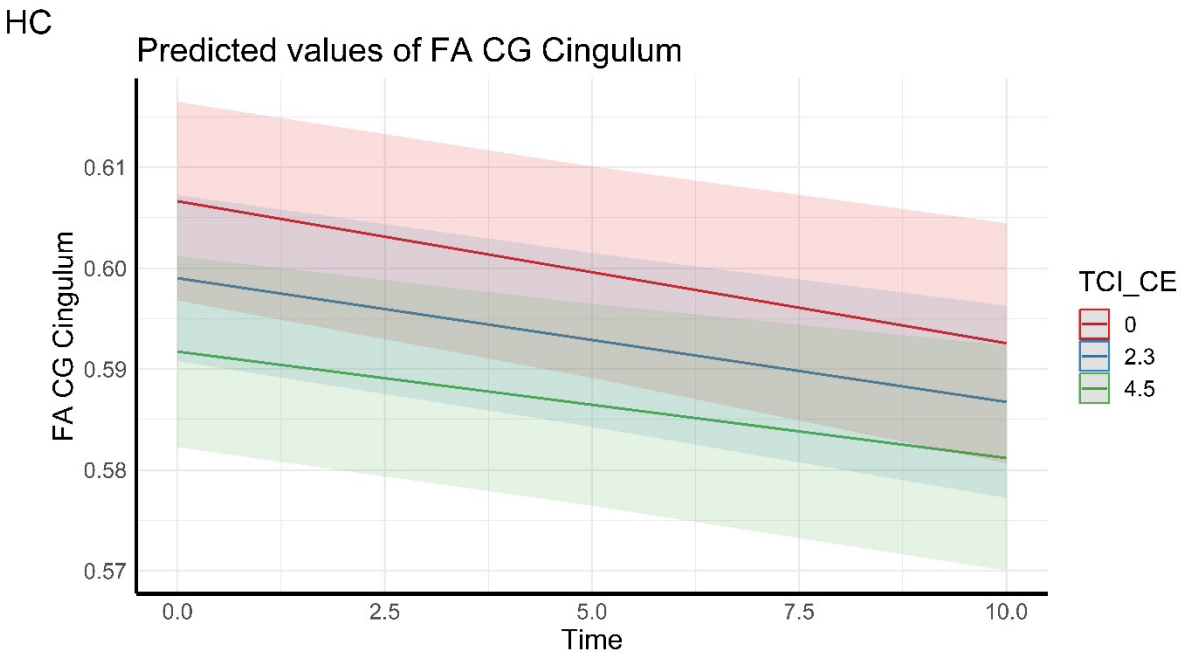
Figure 5.5. Longitudinal effect of time on right hippocampal volume in HC subsample.



Legend: TCI_CE = Closeness to Experience score assessed with Temperament and Character Inventory.

Regarding network analyses, main effects of time on fornix and right cingulate-cingulum FA are observed: fractional anisotropy (FA) decrease over time (in both full and HC sample). Effects of time on left cingulate-cingulum and cingulate hippocampus FA (full sample) did not survive the FDR. Cross-sectional effect of CE on left cingulate-cingulum FA was highlighted in both groups (the higher the CE, the lower the FA). In the full sample, the effect of CE on right cingulate cingulum FA did not survive the FDR correction, whereas it was confirmed in the HC subsample. No longitudinal interaction effects with personality factors on FA were observed. Longitudinal effect of time on cingulate-cingulum FA in HC subsample are plotted in Figure 5.4.

Figure 5.6. Longitudinal effect of time on Cingulate-cingulum fractional anisotropy in HC subsample.



Legend: FA = Fractional Anisotropy, CG = Cingulate, TCI_CE = Closeness to Experience score assessed with Temperament and Character Inventory.

Table 5.9. Relationship between time, personality factors and their interactions on grey matter volumes

		Full Sample						HC Sample					
Dependant	Fixed factors	Coef.	Std.Err.	P>|z|	[0.025	0.975]	p_fdr	Coef.	Std.Err.	P>|z|	[0.025	0.975]	p_fdr
Hipp L	Time	-0.026	0.003	**<.001*** **	-0.033	-0.019	**<.001*** **	-0.027	0.003	**<.001*** **	-0.033	-0.020	**<.001*** **
	CE	-0.055	0.052	0.293	-0.158	0.047	0.540	-0.056	0.055	0.311	-0.165	0.052	0.596
	Time*CE	-0.008	0.003	**0.004** **	-0.013	-0.002	**0.016***	-0.006	0.003	**0.023***	-0.011	-0.001	*0.062†*
Hipp R	Time	-0.027	0.004	**<.001*** **	-0.034	-0.020	**<.001*** **	-0.027	0.003	**<.001*** **	-0.034	-0.021	**<.001*** **
	TL	-0.030	0.052	0.563	-0.133	0.072	0.814	-0.010	0.058	0.858	-0.124	0.103	0.982
	Time*TL	-0.003	0.003	0.359	-0.008	0.003	0.626	-0.004	0.003	0.170	-0.010	0.002	0.379
	Time	-0.029	0.004	**<.001*** **	-0.037	-0.021	**<.001*** **	-0.029	0.004	**<.001*** **	-0.036	-0.022	**<.001*** **
	CE	-0.085	0.053	0.111	-0.189	0.020	0.267	-0.066	0.052	0.205	-0.167	0.036	0.418
	Time*CE	-0.006	0.003	**0.033***	-0.012	-0.001	*0.092†*	-0.007	0.003	**0.008** **	-0.013	-0.002	**0.022***
Cortex L	Time	-0.030	0.004	**<.001*** **	-0.038	-0.022	**<.001*** **	-0.030	0.004	**<.001*** **	-0.037	-0.023	**<.001*** **
	TL	-0.002	0.054	0.975	-0.107	0.103	0.996	0.005	0.054	0.924	-0.101	0.111	0.986
	Time*TL	-0.004	0.003	0.198	-0.011	0.002	0.432	-0.005	0.003	0.114	-0.011	0.001	0.274
	Time	-0.043	0.002	**<.001*** **	-0.048	-0.039	**<.001*** **	-0.041	0.002	**<.001*** **	-0.045	-0.037	**<.001*** **
	CE	-0.031	0.049	0.528	-0.127	0.065	0.792	-0.020	0.052	0.698	-0.122	0.082	0.938
	Time*CE	0.000	0.002	0.845	-0.003	0.004	0.978	0.001	0.002	0.674	-0.002	0.004	0.938
Cortex R	Time	-0.043	0.002	**<.001*** **	-0.048	-0.039	**<.001*** **	-0.041	0.002	**<.001*** **	-0.045	-0.037	**<.001*** **
	TL	-0.011	0.049	0.821	-0.107	0.085	0.973	0.001	0.054	0.983	-0.105	0.108	0.996
	Time*TL	0.002	0.002	0.274	-0.002	0.006	0.526	0.002	0.002	0.179	-0.001	0.006	0.381
	Time	-0.043	0.002	**<.001*** **	-0.048	-0.039	**<.001*** **	-0.041	0.002	**<.001*** **	-0.045	-0.037	**<.001*** **
	CE	-0.031	0.049	0.528	-0.127	0.065	0.792	-0.020	0.052	0.698	-0.122	0.082	0.938
	Time*CE	0.000	0.002	0.845	-0.003	0.004	0.978	0.001	0.002	0.674	-0.002	0.004	0.938
Frontal L	Time	-0.038	0.002	**<.001*** **	-0.042	-0.033	**<.001*** **	-0.036	0.002	**<.001*** **	-0.040	-0.032	**<.001*** **
	CE	-0.048	0.053	0.365	-0.152	0.056	0.626	-0.035	0.056	0.531	-0.145	0.075	0.864
	Time*CE	-0.000	0.002	0.984	-0.004	0.004	0.996	0.000	0.002	0.984	-0.003	0.003	0.996
Temporal L	Time	-0.038	0.002	**<.001*** **	-0.042	-0.033	**<.001*** **	-0.036	0.002	**<.001*** **	-0.040	-0.032	**<.001*** **
	TL	-0.017	0.053	0.746	-0.121	0.087	0.918	0.002	0.059	0.973	-0.113	0.117	0.996
	Time*TL	0.002	0.002	0.306	-0.002	0.006	0.555	0.002	0.002	0.282	-0.002	0.005	0.553
	Time	-0.037	0.003	**<.001*** **	-0.043	-0.031	**<.001*** **	-0.038	0.003	**<.001*** **	-0.043	-0.032	**<.001*** **
	CE	-0.020	0.049	0.685	-0.116	0.076	0.877	-0.012	0.052	0.814	-0.115	0.090	0.982
	Time*CE	0.002	0.002	0.350	-0.002	0.006	0.623	0.003	0.002	0.131	-0.001	0.007	0.306
Cingulate L	Time	-0.037	0.003	**<.001*** **	-0.043	-0.031	**<.001*** **	-0.037	0.003	**<.001*** **	-0.043	-0.032	**<.001*** **
	TL	-0.002	0.049	0.973	-0.097	0.094	0.996	0.013	0.055	0.809	-0.094	0.120	0.982
	Time*TL	0.003	0.002	0.224	-0.002	0.007	0.468	0.004	0.002	0.106	-0.001	0.008	0.262
	Time	-0.028	0.002	**<.001*** **	-0.032	-0.023	**<.001*** **	-0.026	0.002	**<.001*** **	-0.030	-0.022	**<.001*** **
	CE	-0.027	0.055	0.618	-0.135	0.080	0.842	-0.022	0.058	0.699	-0.135	0.091	0.938

	Time*CE	-0.001	0.002	0.469	-0.005	0.002	0.739	-0.001	0.002	0.617	-0.004	0.002	0.911
	Time	-0.028	0.002	**<.001*** **	-0.032	-0.024	**<.001*** **	-0.026	0.002	**<.001*** **	-0.030	-0.022	**<.001*** **
	TL	0.027	0.055	0.623	-0.080	0.134	0.842	0.032	0.060	0.597	-0.086	0.150	0.911
	Time*TL	-0.001	0.002	0.664	-0.004	0.003	0.867	0.000	0.002	0.854	-0.003	0.004	0.982
Frontal R	Time	-0.039	0.002	**<.001*** **	-0.044	-0.034	**<.001*** **	-0.037	0.002	**<.001*** **	-0.041	-0.033	**<.001*** **
	CE	-0.017	0.053	0.744	-0.121	0.086	0.918	-0.001	0.055	0.991	-0.109	0.108	0.996
	Time*CE	0.000	0.002	0.902	-0.004	0.004	0.995	0.000	0.002	0.828	-0.003	0.004	0.982
	Time	-0.040	0.002	**<.001*** **	-0.044	-0.035	**<.001*** **	-0.037	0.002	**<.001*** **	-0.042	-0.033	**<.001*** **
	TL	-0.007	0.053	0.896	-0.110	0.096	0.995	0.020	0.058	0.731	-0.093	0.133	0.952
	Time*TL	0.002	0.002	0.236	-0.002	0.006	0.482	0.002	0.002	0.347	-0.002	0.005	0.629
Temporal R	Time	-0.038	0.003	**<.001*** **	-0.044	-0.032	**<.001*** **	-0.038	0.003	**<.001*** **	-0.043	-0.033	**<.001*** **
	CE	-0.018	0.049	0.713	-0.114	0.078	0.901	-0.011	0.052	0.830	-0.112	0.090	0.982
	Time*CE	0.004	0.002	*0.056†*	-0.000	0.009	0.145	0.005	0.002	**0.017***	0.001	0.009	**0.045***
	Time	-0.038	0.003	**<.001*** **	-0.044	-0.032	**<.001*** **	-0.037	0.003	**<.001*** **	-0.043	-0.032	**<.001*** **
	TL	-0.001	0.049	0.982	-0.097	0.095	0.996	-0.008	0.054	0.878	-0.114	0.097	0.982
	Time*TL	0.005	0.002	**0.048***	0.000	0.009	0.131	0.006	0.002	**0.008****	0.002	0.010	**0.022***
Cingulate R	Time	-0.024	0.002	**<.001*** **	-0.028	-0.020	**<.001*** **	-0.023	0.002	**<.001*** **	-0.027	-0.019	**<.001*** **
	CE	-0.051	0.058	0.381	-0.164	0.063	0.641	-0.051	0.062	0.411	-0.173	0.071	0.704
	Time*CE	0.000	0.002	0.970	-0.003	0.003	0.996	0.001	0.002	0.656	-0.002	0.004	0.938
	Time	-0.024	0.002	**<.001*** **	-0.028	-0.020	**<.001*** **	-0.023	0.002	**<.001*** **	-0.027	-0.019	**<.001*** **
	TL	0.005	0.058	0.937	-0.109	0.118	0.996	0.010	0.065	0.876	-0.117	0.137	0.982
	Time*TL	0.001	0.002	0.576	-0.003	0.005	0.814	0.000	0.002	0.888	-0.003	0.004	0.982

Legend: hipp = hippocampus; Cx = Cortex; L = Left; R = Right; CE = Closeness to Experience; TL = Tendence to Liability. Models are adjusted for age, sex, education, and *APOE* status of participants. †p<.10; *p<.05; **p<.01; ***p<.001

Table 5.10. Relationship between time, personality factors and their interactions on white matter volumes

		Full Sample						HC Sample					
Dependant	Fixed factors	Coef.	Std.Err.	P>|z|	[0.025	0.975]	p_fdr	Coef.	Std.Err.	P>|z|	[0.025	0.975]	p_fdr
Frontal WM L	Time	-0.037	0.002	**<.001*** **	-0.041	-0.033	**<.001*** **	-0.033	0.002	**<.001*** **	-0.036	-0.029	**<.001*** **
	CE	-0.039	0.052	0.454	-0.140	0.063	0.726	-0.026	0.051	0.610	-0.126	0.074	0.911
	Time*CE	-0.000	0.002	0.821	-0.004	0.003	0.973	-0.001	0.001	0.553	-0.004	0.002	0.884
	Time	-0.037	0.002	**<.001*** **	-0.041	-0.033	**<.001*** **	-0.033	0.002	**<.001*** **	-0.037	-0.029	**<.001*** **
	TL	-0.064	0.051	0.217	-0.164	0.037	0.462	-0.052	0.053	0.331	-0.156	0.053	0.611
	Time*TL	0.000	0.002	0.901	-0.003	0.004	0.995	0.000	0.002	0.917	-0.003	0.003	0.986
Frontal WM R	Time	-0.039	0.002	**<.001*** **	-0.044	-0.035	**<.001*** **	-0.036	0.002	**<.001*** **	-0.040	-0.032	**<.001*** **
	CE	-0.021	0.049	0.667	-0.118	0.076	0.866	-0.019	0.050	0.703	-0.117	0.079	0.938
	Time*CE	-0.003	0.002	0.124	-0.006	0.001	0.290	-0.002	0.002	0.183	-0.005	0.001	0.383
	Time	-0.039	0.002	**<.001*** **	-0.044	-0.035	**<.001*** **	-0.036	0.002	**<.001*** **	-0.040	-0.032	**<.001*** **
	TL	-0.053	0.049	0.282	-0.149	0.043	0.531	-0.047	0.052	0.364	-0.150	0.055	0.647
	Time*TL	-0.003	0.002	*0.063†*	-0.007	0.000	0.159	-0.003	0.002	0.101	-0.006	0.001	0.254
Temporal WM L	Time	-0.038	0.003	**<.001*** **	-0.044	-0.032	**<.001*** **	-0.033	0.003	**<.001*** **	-0.038	-0.028	**<.001*** **
	CE	-0.022	0.050	0.665	-0.119	0.076	0.866	-0.025	0.048	0.599	-0.121	0.070	0.911
	Time*CE	-0.004	0.002	*0.089†*	-0.009	0.001	0.220	-0.003	0.002	0.138	-0.007	0.001	0.317
	Time	-0.038	0.003	**<.001*** **	-0.044	-0.032	**<.001*** **	-0.033	0.003	**<.001*** **	-0.038	-0.028	**<.001*** **
	TL	-0.029	0.050	0.560	-0.126	0.068	0.814	-0.035	0.051	0.484	-0.134	0.064	0.802
	Time*TL	-0.004	0.002	0.144	-0.009	0.001	0.329	-0.002	0.002	0.258	-0.007	0.002	0.515
Temporal WM R	Time	-0.037	0.002	**<.001*** **	-0.041	-0.033	**<.001*** **	-0.036	0.002	**<.001*** **	-0.039	-0.032	**<.001*** **
	CE	-0.033	0.051	0.519	-0.134	0.067	0.792	-0.016	0.054	0.768	-0.123	0.091	0.978
	Time*CE	0.000	0.002	0.985	-0.003	0.003	0.996	-0.000	0.002	0.896	-0.003	0.003	0.982
	Time	-0.037	0.002	**<.001*** **	-0.041	-0.033	**<.001*** **	-0.036	0.002	**<.001*** **	-0.039	-0.032	**<.001*** **
	TL	-0.066	0.051	0.198	-0.165	0.034	0.432	-0.055	0.057	0.329	-0.166	0.056	0.611
	Time*TL	0.000	0.002	0.999	-0.003	0.003	0.999	0.000	0.002	0.775	-0.003	0.004	0.978
Cingulate WM L	Time	-0.043	0.002	**<.001*** **	-0.048	-0.039	**<.001*** **	-0.042	0.002	**<.001*** **	-0.046	-0.038	**<.001*** **
	CE	-0.039	0.049	0.429	-0.136	0.058	0.698	-0.028	0.053	0.592	-0.131	0.075	0.911
	Time*CE	-0.000	0.002	0.939	-0.004	0.003	0.996	-0.001	0.002	0.734	-0.004	0.003	0.952
	Time	-0.043	0.002	**<.001*** **	-0.048	-0.039	**<.001*** **	-0.042	0.002	**<.001*** **	-0.046	-0.038	**<.001*** **
	TL	-0.095	0.049	*0.052†*	-0.190	0.001	0.138	-0.100	0.054	*0.066†*	-0.207	0.007	0.171
	Time*TL	-0.001	0.002	0.572	-0.005	0.003	0.814	-0.000	0.002	0.900	-0.004	0.003	0.982
Cingulate WM R	Time	-0.037	0.003	**<.001*** **	-0.044	-0.031	**<.001*** **	-0.036	0.003	**<.001*** **	-0.041	-0.030	**<.001*** **
	CE	-0.059	0.053	0.267	-0.163	0.045	0.526	-0.050	0.057	0.374	-0.161	0.061	0.652
	Time*CE	0.000	0.003	0.881	-0.005	0.006	0.995	-0.000	0.002	0.996	-0.004	0.004	0.996
	Time	-0.037	0.003	**<.001*** **	-0.044	-0.031	**<.001*** **	-0.036	0.003	**<.001*** **	-0.041	-0.030	**<.001*** **
	TL	-0.044	0.053	0.403	-0.148	0.060	0.667	-0.042	0.059	0.477	-0.158	0.074	0.802
	Time*TL	0.001	0.003	0.600	-0.004	0.007	0.835	-0.001	0.002	0.794	-0.005	0.004	0.982

Legend: L = Left; R = Right; WM = White matter; CE = Closeness to Experience; TL = Tendence to Liability. Models are adjusted for age, sex, education, and *APOE* status of participants. †p<.10; *p<.05; ***p<.001

Table 5.11. Relationship between time, personality factors and their interactions on white matter tracts

		Full Sample						HC Sample					
Dependant	Fixed factors	Coef.	Std.Err.	P>|z|	[0.025	0.975]	p fdr	Coef.	Std.Err.	P>|z|	[0.025	0.975]	p fdr
Fornix	Time	-0.036	0.004	**<.001*** **	-0.045	-0.027	**<.001*** **	-0.035	0.004	**<.001*** **	-0.044	-0.027	**<.001*** **
	CE	-0.006	0.059	0.914	-0.123	0.110	0.936	0.004	0.063	0.944	-0.118	0.127	0.970
	Time*CE	0.002	0.003	0.509	-0.005	0.009	0.815	0.002	0.003	0.640	-0.005	0.008	0.853
	Time	-0.035	0.004	**<.001*** **	-0.044	-0.026	**<.001*** **	-0.034	0.004	**<.001*** **	-0.043	-0.026	**<.001*** **
	TL	-0.026	0.059	0.660	-0.142	0.090	0.815	-0.030	0.062	0.634	-0.152	0.092	0.853
	Time*TL	-0.002	0.004	0.654	-0.009	0.005	0.815	-0.002	0.003	0.650	-0.008	0.005	0.853
Cingulate cingulum R	Time	-0.034	0.006	**<.001*** **	-0.046	-0.023	**<.001*** **	-0.031	0.006	**<.001*** **	-0.043	-0.019	**<.001*** **
	CE	-0.146	0.059	**0.014***	-0.263	-0.030	0.073	-0.179	0.061	**0.004****	-0.299	-0.058	**0.025***
	Time*CE	0.000	0.004	0.938	-0.008	0.009	0.938	0.004	0.005	0.374	-0.005	0.013	0.628
	Time	-0.035	0.006	**<.001*** **	-0.046	-0.024	**<.001*** **	-0.031	0.006	**<.001*** **	-0.043	-0.020	**<.001*** **
	TL	-0.047	0.060	0.438	-0.164	0.071	0.815	-0.090	0.062	0.149	-0.212	0.032	0.483
	Time*TL	0.002	0.005	0.591	-0.006	0.011	0.815	0.006	0.005	0.240	-0.004	0.015	0.561
Cingulate cingulum L	Time	-0.015	0.006	**0.020***	-0.027	-0.002	*0.083†*	-0.009	0.006	0.138	-0.021	0.003	0.483
	CE	-0.183	0.060	**0.002****	-0.301	-0.065	**0.020***	-0.214	0.062	**0.001****	-0.335	-0.093	**0.004****
	Time*CE	-0.002	0.005	0.621	-0.012	0.007	0.815	-0.000	0.005	0.970	-0.009	0.009	0.970
	Time	-0.015	0.006	**0.018***	-0.027	-0.002	*0.083†*	-0.009	0.006	0.134	-0.021	0.003	0.483
	TL	-0.041	0.061	0.506	-0.161	0.079	0.815	-0.091	0.063	0.150	-0.215	0.033	0.483
	Time*TL	-0.002	0.005	0.716	-0.012	0.008	0.859	0.000	0.005	0.933	-0.009	0.010	0.970
Cingulate Hippocampus R	Time	-0.007	0.008	0.382	-0.023	0.009	0.815	-0.011	0.009	0.186	-0.028	0.006	0.523
	CE	0.008	0.059	0.895	-0.108	0.123	0.936	0.014	0.061	0.821	-0.105	0.132	0.958
	Time*CE	-0.006	0.006	0.333	-0.018	0.006	0.815	-0.008	0.007	0.228	-0.021	0.005	0.561
	Time	-0.007	0.008	0.391	-0.023	0.009	0.815	-0.013	0.009	0.136	-0.030	0.004	0.483
	TL	-0.008	0.059	0.891	-0.124	0.108	0.936	-0.003	0.062	0.963	-0.125	0.119	0.970
	Time*TL	-0.006	0.007	0.374	-0.019	0.007	0.815	-0.007	0.007	0.292	-0.021	0.006	0.588
Cingulate Hippocampus L	Time	0.021	0.008	**0.012***	0.005	0.037	*0.072†*	0.017	0.009	*0.061†*	-0.001	0.034	0.319
	CE	-0.075	0.059	0.204	-0.191	0.041	0.713	-0.081	0.064	0.204	-0.206	0.044	0.535
	Time*CE	-0.003	0.007	0.622	-0.017	0.010	0.815	-0.005	0.007	0.485	-0.020	0.009	0.728
	Time	0.020	0.008	**0.009****	0.005	0.035	*0.064†*	0.017	0.009	*0.052†*	-0.000	0.034	0.312
	TL	0.020	0.063	0.747	-0.103	0.143	0.872	0.016	0.064	0.800	-0.108	0.141	0.958
	Time*TL	-0.005	0.006	0.450	-0.017	0.007	0.815	-0.008	0.007	0.268	-0.021	0.006	0.588
Uncinate R	Time	0.007	0.010	0.459	-0.012	0.026	0.815	0.010	0.010	0.322	-0.009	0.029	0.588
	CE	-0.062	0.062	0.318	-0.185	0.060	0.815	-0.042	0.065	0.522	-0.170	0.086	0.756

	Time*CE	-0.004	0.007	0.549	-0.019	0.010	0.815	-0.007	0.007	0.370	-0.021	0.008	0.628
	Time	0.007	0.010	0.455	-0.012	0.026	0.815	0.011	0.010	0.295	-0.009	0.030	0.588
	TL	-0.051	0.063	0.421	-0.174	0.073	0.815	-0.065	0.066	0.321	-0.193	0.063	0.588
	Time*TL	-0.004	0.007	0.560	-0.019	0.010	0.815	-0.006	0.008	0.474	-0.021	0.010	0.728
Uncinate L	Time	-0.005	0.010	0.577	-0.025	0.014	0.815	-0.002	0.011	0.818	-0.023	0.018	0.958
	CE	0.007	0.064	0.908	-0.117	0.132	0.936	-0.003	0.065	0.958	-0.132	0.125	0.970
	Time*CE	-0.007	0.008	0.340	-0.022	0.008	0.815	-0.007	0.008	0.402	-0.023	0.009	0.650
	Time	-0.005	0.010	0.614	-0.024	0.014	0.815	-0.002	0.011	0.866	-0.022	0.019	0.970
	TL	0.012	0.064	0.849	-0.113	0.138	0.936	0.019	0.066	0.773	-0.110	0.149	0.958
	Time*TL	-0.011	0.008	0.178	-0.026	0.005	0.679	-0.011	0.008	0.187	-0.028	0.005	0.523

Legend: L = Left; R = Right; CE = Closeness to Experience; TL = Tendence to Liability. Models are adjusted for age, sex, education, and *APOE* status of participants. †p<.10; *p<.05; **p<.01; ***p<.001

Risk factors for AD dementia conversion

The results of the proportional hazards model are summarized in Table 5.12 and Figure 5.7. Of the 1325 participants included in the analysis, 142 developed a dementia state due to AD during their follow-up visits.

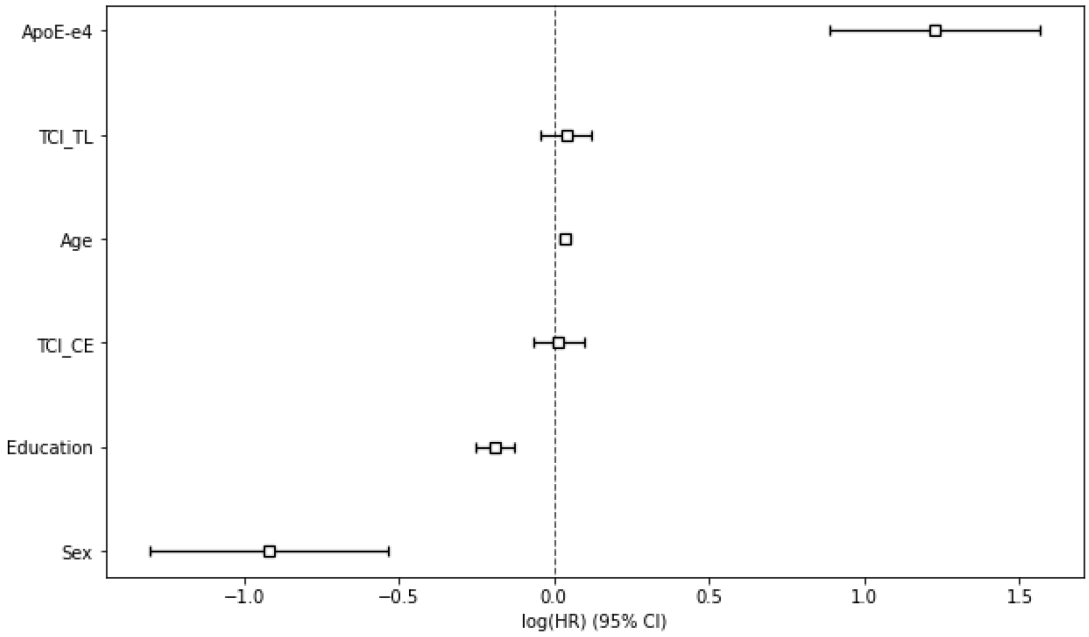
The risk of developing the dementia state was significantly impacted by sex, where being male reduced the risk of developing a dementia state by 60%; age, where each additional year increased the risk of dementia by 4%; years of education, where each additional year of education reduced the risk by 17%; and APOE status, where being a carrier of an ApoE-ε4 mutation increased the risk by 3.41 times.

Table 5.12. Assessment of risk factors for dementia using Cox proportional hazards regression.

Variable	Exp(coef)	lower 95%	upper 95%	p-value	p-adjusted
Sex	0.40	0.27	0.59	< 0.005	0.0075
Age	1.04	1.02	1.06	< 0.005	0. 0075
Education	0.83	0.78	0.88	< 0.005	0. 0075
***APOE*-ε4**	3.41	2.43	4.77	< 0.005	0. 0075
CE	1.02	0.94	1.10	0.72	0.72
TL	1.04	0.96	1.13	0.34	0.408

Legend: Exp(coef) = exponential regression coefficient indicating increased (>1) or decreased (<1) risk for each additional point to the variable of interest; CE = Closeness to Experience; TL = Tendence to Liability.

Figure 5.7. Risk ratio plot with 95% confidence intervals of the global model



Finally, none of the personality factors (CE and TL) significantly predicted the conversion to AD-type dementia in Cox regression models adjusted for age, sex, education level and *APOE*-ε4.

Discussion

This work aimed to understand the impact of personality factors predictive of mental disorders [272] on neuropsychiatric, cognitive, and neuroanatomical trajectories of participants from the population-based longitudinal Betula study. The results show that the revised personality factors CE and TL are associated with greater NPS as well as greater cognitive decline over time, as well as accelerated reduction of certain cortical volumes (hippocampus and cingulate).

Firstly, we demonstrate that two of the revised personality factors based on TCI, the CE and TL factors both had acceptable internal consistencies (>.70) and were associated cross-sectionally

and longitudinally with NPS and cross-sectionally with sleep disturbances in our sample. We thereby partially verify the initial observations made by Dell'Orco et al. (2018) in a younger clinical population with high psychiatric illness burden.

Interestingly, in our study, associations were demonstrated when NPS and sleep disturbances were measured between 10 and 17 years after personality assessment with the TCI. Personality is considered stable in healthy population [314], which was the case for our revised personality factors with a high significant positive correlation (Table 2), whereas the NPS measured focus on manifestations that occurred over a limited period of time: the last year for the PSQ [295], the last three months for the KSQ [296], the last two weeks for the PHQ-9 [293] and the last week for the CES-D [294]. These findings are in line with other work that has shown associations between negative personality traits like neuroticism with NPS such as anxiety, agitation, apathy or irritability, where personality was retrospectively assessed by relatives (midlife personalities)[288,315], but it also appears that NPS occur mostly in participants with higher personality changes across time. Indeed, Pocnet et al. showed that premorbid personality, as assessed by the NEO Personality Inventory Revised, was not related to neuropsychiatric manifestations in early AD, whereas current personality changes accompanied the onset of NPS [289]. It should be noted that in the Betula study, both personality and NPS are self-evaluated via questionnaire. These data suggest an important relationship between these revised personality factors and future NPS. However, previous studies have examined these relationships in AD and MCI and not in predominantly healthy older participants.

We hypothesized that participants with higher scores on personality factors associated with higher NPS scores, CE and TL, would have poorer and more rapidly declining performance on age-sensitive cognitive domains such as memory, executive (verbal fluency) and visuoconstructive performance, whereas vocabulary ability was expected more stable across aging.

Our results show that, in the full sample, greater scores on CE and TL were associated with greater episodic memory, vocabulary and verbal fluency decline. In the healthy control subset, only the longitudinal effect of CE on episodic memory was highlighted. This suggests that these personality factors have a greater negative impact on cognitive decline when considering participants

converting to AD. The fact that the effect of CE and TL were not as significant in the healthy subset than in the full sample may have indicated that the effect is driven by individuals with AD-related memory decline. However, our follow-up Cox regression analysis did not indicate that CE or TL at baseline was a predictor of AD conversion. Alternatively, the loss of significance in the healthy subset may have been caused by loss of statistical power due to the smaller sample size. Nevertheless, the CE personality factor has a significand effect on 25-year memory decline regardless of AD conversion status.

In their conception and definition, CE and TL factors seem close to neuroticism or the opposite of extraversion from the Big Five theory. As a reminder, the neuroticism trait of the Big Five theory (tendency to experience negative and stressful life events) is positively correlated with the harm avoidance trait assessed by the TCI (tendency toward an inhibitory response to signals of aversive stimuli that lead to avoidance of punishment and non-reward) [291]. Moreover, CE and TL factors share with harm avoidance the characteristic of being a risk factor for mental disorders [272]. It has been shown that high neuroticism is associated with increased risk of cognitive impairment in individuals without dementia, as well as accelerated memory and executive decline [273,274,276,277]. Thus, our findings for CE, and to a lesser extent TL, support these trends in their longitudinal effects on normative cognitive aging but also in the risk of cognitive impairment because of their greater effects sizes in the sample including AD converting participants. This supports our hypothesis that negative personality traits are associated with lower or declining memory and executive performance.

Studies on the relationships between personalities and performances in different cognitive domains are rare. Studies often focus on the risk of dementia or dementia-free cognitive impairment based on different personality factors, usually based on the big-five. Among these studies, it was shown that: high neuroticism, low agreeableness and low conscientiousness were risk factors for developing dementia in individuals without baseline cognitive impairment; high neuroticism and low conscientiousness were risk factors for developing dementia-free cognitive impairment in individuals without baseline cognitive impairment; while low conscientiousness was a risk factor for developing dementia in individuals with non-dementia cognitive

impairment[275]. Our results focused particularly on negative personality factors, previously associated with risk of mental disorders, and conceptually close to neuroticism (anxiety, tendency to pessimism, low novelty seeking for CE, inability to change, low autonomy, low self-esteem for TL) and showed that these factors were associated with greater declines in cognitive performance over time. These more rapid declines were particularly present in the full sample, composed in part of participants converting to AD. A meta-analysis also showed that high agreeableness and openness traits reduced the risk of developing Alzheimer's dementia [274]. More recently, a meta-analysis highlighted that high neuroticism and low conscientiousness were the most robust risk factors for dementia, while low extraversion, openness, and agreeableness, although also risk factors, were less robust through studies [316]. Our results are in line with these findings on neuroticism, since higher CE and TL were associated with higher memory and executive decline in the full sample.

With regards to brain characteristics, in both full and HC samples, cortical grey matter, white matter and hippocampal volumes decreased over time. Negative longitudinal effects were observed of CE on left hippocampal volume in full sample, of CE on right hippocampal volume and of CE and TL on left cingulate volume in HC sample. The implications for the hippocampi are in line with the cognitive results, showing a more rapid decline in episodic memory in individuals with higher CE scores. Cingulate volumes were also affected at the longitudinal level in HC individuals with a higher CE or TL, supporting the relationship found between these personality factor and the reduction in executive performance over time. Indeed, the hippocampus and cingulate regions have been already associated with episodic memory processes and motivational processes, action initiation, etc., respectively[317–321]. Other work has associated personality traits in healthy elderly individuals with prefrontal, cingular, insular and temporal cortical volumes [280,281,303,305,307,322]. The authors highlighted the implications of these regions in emotional processes (experience, expression, regulation), emotional memory and social cognition [322]. In a cross-sectional design within a sample of older or middle-aged individuals, brain volumes were smaller with age, and more so in individuals with high neuroticism and less in individuals with high conscientiousness, especially in the dorsal and ventral lateral prefrontal, orbitofrontal, but also parahippocampal and amygdala regions [304]. However, if our results didn't highlight any cross-

sectional effects of personality factors on brain volumes, a negative cross-sectional effect of the CE factor is observed on the left cingulate-cingulum network FA. The association of the cingulate with different personality traits such as neuroticism has been previously demonstrated [299,309–311]. Other data showed associations between personality traits and white matter damage in participants with MCI: white matter lesions were greater in individuals with low conscientiousness or high neuroticism[323]. However, these data did not find associations with hippocampal atrophy, suggesting that personality changes in individuals at risk of developing Alzheimer's dementia would be associated with white matter lesions rather than medial temporal regions, which could induce dysexecutive disorders [323]. In addition to structural personality associations, other data suggest a relationship with stages of neurofibrillary aggregation, particularly more advance stages in participants with lower agreeableness and higher neuroticism[324].

Despite the longitudinal associations between CE and TL and cognitive decline, our Cox proportional hazard analyses did not show any implications of CE and TL personality factors as risk factors of AD-type dementia. Instead, in line with much previous research the risk increased with increasing age, being a woman and carrying APOE-ε4, and decreased with the years of education. However, other studies have shown that certain personality traits are risk factors for dementia or cognitive decline, in particular neuroticism[274,276,325]. Also, mid-life personality was demonstrated as dementia risk factor by Johansson et al. (2014): after 38 years of follow-up in women without dementia: higher neuroticism was associated with a higher risk of dementia and distress [326]. However, after control for the distress factor, the association between neuroticism and the risk of dementia decreased, suggesting that the risk is higher when neuroticism is associated with distress. High neuroticism associated with low extraversion was also reported to be the highest risk for dementia [326]. These data suggest that neuroticism is a reliable factor in estimating the risk of conversion to dementia, whereas CE and TL factors seem more reliable in estimating longitudinal cognitive decline. Furthermore, the associations between CE / TL and cognitive decline were also demonstrated in the HC subsample, and may not be related to a degenerative process.

Strengths and limitations

This work is the first to consider the revised mental disorders-related factors of the TCI as potential predictors of neuropsychiatric symptoms in aging and cognitive and cerebral decline. As such, it extends previous work based on personality assessments from the Big Five model. In addition to focusing on long-term longitudinal age-related changes in four cognitive domains and not just general cognitive status (MCI, dementia), the revised factors were submitted to two stages of validation: their internal consistency was verified as well as their association with future neuropsychiatric symptoms. Thereby this work has deepened the clinical knowledge of the TCI tool for NPS assessment in aging, as well as understanding its relationship to cognitive decline in different domains. Moreover, based on the Betula database, samples of relatively large sizes and one of the longest longitudinal follow-ups could be studied. A particular noteworthy feature of the relationships between personality and neuropsychiatric symptoms is that the former was significantly associated with the severity and evolution of the latter even if they were evaluated 10 to 17 years later. Suggesting that personality as considered here indicates the potential risks of having NPS in the future. One potential caveat, however, is that at the time of the personality assessment, the presence or not of NPS was not available. Thus, it is not possible to conclusively determine whether personality assessments were influenced by NPS, or whether personality factors were driving later development of NPS. Another limitation was that the neuroimaging subsample was significantly smaller than the original sample and had very few participants converting to AD.

Perspectives

Given its results, confirming or extending previous work, several future direction can be considered: 1) considering that some personality factors contribute to cognitive decline (neuroticism[275]) while others are protective (openness, agreeableness[276]), or have an effect depending on their height and interaction with others (extraversion contributes to decline if very high and associated with neuroticism[277]), it would be important to distinguish between the isolated impact of the different factors and their interaction effects on cognitive trajectories; 2) investigate the role of the personality in other etiologies of cognitive decline such as Parkinson's disease; 3) study the contribution of personality as a predictor of decline using machine learning

models in comparison to regression models (By estimation of cognitive decline prediction accuracy); 4) explore the existence of new factors or personality changes that are more predictive of neuropsychiatric symptoms or neurodegeneration similar to the work of Dell'Orco et al. (2018)[272] ; 5) defining brain longitudinal trajectories over longer follow-up periods; 6) determining personality interactions and modulations with AD risk factors such as *APOE*-ε4 status or amyloid and tau biomarkers.

These approaches allow an integrated view of AD and neurodegenerative diseases in general, including physiological markers and psychological risk factors.

Disclosure statement

The authors have no current or potential conflicts of interest.

Data availability statement

The data that support the findings of this study are not publicly available due to privacy or ethical restrictions, but are available upon reasonable request.

Transition

Cette cinquième étude, quoique sortant du lot des précédentes, a apporté des résultats intéressants notamment sur le plan cognitif. Mais tout d'abord, sur le plan neuropsychiatrique, il semble que les associations avec les facteurs de personnalité étaient limitées. Cela peut s'expliquer par la distance temporelle espaçant les facteurs de personnalité et les évaluations neuropsychiatriques. Sur le plan cognitif, certains facteurs comme la proximité à l'expérience (caractérisé par des comportements d'évitement et d'isolement) étaient positivement associés à un déclin cognitif (plus élevé est le facteur de personnalité, plus rapide est le déclin). Les associations avec les structures cérébrales montraient notamment un déclin des volumes hippocampiques plus rapides chez les personnes ayant une proximité à l'expérience plus élevée. Ces résultats suggèrent la nécessité de considérer les facteurs de personnalité dans l'étude du déclin cognitif normal et pathologique, que ce soit au travers des symptômes neuropsychiatriques ou non.

Discussion générale

Résumé des conclusions de travaux et élaboration autour des résultats

Les travaux exposés dans ce manuscrit démontrent plusieurs éléments. D'une part les SNP sont impactés par plusieurs facteurs comme le sexe (Chapitre 1), les habiletés fonctionnelles (Chapitre 3), les traits de personnalité (Chapitre 5), ils sont plus prévalents au cours du déclin cognitif et diffèrent selon les maladies neurodégénératives. Ils sont associés à différentes structures cérébrales, corticales et sous corticales (Chapitre 2), à des performances cognitives globalement plus faibles ainsi qu'à un risque accru de déclin cognitif (Chapitre 1-4-5), même après contrôle de différents paramètres démographiques et génétiques. Ils sont par ailleurs plus fréquents chez des individus présentant aussi un trouble dépressif majeur, qu'importe son statut cognitif (sain, TCL, MA) (Chapitre 4).

Le premier chapitre mettait en évidence que les prévalences des symptômes neuropsychiatriques différaient selon le sexe et que leurs interactions sur les performances cognitives différaient selon le stade cognitif des participants (sains, TCL, MA), où les hommes TCL ou MA avec SNP étaient moins performants que ceux sans SNP alors que le profil inverse pouvait s'observer chez les femmes avec SNP. L'impact du sexe revêt une problématique particulière dans ses interactions avec les SNP, le déclin cognitif ou encore le risque de MA, particulièrement chez les femmes chez lesquelles la phase de ménopause conduit à des réduction des sécrétions des œstrogènes, laquelle marque l'apparition de plaintes cognitives subjectives ou encore de changements cognitifs mnésiques verbales et de fluences[327]. Malgré ces effets, les femmes semblent maintenir de meilleures performances verbales que les hommes. La réduction des œstrogènes peut conduire à une dysrégulation des sécrétions d'hormone lutéinisante, laquelle a pu être associée à de plus faibles performances cognitives chez les femmes, mais aussi chez les hommes, ou encore à la présence de protéine B-amyloïde dans le plasma[328,329]. Malgré tout cela, la prédisposition plus grande des femmes à développer la MA, considérant leur plus longue longévité et le rôle principal de l'âge dans le développement de la maladie, reste incertaine[121]. Le rôle des hormones sexuelles peut aussi varier au cours du déclin. Notamment, il a pu être montré que de plus hauts taux de testostérone et de gonadotrophine chez les femmes étaient associés à de plus faibles positivités

amyloïdes cérébrales et à de plus importants volumes hippocampiques chez les hommes. Ces associations étaient seulement présentes chez les participants présentant des troubles cognitifs et non chez les personnes cognitivement saines[330]. A l'inverse, les hommes ayant un TCL montrent de plus faibles taux de testostérone[331]. Il semble aussi que certains génotypes puissent venir impacter le déclin en fonction du sexe : par exemple, chez les porteurs de *APOE*-ε4 amyloïde positifs, les femmes déclinent plus rapidement sur le plan cognitif que les hommes[332]. D'autres facteurs indirects peuvent être soulevés, notamment du côté du sommeil et des SNP puisqu'en effet, les femmes présentent une prévalence plus élevée de dépression tout au long de la vie, ainsi que d'apnée du sommeil postménopause, lesquelles ont été associées à un risque accru de MA[121,333–336]. S'il a pu être démontré des associations entre hormones sexuelles et SNP dans la MA : notamment une association négative entre estrogène et agitation chez les hommes, et une association positive entre testostérone et agitation chez les femmes, il semble que les femmes porteuses de *APOE*-ε4 ayant davantage de testostérone présentent davantage d'hallucinations. Cet effet n'étant pas retrouvé chez les hommes, cela suggère des interactions entre hormones sexuelles et certains génotypes dans l'émergence des SNP au sein de la MA[123]. Par ailleurs, il a pu être montré que certaines thérapies hormonales contribuent à réduire certains comportements d'agressivité lors de phases avancées de démence ou encore à réduire le risque de MA et de déclin cognitif en cas d'application précoce, mais ces résultats semblent controversés[120,327]. Ainsi les raisons pour lesquelles les femmes et les hommes diffèrent dans les risques de MA, de SNP, ou de déclin cognitif sont d'une grande complexité et mettent en jeu des interactions entre génotypes, hormones sexuelles (dont les effets peuvent varier entre elles et entre les sexes) et stades de déclin cognitif. Malgré l'ensemble de connaissances récoltées dans la littérature, il reste incertain de pouvoir expliquer de manière fiable certains résultats du chapitre 1, à savoir que les femmes avec SNP se montraient meilleures à certaines tâches cognitives alors que l'effet inverse était plutôt retrouvé chez les hommes. Une hypothèse possible serait que des profils hormonaux spécifiques pourraient se retrouver dans les deux sous-groupes : faibles taux d'estrogènes favorisant la dépression chez les femmes, testostérone plus élevée permettant un meilleur maintien cognitif *vs*. une testostérone élevée induisant l'agitation et l'irritabilité chez les hommes, hormone lutéinisante élevée associée aux plus faibles performances cognitives.

Les chapitres 2 et 3 s'intéressaient respectivement aux associations structurelles cérébrales des SNP et leurs rôles dans la prédiction de la conversion de participants cognitivement sains à TCL et de TCL à MA sous la forme d'une étude rétrospective. Si les analyses d'associations structurelles des SNP montraient des structures corticales différentes associées aux différents SNP, les associations pouvaient différer entre les participants sains, avec TCL ou MA, où certains SNP pouvaient être davantage latéralisés à droite comme l'agitation, la dépression, l'apathie ou l'irritabilité. Les analyses rétrospectives et de prédiction montraient que les SNP n'étaient pas systématiquement impliqués dans la prédiction du déclin cognitif, rendant les résultats controversés. Notamment, lorsqu'ils sont associés aux habiletés fonctionnelles, ils n'étaient pas significatifs dans la prédiction de la conversion du TCL à la MA. Alors qu'ils étaient impliqués comme facteurs de risque du TCL dans la MP (la dépression et l'anxiété). Si les liens entre habilités fonctionnelles et SNP semble aller de soi, ces liens n'ont été que très peu investigués dans la littérature. Il a pu être montré que l'apathie, les comportements moteurs aberrants et les perturbations de l'appétit étaient associés à de plus importantes perturbations des activités de vie quotidienne en devis longitudinal[337] et transversal[338]. Par ailleurs, il semble que les SNP soient plus fortement impliqués dans ces perturbations chez les individus cognitivement sains ou ayant un TCL alors que les troubles cognitifs y sont plus fortement impliqués dans la démence[338]. Cependant, les modèles mis en évidence dans le Chapitre 3 concernant les implications cérébrales de la conversion en TCL ou en MA montraient une implication plus importante des structures de l'hémisphère droit. Une interprétation possible, en se référant aux résultats du Chapitre 2, est que certains SNP semblent davantage associés à des structures de l'hémisphère droit, comme l'agitation, la dépression, l'irritabilité, ou même l'apathie. Or l'analyse des données a pu révéler que si l'agitation et l'apathie étaient impliquées dans la prédiction de la conversion de TCL à MA, ces effets disparaissaient dès lors que les habiletés fonctionnelles étaient considérées. Il est par conséquent attendu que des structures droites viennent en partie soutenir la prédiction de cette conversion. Cependant, si les asymétriques cérébrales impliquées dans la conversion entre TCL et MA peuvent impliquer l'hémisphère droit, d'autres travaux montrent de plus grandes implications de l'hémisphère gauche. Par exemple, des asymétries en faveur de l'hémisphère gauche ont pu être montrées chez des participants TCL convertissant en MA et d'autres non

convertissant dans le gyrus temporal transverse, et en faveur de l'hémisphère droit dans le gyrus orbitofrontal latéral et le lobule pariétal inférieur[339]. Chez les non-convertisseurs, une latéralisation à gauche était retrouvée pour le cortex entorhinal et dans le gyrus cingulaire antérieur chez les convertisseurs, alors qu'une latéralisation droite était montrée dans le cingulaire antérieur chez les non-convertisseurs. Par ailleurs l'étude révélait aussi une réduction des asymétries au cours du temps dans des régions temporales latérales et médianes, préfrontales et pariétales[339]. D'autres résultats soutiennent la réduction des asymétries au cours du temps, des jeunes adultes sains aux personnes âgées saines et des personnes TCL aux personnes développant une MA[340]. D'autres résultats en TEP-FDG montraient que les changements transversaux et longitudinaux des régions hippocampiques et amygdaliennes droites permettaient de représenter la différence entre des personnes atteintes de MA et des témoins sains[341,342]. D'autres données suggèrent que l'atrophie due à la MA est asymétrique mais non latéralisée. La latéralisation serait plutôt contributive aux déficits cognitifs spécifiques[343].

A l'heure où les connaissances biologiques et neurologiques s'accumulent dans la compréhension de ces maladies, et où les modèles prédictifs s'affinent grâce aux données épidémiologiques et au développement des modèles d'apprentissage machine, des modèles de plus en plus intégratifs voient le jour et permettent alors de combiner des données comportementales, psychologiques, affectives, cognitives, cérébrales, génétiques, mais aussi biologiques au sens large (analyses des fluides corporels).

Afin de contribuer à l'avancée des connaissances sur l'impact psychologique envers le déclin cognitif, les Chapitres 4 et 5 proposaient respectivement d'étudier les associations neuropsychiatriques et cognitives du TDM dans différents stades cognitifs (sain, TCL et MA) en devis transversal, et de considérer la personnalité comme facteur explicatif du déclin, à la fois chez des individus développant une MA au cours du temps, et chez des individus âgés sains, dans un devis longitudinal. Les résultats du Chapitre 4 montraient que dans tous les groupes, le TDM était associé à de plus hautes prévalences de la plupart des SNP (agitation, anxiété, apathie, irritabilité…). De plus, dans les groupes TCL et MA, la présence de TDM était aussi généralement associée à des performances cognitives plus faibles. Ces résultats sont discutés dans la partie suivante, au regard de l'implication potentielle de l'utilisation de psychotropes chez les patients

inclus, et de l'impact de ces traitements sur le vieillissement cognitif. Les résultats du Chapitre 5 quant à eux montraient des effets longitudinaux à la fois sur le développement futur de SNP, sur le déclin cognitif mnésique et exécutif, ainsi que sur le déclin des volumes hippocampiques par exemple et ce même chez les individus ne développant pas de MA. Le facteur APOE était contrôlé dans son effet transversal comme longitudinal afin de pallier le biais explicatif qu'il pouvait apporter dans le déclin. Concernant les liens entre personnalité et effets sur le cerveau vieillissant, plusieurs éléments sont à considérer. La personnalité a pu être identifiée au sein de plusieurs réseaux, impliquant notamment les régions préfrontales et cingulaires. Typiquement, certaines lésions cérébrales acquises ou maladies neurodégénératives de ces régions conduisent à des changements, perturbations de la personnalité, comme dans le cas de traumatismes crâniens ou de dégénérescences fronto-temporales[344,345]. Un effet indirect est lié au style de vie lié à la personnalité. Que ce soit dans l'approche du BIG-FIVE ou du TCI, certains traits de personnalité se caractérisent par la recherche de nouveauté, d'expériences nouvelles, de récompenses, de contacts sociaux, de relations, d'aides (Extraversion, *agréabilité*, *ouverture* d'une part, recherche de nouveauté, coopérativité)[271,290]. Comme décrit dans le Chapitre 5, les traits d'intérêts de proximité à l'expérience et de tendance à la passivité sont proches dans leurs caractéristiques du neuroticisme et de l'évitement de la souffrance (isolement, affects négatifs, passivité, faible autonomie, faible estime de soi). Ces comportements montrent la similarité entre les facteurs de personnalité et expliquent en partie leurs proximité en termes d'associations avec le déclin cognitif et cérébral[274,275]. Pourtant, la personnalité pourrait aussi bien être médiateur d'un effet sur le vieillissement, soit dans un effet issu de composantes génétiques, soit au travers de modes de vie et d'autres conditions de santé. En effet, plusieurs travaux soutiennent l'explication génétique partielle ou totale de certains facteurs de personnalités et même, de manière inattendue, des caractères décrits dans l'approche de Cloninger[346–348]. D'autres travaux ont tenté de mettre en évidence des relations entre polymorphismes des transporteurs et récepteurs dopaminergiques, sérotoninergiques et de norépinéphrine, et les facteurs de personnalité. Les résultats démontrés semblent cependant inconsistants, certaines relations étant seulement montrées entre des sous-dimensions de l'inventaire : la dépendance à la récompense étant différentes entre des polymorphismes du transport de la dopamine, et l'évitement de la

souffrance étant différent entre des polymorphismes du transport de la sérotonine[349,350]. Outre les relations génétiques/personnalité à travers l'implication de gènes dans les systèmes de neurotransmetteurs, la mise en place de la personnalité dans la vie quotidienne conduit à des modes de vie divers, plus ou moins stimulants et riches en relations sociales (extraversion, agréabilité, ouverture) ou au contraire négativistes et isolés (neuroticisme, évitement de la souffrance). Certains travaux ont ainsi associé certaines caractéristiques de personnalité avec la qualité de vie, le bien-être ou encore la santé reliée à la qualité de vie[351,352]. La santé reliée à la qualité de vie se jugeant par la qualité de vie globale, la perception générale de la santé, le fonctionnement psychologique, physique, social, la vitalité, la douleur corporelle et les symptômes somatiques. Certains facteurs de personnalité ont été typiquement associés à une meilleure santé reliée à la qualité de vie comme de plus grandes extraversion, ouverture, agréabilité, conscienciosité, optimisme, estime de soi, efficacité personnelle, alors que de plus importants neuroticisme et affects négatifs étaient associés à une plus mauvaise santé reliée à la qualité de vie[352]. Plusieurs travaux montrent même des associations entre un neuroticisme élevé ou des émotions négatives, et un risque accru de maladies chroniques comme des maladies cardiaques (sténose artérielle, infarctus du myocarde), troubles mentaux, VIH, diabète, hypertension[353–357]. Par ailleurs, certaines de ces conditions comme une tension artérielle élevée, le diabète, ou encore l'obésité, le tabagisme, la dysfonction rénale ont été associés à des risques accrus de maladie d'Alzheimer ou de démence[358–360]. Ainsi plusieurs facteurs peuvent venir contribuer à la relation entre personnalité et déclin cognitif et cérébral dans le vieillissement : certains gènes de transporteurs de neurotransmetteurs, le mode de vie, des conditions médicales chroniques.

Pour finir, malgré leur caractère presque universel dans la maladie d'Alzheimer, les SNP et leurs conséquences sur le bien-être des patients et de leurs proches, leurs associations cérébrales et cognitives, souffrent d'un manque de traitements efficaces en dépit des nombreuses études s'y intéressant. Plusieurs explications à cela ont pu être soulevées comme le manque de mesures fiables et efficaces des SNP, le manque de biomarqueurs spécifiques aux symptômes et le manque de clarté des relations entre les SNP et les processus pathologiques des maladies neurodégénératives[38]. Les auteurs soulèvent d'ailleurs le manque d'études sur les SNP

comorbides : en effet, la plupart des études s'intéressent à l'étude d'un ou plusieurs symptômes, considérés isolément des autres, alors qu'il semble plus opportun d'étudier les groupes de symptômes dans le risque de démence chez les individus[38,361].

Apports cliniques

L'objectif des approches prédictives est de parvenir à déterminer, sur la base de données biologiques, cliniques, comportementales, le phénotype diagnostique d'une maladie, d'un trouble, ses issues pronostiques ou encore d'en anticiper l'effet des traitements chez un individu donné[362–364]. En cela, la mise au point d'un algorithme fiable et sensible doit permettre à ses utilisateurs (cliniciens ou chercheurs) de déterminer plus efficacement l'évolution des maladies, de développer des prises en charges plus adaptées, estimer les probabilités de déclin ou de rémission de personnes ayant des maladies chroniques… C'est pourquoi plusieurs disciplines s'accordent à développer ce type d'approche, au moins sur un plan expérimental, comme l'étude du vieillissement, la psychiatrie, la neurologie, ou d'autres spécialités médicales abordant les maladies chroniques[365–367].

Nos travaux, centrés sur les symptômes neuropsychiatriques et les structures cérébrales, visaient à mettre en évidence les déterminants du déclin cognitif dans la MA. L'apport des résultats obtenus est double : d'une part, il est souligné les facteurs impliqués dans le déclin, indépendamment des modèles et de la prédiction, suggérant des marqueurs cliniques sur lesquels l'attention des cliniciens doit être portée, notamment lors d'examens de routine ; d'autres parts, dépendamment des modèles longitudinaux, il est envisageable de coupler l'évaluation clinique à l'utilisation des probabilités fournies par ces modèles, basées sur les caractéristiques individuelles des patients.

Pour aller plus loin dans ces approches, il semble nécessaire d'envisager la mise en place d'apprentissage machine continue. Il s'agit d'un apprentissage "tout au long de la vie" via lequel un modèle apprend et évolue de manière continue à l'aide des nouvelles données qui y sont incorporées. Le modèle met ainsi à jour ses issues tout en continuant de tenir compte de ses apprentissages précédents[368].

Retour sur des éléments méthodologiques

L'utilisation conjointe de bases de données

Si certains choix méthodologiques sont discutables, voire questionnables, ils en sont toutefois justifiables au regard des objectifs de recherches choisis. Nous pouvons citer par exemple le choix d'utiliser ensemble deux cadres de donnés différents en certains points dans le chapitre 1. Particulièrement, les critères de classification et d'inclusion des participants ayant un trouble cognitif léger diffère entre les deux bases de données ADNI et NACC : « *The Mild Cognitive Impairment group (MCI) from the ADNI database consisted of individuals whose cognitive characteristics meet the criteria for MCI*[115]*. Entry criteria for patients with amnestic MCI included a Mini-Mental State Examination score of >24 and a Memory Box score of at least 0.5. The MCI participants from the NACC database had to have cognitive changes from the person's previous assessment (complaint) and a disorder in at least one cognitive domain*[116] *»*. Ces différences de critères d'inclusion indiquent une différence de sévérité des troubles cognitifs entre les participants : les participants de NACC ayant au moins un trouble cognitif dans un domaine cognitif alors que les participants de ADNI présentent jusqu'à un MMSE à 24/30 et une atteinte mnésique légère à l'échelle CDR. Il serait donc attendu ici d'avoir un large spectre de sévérité des participants ayant un TCL et que des associations différentes entre les SNP et les performances cognitives puissent émerger dans les analyses. En cela, il aurait aussi pu être envisagé de distinguer les participants TCL entre les formes précoces et tardives dans un objectif d'approfondissement des résultats.

Dans le même registre, la considération du TCL dans sa globalité et non dans ses différentes formes cognitives (amnésique vs. non-amnésique, domaine simple vs. domaine multiple) peut aussi poser question en raison des étiologies différentes qui peuvent induire les différentes formes, ainsi que des progressions longitudinales différentes. Plusieurs contrôles méthodologiques viennent limiter l'impact que ces considérations ont pu avoir sur les résultats. D'une part, l'inclusion au sein du groupe TCL de la base de données ADNI est focalisée sur les formes amnésiques (plus souvent dues à la MA). D'autres parts, malgré l'inclusion de formes autres que amnésiques dans la base de données NACC, toutes étiologies autres que la MA

retrouvées chez certains participants ont mené à leur exclusion. Ainsi la probabilité d'étiologies de types dégénérescence lobaire fronto-temporale, vasculaire, maladies à corps de Lewy ou autres étiologies neurologiques ou psychiatriques a été limitée. Toutefois, cela n'exclut pas la possibilité de mise en évidence ultérieure d'une de ces étiologies.

Questionnements liés aux outils cliniques utilisés

Forces et faiblesses des instruments : Concernant les mesures utilisées, particulièrement les mesures cliniques subjectives du NPI et du FAQ, certaines limitations peuvent être énoncées quant à la robustesse des résultats qui en découlent. Malgré leur validation clinique et psychométrique, leur application en recherche soulève quelques faiblesses pour répondre aux objectifs de recherche. Concernant le NPI, son utilisation est clinique et subjective, que ce soit dans la forme utilisée par le clinicien ou dans la forme utilisée par un proche. Par ailleurs, la période de l'évaluation des SNP porte sur les 4 dernières semaines, ce qui ne rend pas compte de l'aspect longitudinal des troubles, ni de leur caractère fluctuant au cours du temps, et ce particulièrement dans le TCL et la MA, où les SNP peuvent être présents depuis plusieurs années. Par ailleurs, le NPI ne permet pas de distinguer les contextes d'apparition des symptômes : sont-ils survenus avant, pendant ou après l'identification des difficultés cognitives, du langage, de la communication ou lors des activités de vie quotidienne ? Par ailleurs, à la manière du FAQ, l'évaluation par les proches peut souffrir d'un biais d'évaluation en faveur ou non du diagnostic des individus : l'aidant naturel évaluant son proche ayant un diagnostic quelconque pourrait être enclin à surévaluer les SNP en lien avec le diagnostic ou au contraire à minimiser ces symptômes dans un objectif de normalisation des comportements réactionnels à la nouvelle condition cognitive du proche. Cela étant, plusieurs études ont permis de montrer la bonne fiabilité inter-juge du NPI ou encore de mettre en évidence la fiabilité statistique de l'évaluation par les proches avec certaines échelles dans la prévision du déclin cognitifs, notamment à l'aide du Mild Behavioral Impairment Checklist.

Le FAQ quant à lui vise à évaluer les capacités des individus à réaliser des activités quotidiennes (préparer un repas, se déplacer hors de son quartier, suivre les actualités etc…). Dans son étude de validation, l'outil présentait une bonne sensibilité et spécificité vis-à-vis du diagnostic de

démence, ainsi qu'une bonne fidélité inter-juges[369]. Aussi, le questionnaire a présenté de bonnes corrélations avec le fonctionnement social et les résultats aux tests cognitifs[369,370]. Toutefois plusieurs questionnements peuvent être énoncés vis-à-vis de sa construction. Tout d'abord, certains items sont proches dans les activités qu'ils représentent ou peuvent être liés, comme la préparation d'un repas ou la préparation d'une tasse de café. Une difficulté à réaliser l'un pouvant se traduire aussi par une difficulté dans l'autre. Il en est de même pour le fait de suivre les événements courants ainsi que la capacité à suivre un film, une émission, une lecture, les comprendre et pouvoir en discuter. Par ailleurs, si l'outil a été corrélé aux performances cognitives, il ne semble pas y avoir d'associations directes avec les troubles du comportement, où des troubles de la motivation ou de l'humeur peuvent altérer la coopérativité des patients ainsi que leur aptitude à réaliser certaines tâches. Ainsi ce qui peut être interprété comme une incapacité à accomplir une tâche ou une action peut autant provenir d'une incapacité cognitive, émotionnelle ou comportementale/motivationnelle. Aussi, il est à noter que contrairement au NPI, le FAQ n'a pas été validé à travers autant de cultures et ethnies et n'a pas fait l'objet d'une revalidation récente auprès d'une population anglophone et n'a porté que sur un échantillon de 195 participants âgés sains ou avec démence sénile légère lors de sa première validation[369]. Malgré tout, ces deux outils comportent de bonnes qualités psychométriques malgré l'aspect subjectif de leurs applications.

Importance de la médication dans les études sur les SNP

Un sujet d'importance, ouvrant la voie à de nombreux travaux complémentaires, lorsque l'on s'intéresse à la fois aux SNP, troubles comportementaux, ou à la psychiatrie du vieillissement, concerne les effets de la médication sur les différentes composantes du vieillissement : émotionnelles, cognitives, comportementales, cérébrales… Puisqu'il a été démontré à plusieurs reprises les effets des psychotropes sur ces sphères, il paraît évident de considérer l'utilisation des traitements chez les participants inclus dans les études sur le vieillissement. Il ne nous a pas échappé qu'il ne s'agissait cependant pas d'une composante majeure dans les travaux abordés précédemment. Cependant, nous pouvons rappeler que, parmi les critères d'exclusions de la base de données ADNI comprenaient à la ligne de base et au suivi l'utilisation de médication psychoactive dont les antidépresseurs, neuroleptiques, anxiolytiques chroniques ou les

hypnotiques sédatifs. Ainsi il peut déjà être confirmé qu'au sein des données analysées dans les chapitres 1-2-3, les participants issus de la base de données ADNI n'étaient pas traités par ce type de médication. Ainsi les résultats n'ont pas pu être influencés par ces variables, à l'exception du chapitre 1 dont les participants issus de la base de données NACC pouvaient bénéficier de ces médications. La même remarque peut être faite concernant le chapitre 4. En revanche, tout participant souffrant de troubles mentaux ont été exclus dans l'étude du chapitre 1, limitant la probabilité que l'un d'eux soit traité par ces types de traitements. Similairement dans le chapitre 4, tout autre trouble que le trouble dépressif majeur (TDM) a été exclu. Ainsi, il peut être attendu que les sous-groupes caractérisés par le TDM bénéficiaient davantage de traitements psychotropes que les groupes sans TDM. Les résultats tendaient à montrer de plus hautes prévalences de SNP et de plus faibles performances cognitives chez les participants avec TDM, particulièrement chez les participants avec un TCL ou une MA. Cependant, l'impact des traitements sur ces prévalences et performances peut poser question. Même si, tel que discuté dans le chapitre 4, certains traitements antidépresseurs ont pu montrer des effets bénéfiques sur l'humeur, la motivation et cognition, il pourrait alors être attendu que, à l'exclusion des traitements présents, les différences de prévalences de SNP et de performances entre les participants avec vs. sans TDM soient plus importantes, ou que la performance de mémoire de travail retrouvée plus élevée chez les MA avec TDM que chez les MA sans ne soit pas retrouvée, voire que la différence soit inversée. Deux perspectives statistiques pourraient être alors proposées ici : employer les traitements potentiels comme covariables des modèles statistiques, ou envisager une étape supplémentaire d'analyses pour comparer les performances des participants ayant un TDM avec vs. sans traitements.

Dans le Chapitre 5, les participants étaient sains à l'inclusion sur les plans neurologiques et psychiatriques, limitant la probabilité d'utilisation de psychotropes. Par ailleurs, les participants étaient exclus en cas de diagnostics psychiatriques lors des visites de suivis. Enfin, les travaux supplémentaires excluaient respectivement les participants sous médication anxiolytique ou antidépresseur d'une part, ou sous médication chronique affectant le système nerveux central (incluant les traitements de plus de 6 mois pour l'hypertension et l'hypothyroïdisme). Par ces

contrôles lors des inclusions des différentes bases de données, les effets transversaux et longitudinaux potentiels des médications psychotropes ont été restreintes.

Concernant les travaux s'étant intéressés aux effets des psychotropes dans le vieillissement, plusieurs montrent des impacts négatifs et positifs sur la cognition, les troubles comportementaux, de l'humeur etc. voire préservent mieux certaines structures cérébrales (augmentation de la neurogenèse des hippocampes chez le rat par exemple après traitement par ISRS type fluoxétine). Il était déjà abordé dans le Chapitre 4 que certaines études montraient un rôle protecteur de certains antidépresseurs face au déclin cognitif (réduction du risque de démence et de TCL[263–265]. Particulièrement, il semble que les médications à base de lithium et de clozapine soient inversement corrélées à la sévérité de la démence chez des individus avec dépression unipolaire ou trouble bipolaire[263]. L'effet protecteur du lithium semble se démontrer aussi face aux marqueurs de la MA chez la souris et est associé à une réduction de plaques amyloïde et de charges tau, une préservation dendritique dans les hippocampes et le cortex frontal[371]. Un autre travail rapportait une réduction du risque de démence chez des patients ayant une dépression majeure chez les utilisateurs de médication tricyclique. Au contraire, le risque de démence était augmenté chez les utilisateurs d'inhibiteurs sélectifs de la recapture de la sérotonine, d'inhibiteurs de la monoamine oxydase ou encore d'antidépresseurs hétérocycliques. Respectivement, l'augmentation des doses utilisées étaient associées à la réduction ou l'augmentation du risque de démence[264]. L'augmentation du risque de démence liée à prise d'ISRS est contre-intuitive avec certaines données récoltées chez le jeune rat, où la prise de Fluoxétine (ISRS) augmente la neurogenèse hippocampique ainsi que le taux de survie des neurones nouvellement générés, alors que la prise d'IMAO augmente la neurogenèse sans améliorer le taux de survie des nouveaux neurones[372]. D'autres données mettent en évidence une augmentation de l'angiogenèse en corrélation avec l'augmentation du nombre de précurseurs neuronaux dans les gyrus dentés suite à l'utilisation de traitements ISRS ou tricycliques[373]. Il est toutefois notable que ces résultats sont issus de données chez l'adulte ayant une dépression majeure et non chez la personne âgée. Dans une étude chez les femmes très âgées (moyenne supérieure à 80 ans), l'utilisation d'ISRS ou de tricycliques augmentait le déclin cognitif suivi sur 5 années (augmentation du risque de TCL et de démence) et cela même en

contrôlant les facteurs démographiques, les comorbidités médicales et le niveau cognitif de base[265]. La méta-analyse de Chan et al. (2019) concluait par ailleurs que si la présence d'un trouble dépressif augmentait le risque de TCL ou de démence, l'utilisation d'antidépresseurs ne réduisait pas ce risque et tendait même à l'augmenter davantage[266].

Ainsi, la considération des traitements psychotropes revêt une forme de difficulté additionnelle au sein des modèles statistiques en raison de leurs effets différents entre eux, et entre les âges auxquels ils sont utilisés. Considérant le facteur de risque qu'ils représentent de développer un TCL ou une démence, il paraît légitime de se questionner sur leur rôle vis-à-vis des SNP : des SNP plus sévères peuvent conduire à des utilisations plus élevées de psychotropes, induisant un risque plus important de déclin cognitif.

Concernant les résultats décrits dans le chapitre 4, les patients ayant un TDM présentent davantage de SNP ainsi que des performances cognitives plus faibles. Il peut ainsi être supposé que les traitements possibles du TDM aient pu accentuer les différences cognitives entre les groupes. Une solution dans ce type de devis serait par exemple de ne considérer que des participants n'utilisant aucun psychotrope. D'autres questions peuvent aussi avoir leur importance comme la durée depuis laquelle les traitements sont utilisés, pour quelles raisons ils ont été appliqués et dans quel objectif ? On se remémorera notamment les différents effets que les psychotropes peuvent avoir en fonction de leur dose et de leurs couplages (amélioration de l'humeur, de la motivation, sédation…).

Forces et limitations

Plusieurs éléments viennent soutenir la robustesse des résultats démontrés dans les travaux présentés ici. Tout d'abord, chaque étude s'appuie sur des échantillons de tailles importantes, car issus de cadres de données multicentriques, pouvant dépasser plusieurs milliers d'observations transversales et longitudinales. Ces échantillons permettaient d'étudier à la fois le vieillissement normal et le vieillissement pathologique au travers du déclin cognitif (trouble cognitif léger, maladie d'Alzheimer). Plusieurs modèles ont été employés afin de répondre aux hypothèses, permettant de soutenir l'intérêt de différentes approches d'analyses de données comme le modèle linéaire général, ou des régressions à effets mixtes (soulignées par leur importante

robustesse face à l'absence de validation des conditions d'applications de tests paramétriques). L'intégration de différents aspects des symptômes neuropsychiatriques a aussi permis d'en déterminer les associations de personnalité, cognitives, et cérébrale d'une part, et d'en estimer la contribution en association avec d'autres facteurs dans la prédiction du trouble cognitif léger. Par ailleurs, chaque étude assurait la considération de covariables connues pour impacter le vieillissement et la probabilité de déclin cognitif comme l'âge, le sexe, le niveau d'études ou encore le statut génétique *APOE*. Ces contrôles permettaient de s'assurer de l'effet isolé des symptômes neuropsychiatriques sur les performances cognitives ou de l'association entre ces symptômes et la taille des structures cérébrales. Enfin, les analyses considéraient aussi différents types de corrections statistiques afin de réduire le risque d'erreurs de Type I dans l'interprétation des résultats.

Quelques limitations peuvent toutefois être soulevées. Notamment, étant donné l'intérêt principal autour de la maladie d'Alzheimer, il aurait été opportun de considérer la présence des biomarqueurs chez les individus ayant une cognition normale ou un trouble cognitif léger sans diagnostic de maladie d'Alzheimer afin d'identifier les individus à risque. Par ailleurs, et pour des raisons de restriction des contrastes et du nombre d'analyses réalisées, les personnes présentant un trouble cognitif subjectif n'ont pas été considérées. Sur un plan méthodologique, il peut être relevé une variabilité inter-études concernant les procédures d'évaluation des participants (tests cognitifs et questionnaires neuropsychiatriques différents entre les bases de données), de nettoyage des données, concernant notamment l'inclusion/exclusion des participants, vérification des conditions d'application des tests paramétriques, ou encore les corrections statistiques utilisées. Ces divergences peuvent expliquer au moins en partie la diversité des résultats retrouvés. Enfin, certaines études étaient uniquement transversales, celles-ci auraient gagné à inclure une partie d'analyses longitudinales.

Perspectives de recherche

Actuellement, il semble que différentes catégories de données soient déterminantes dans la prédiction du développement de maladies neurodégénératives ou de la conversion d'un état de santé à un état de troubles cognitifs (légers ou démentiels).

Ainsi les études futures pourraient s'axer (voire s'axent déjà) sur l'association, l'intégration de ces différents marqueurs au sein des algorithmes. Notamment, plusieurs travaux se sont appuyés sur les données du liquide céphalo-rachidien[374], d'IRM[375–378], les imageries de TEP (glucose et biomarqueurs amyloïde et tau de la maladie d'Alzheimer)[376,377,379], les biomarqueurs sanguins[380–383], afin de prédire la présence ou l'apparition future de la MA. L'intégration de ces facteurs avec des évaluations comportementales, cognitives et subjectives de plaintes ont aussi pu démontrer de bonnes performances de prédiction[384]. Cependant, certaines associations restent à tester, de même que la vérification de la fiabilité de différentes familles d'évaluations (les évaluations cognitives et comportementales présentent-elles la même fiabilité dans l'établissement de la prédiction ?).

Par ailleurs, il serait intéressant de déterminer l'impact d'accompagnements, de traitements et prises en charges, médicamenteuses ou non, sur les prédictions apportées par les algorithmes et autres modèles prédictifs. En cela, déterminer une issue diagnostique serait primordial pour cibler davantage les individus à risques de développer des maladies ou des complications, tout autant qu'être en capacité d'offrir des remédiations et des soins adaptés à ces personnes pour en réduire les risques de conversions ou d'issues négatives.

Mot de la fin

Comme nous l'avons vu, les symptômes neuropsychiatriques, les troubles du comportement, les changements de personnalité, ou autres formes de perturbations psychologiques des personnes sont susceptibles d'altérer leur qualité de vie ainsi que celle de leurs proches. Facteurs de risques d'institutionnalisation et de déclin accéléré, ils suscitent l'incompréhension chez les personnes qui en sont atteintes, chez leur famille mais aussi chez les soignants. C'est pourquoi il reste important de bien les caractériser et de démocratiser leur évaluation en pratique clinique afin d'en optimiser l'accompagnement et la prise en charge.

Malgré les limitations liées aux traitements et à leur issue pronostique, il est aussi du devoir du clinicien d'apporter des éléments de réponse aux patients et aux proches qui questionnent ces manifestations symptomatiques, qui souhaitent comprendre pourquoi elles surviennent. Il est alors important de souligner la réassurance apportée lorsque ces personnes sentent une

confirmation de la légitimité de ces questionnements, mais aussi de la légitimité de leur souffrance. Quand bien même il n'est pas rassurant de voir émerger des changements de personnalité chez un être cher et proche, y voir une explication clinique, cognitive, neurologique tout comme des pistes de remédiation ou d'atténuation, peut être source de soulagement. Si le phénomène décrit est fréquent, les personnes peuvent ne plus s'y sentir aussi seules, ni s'y sentir incomprises.

Là est toute l'importance de la recherche clinique sur ces symptômes, apporter des éléments de réponses à la clinique et indirectement aux individus en pertes de repères à ce moment de leur vie. A terme, ces recherches pourraient permettre de mieux les cerner et d'en proposer des prises en charge plus précocement.

Annexes - Travaux Supplémentaires

Symptômes neuropsychiatriques, métabolisme cérébral et déclin cognitif normal et pathologique au cours du vieillissement. Projet basé sur deux cohortes belges.

Lucas Ronat[a,b,c], Alexandru Hanganu[b,d] & Christine Bastin[c,e]

[a]Faculté de Médecine, Département de Médecine, Université de Montréal, Montréal, Québec, Canada

[b]Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, Laboratoire Neuroimagerie des émotions, Montréal, Québec, Canada

[c]GIGA-Centre de Recherche du Cyclotron – In vivo Imaging, Université de Liège, Liège, Belgique

[d]Faculté des Arts et des Sciences, Département de Psychologie, Université de Montréal, Montréal, Québec, Canada

[e]F.R.S.-Fonds National de la Recherche Scientifique, Bruxelles, Belgique

Corresponding author:

Lucas Ronat

Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal

4545 Chemin Queen Mary, Office 7806, Montréal, QC, H3W 1W4, Canada

Mail: lucas.ronat@umontreal.ca

Phone: +1(438)408-6806

Part 1 : Prediction of MCI and AD based on neuropsychiatric symptoms and FDG-PET characteristics

Introduction

Since the 1980s, the reduction in the rate of cerebral glucose metabolism has been linked to cognitive performance and disease status, particularly in Alzheimer's disease[385]. Thus, this metabolic reduction is currently described as an early and progressive feature of AD, reflecting neurodegeneration[386–388].

Hypometabolism may involve medial temporal, lateral temporal, inferior parietal, posterior cingulate regions, depending on the genetic status of the patients (APOE-4)[386], or even in the frontal regions in more advanced stages[387]. On the contrary, other regions are better preserved, such as the primary visual and motor areas, the thalami, the cerebellum and the basal ganglia[389]. At the stage of Mild Cognitive Impairment (MCI), hypometabolism is mainly in the medial temporal lobes, while other cortical regions are less involved. MTL hypometabolism seems more characteristic of MCI compared to healthy subjects, whereas cortical hypometabolism is more discriminative of AD compared to MCI[390–392]. However, it has been shown more recently that the standardized uptake value ratio (SUVr) of PET-FDG was lower in AD than in MCI and in MCI than in controls, in the precuneus and posterior cingulate, while the atrophy markers were not significant. Thus, FDG seems to be a marker of neurodegenerative processes[393]. In particular, the retrosplenial cortex showed also hypometabolism in the retrosplenial cortex in prodromal AD[394].

Additionally, whereas memory impairment was associated in both mild AD and amnestic MCI with hypometabolism in the hippocampal complex, medial thalamus, mammillary bodies, and posterior cingulate, it was also associated with hypometabolism in amygdala, temporoparietal, and prefrontal hypometabolism in AD but not in MCI[395].

Other characteristics have been associated with an increased risk of pathological cognitive decline in aging and Alzheimer's disease. This is the case for neuropsychiatric symptoms (NPS) such as depression, anxiety, agitation, irritability, and apathy, which are among the most prevalent NPS

in AD[19] (12). While these NPS are common, it would appear that depression and irritability are the most common prior to diagnosis, while apathy and agitation are rarer[396].

These symptoms could be associated with different hypometabolisms: in the bilateral superior frontal and left anterior cingulate cortices (ACC) in connection with depression[46], in the right, middle and superior temporal gyri, insula, precentral and postcentral gyri, middle and inferior frontal gyri linked to irritability[397]. More recent studies seem to agree on the involvement of hypometabolism of the superior frontal gyrus and ACC in affective symptoms such as depression in early-onset AD[398,399] and of the superior frontal gyrus in non-demented individuals with late-life depression[400]. Studies focusing on irritability are more limited[401].

Based on these results, some studies had tried to predict cognitive decline or AD based on NPS or hypometabolism[8,21,402–404], as well as predict hypometabolism in preclinical AD based on NPS[146].

Thus, the objective of this study is to establish predictive models of AD and MCI from binary logistic regression models based on NPS and topography of cerebral hypometabolism. It is expected that the classification of MCI compared to healthy participants as well as the prediction of conversion from MCI to AD would be characterized by higher depression scores, and lower metabolism in medial temporal and/or frontal/cingular regions.

Materials and Methods

Participants

The patient group consisted of 45 participants (19 women) who met the criteria for amnestic MCI following the Mayo Clinic criteria[405] at inclusion. They were referred by neurologists working in memory clinics and were selected on the basis of a general examination, neurological and neuropsychological assessments, neuroimaging, and laboratory evaluation. The patients demonstrated both subjective and objective memory decline. They did not experience many difficulties in their daily activities and they did not fulfill the criteria for dementia. During the 4 year follow-up period, the patients were re-evaluated at least once with a neuropsychological test battery and a neurological assessment. Follow-up stopped when the patient met the clinical diagnosis of Alzheimer's disease[15] or after 4 years if the patient still met aMCI criteria. The current

analyses were performed on the inclusion data as a function of follow-up outcome. The patient groups included in the analyses consisted of 22 MCI patients who progressed to AD 6 to 42 months after inclusion (converters, mean time to conversion: 21.4 months ± 11.8), and 23 patients who still presented with MCI 4 years after inclusion (non-converters).

A control group of 26 healthy older participants (16 women) also participated in the study. At inclusion, subjects in this group had to perform within norms on the Dementia Rating Scale[406] (58). A follow-up consisting of a neuropsychological assessment was also proposed to controls. One participant demonstrated cognitive decline compatible with a degenerative process at follow-up and was therefore excluded from the analyses.

For all participants (aMCI and controls), exclusion criteria were the following: not being native French-speaker, psychiatric antecedents, neurological antecedents (such as stroke, tumor), anxiolytic or anti-depressive medication, excessive consumption of alcohol (>14 units/week), and uncorrected deficient hearing and vision, incomplete data acquisition (lack of demographic, neuropsychiatric, neuropsychological or imaging data).

The converters, non-converters, and control groups were matched in terms of age, education, and sex distributions. On the Geriatric Depression Scale, converters patients scored higher than the non-converters patients but not than the controls ($F(2, 68) = 2.929$, $p = 0.06$). The converters and non-converters patients had a poorer score on the Mattis Dementia Rating Scale than controls for attention ($F(2, 68) = 3.348$, $p = 0.041$), verbal initiation ($F(2, 68) = 11.798$, $p < 0.001$), motor initiation ($F(2, 68) = 4.627$, $p = 0.013$), memory subscales ($F(2, 68) = 16.033$, $p < 0.001$), and total scale ($F(2, 68) = 17.701$, $p < 0.001$).

A second stage of analyses was carried out in the MCI group only by considering their Neuropsychiatric inventory scores. Five patients without assessment were excluded from the analyses. Converters patients do not differ from non-converters based on NPS prevalence, nor NPS severity mean (Table 1).

Table appendix 1.1. Neuropsychiatric characteristics of MCI converters vs MCI non converters.

	MCI-converters	MCI non-converters	T/Khi²	Significance
N	19	21		
NPS Prevalence				
Del (%)	5.3	0	1.134	0.287
Hall (%)	5.3	4.8	0.005	0.942
Agi (%)	15.8	28.6	0.935	0.334
Dep (%)	36.8	52.4	0.973	0.324
Anx (%)	31.6	19	0.835	0.361
Eup (%)	0	0	-	-
Apa (%)	26.3	28.6	0.025	0.873
Dis (%)	5.3	9.5	0.261	0.609
Irr (%)	31.6	33.3	0.014	0.906
Amb (%)	10.5	0	2.327	0.127
Nig (%)	5.3	9.5	0.261	0.609
App (%)	0	4.8	0.928	0.335
NPS Severity				
Del (m/sd)	0.11 / 0.46	0 / 0	-1	0.331
Hall (m/sd)	0.21 / 0.92	0.05 / 0.22	-0.79	0.434
Agi (m/sd)	0.37 / 1.01	0.67 / 1.16	0.865	0.393
Dep (m/sd)	0.891.63	1.38 / 2.16	0.798	0.43
Anx (m/sd)	0.581.07	0.57 / 1.78	-0.016	0.987
Eup (m/sd)	0 / 0	0 / 0	-	-
Apa (m/sd)	0.84 / 1.89	1.29 / 3.07	0.543	0.59
Dis (m/sd)	0.05 / 0.23	0.1 / 0.30	0.5	0.62
Irr (m/sd)	1 / 1.60	0.57 / 1.03	-0.997	0.327
Amb (m/sd)	0.16 / 0.69	0 / 0	-1	0.331
Nig (m/sd)	0.16 / 0.69	0.62 / 2.62	0.744	0.461
App (m/sd)	0 / 0	0.29 / 1.31	0.95	0.348

Legend: NPS = Neuropsychiatric Symptoms; Del = Delusions; Hal = Hallucinations; Agi = Agitation; Dep = Depression; Anx = Anxiety; Eup = Euphoria; Apa = Apathy; Dis = Disinhibition; Irr = Irritability; Amb = Aberrant Motor Behaviors; Nig = Nighttime behaviors; App = Appetite changes.

Neuroimaging Data Acquisition and Preprocessing

Cerebral glucose metabolism was measured with FDG-PET in 22 converters patients, 23 non-converters patients and 26 controls. For each participant, a FDG-PET image was acquired on a Siemens/CTI (Knoxville, TN) ECAT HR+ scanner (3D mode; 63 image planes; 15.2 cm axial field of view; 5.6 mm transaxial resolution and 2.4 mm slice interval) during quiet wakefulness with eyes closed and ears unplugged after intravenous injection of 2-[18F]fluoro-2-deoxy-D-glucose (FDG, 152 to 290 MBq)[407]. Images of tracer distribution in the brain were used for analysis: scan start time was 30 min after tracer injection and scan duration was 20 min. Images were reconstructed using filtered backprojection including correction for measured attenuation and scatter using standard software. FDG-PET image analyses were performed using SPM12 (Wellcome

Department of Cognitive Neurology, London, UK). The PET data were subjected to an affine and non-linear spatial normalization onto the a priori probabilities of the voxels in a spatially normalized (9-parameter affine) brain image belonging to grey matter. A mean image was then generated from all the resulting normalized images and smoothed using an 8-mm full-width at half-maximum isotropic Gaussian filter. This mean image served as a brain template specific to the whole sample. Each PET image was then spatially normalized onto this group-specific brain template. Finally, images were smoothed with a 12-mm full-width at half-maximum filter. This method was compared to the simple normalization based on these a priori (without specific template of the group) as well as to the normalization based on the specific template resulting from the normalization performed with the O-PET template provided by the SPM software. The comparisons of these different methods showed a greater precision of the 1st method in the contrasts between the groups (better localized clusters).

Statistical Analyses

Brain Metabolic Measure

For all analyses, SPM12 statistical analyses were performed by estimating parameters according to the general linear model at each voxel. Moreover, in order to control for individual variation in global FDG uptake, images were proportionally scaled to values from a cluster of preserved activity in the patients situated in the sensorimotor area[408]. As a first analysis, group comparisons were performed by using a factorial design with the preprocessed PET images of the three groups and the groups 2 by 2 (controls vs. MCI, and converters vs non-converters). Linear contrasts examined regions that were less active in converters patients than controls, in non-converters patients than controls, in converters patients than in non-converters patients and vice versa. Additional whole-brain analyses were conducted to evaluate the correlations between cerebral metabolism and NPS: GDS score, NPI severity subscales scores and NPI total score. For whole-brain statistical analyses, the statistical threshold was set at $p < 0.05$ FWE-corrected for multiple comparisons at the voxel-level. Moreover, we assessed the predictive role of metabolism in regions of interest (ROI) based on significant metabolism differences between groups. Coordinates described as significant were labeled with the anatomical automatic labeling (AAL)

atlas[409] (30). Contrast analysis (MCI vs. controls) was used to extract the ROIs that will be used for prediction analyses. These analyses showed that the metabolism of the following regions differed between the two groups: left angular and superior parietal, fusiform (2 clusters), inferior and middle temporal (2 clusters), middle (2 clusters), inferior orbital, orbitomedial frontal, thalamus and right precuneus, inferior parietal (2 clusters), inferior and middle temporal, middle (2 clusters), inferior orbital, precentral and *opercularis* frontal, middle cingulate, thalamus and putamen.

Predictive Analysis

Logistic regression models were performed with the objective of predicting MCI and conversion to AD. For this purpose, 2 binary logistic regression models were proposed: 1) a model based on demographic characteristics, Mattis Dementia Rating scale cognitive scores, GDS score and metabolism of ROIs from the comparison of controls and MCIs, to predict MCI group membership, 2) a model based on demographic characteristics, Mattis Dementia Rating scale cognitive scores, GDS and NPI scores and metabolism of ROIs from the comparison of MCI converters to AD and MCI non-converters to predict MCI converters with reference to the non-converters group.

Sensitivity, specificity, positive and negative predictive value characteristics will be established and compared to determine the most reliable analysis design for determining the probability of having MCI or converting to AD based on NPS and brain metabolism. The statistical threshold for variable inclusions was set at $p < 0.05$.

Results

Binary logistic regression models (Tables 2 and 4) based on the demographic data, Mattis Dementia Rating Scale, GDS/NPI scores and ROIs metabolism provided probabilistic equations for MCI/Controls classification and conversion from MCI participants to AD prediction.

The probability equation for the classification of MCI and Controls is sustained by GDS score (the higher the score, the higher the probability to be MCI), the brain metabolism in right precuneus, inferior temporal, inferior orbital frontal (the lower the metabolism, the higher the probability to be MCI) and the left middle orbital frontal (the higher the metabolism, higher the probability to

be MCI). The model had a sensitivity of 91,11%, specificity of 84,62% (Tables 3) and Yule Q coefficient indicating a very strong link between the diagnosis and the clinical characteristics.

Table appendix 1.2. Binary Logistic Regression for the MCI/Controls classification

	B	Sig.	Exp(B)	95% Confidence Interval	
GDS	1,173	0,014	3,230	1,262	8,266
Right precuneus	-0,534	0,004	0,586	0,409	0,842
Right inferior temporal	-0,452	0,020	0,637	0,435	0,932
Right inferior orbital frontal	-0,726	0,008	0,484	0,284	0,825
Left middle orbital frontal	0,556	0,027	1,743	1,065	2,853
Constant	-2,890	0,037	0,056		

Legend: B = Coefficient from each significant variable; Sig. = Significancy; GDS = Geriatric Depression Scale .

Table appendix 1.3. Psychometric characteristics for regression model of the MCI/Controls classification

		Predicted		Correct (%)
	Groups	CH	MCI	
Observed	CH	22	4	84,62 (Spec.)
	MCI	4	41	91,11 (Sens.)
Accuracy				88,73
Youden Y				0,76
Yule Q Coefficient				0,97

Legend: Spe. = Specificity; Sens. = Sensitivity.

Then, the probability equation for an MCI participant to convert to AD is sustained by GDS score (the lower the score, the higher the probability to convert), the brain metabolism in left angular (the lower the metabolism, the higher the probability to convert) and the left middle frontal (the higher the metabolism, higher the probability to convert). The model had a sensitivity of 73,68%, specificity of 85,71% (Tables 5) and Yule Q coefficient indicating a very strong link between the diagnosis and the clinical characteristics.

Table appendix 1.4. Binary Logistic Regression for the conversion from MCI to AD after 4 years

	B	Sig.	Exp(B)	95% Confidence Interval	
GDS	-0,468	0,031	0,626	0,410	0,957
Left angular	-0,457	0,007	0,633	0,454	0,882
Left middle frontal	0,389	0,067	1,476	0,973	2,239
Constant	0,003	0,997	1,003		

Legend: B = Coefficient from each significant variable; Sig. = Significancy; GDS = Geriatric Depression Scale .

Table appendix 1.5. Psychometric characteristics for regression model of the conversion from MCI to AD

		Predicted		Correct (%)
	Groups	Non-converted	Converted	
Observed	Non-converted	18	3	85,71 (Spec.)
	Converted	5	14	73,68 (Sens.)
Accuracy				85,00
Youden Y				0,59
Yule Q Coefficient				0,89

Legend: Spe. = Specificity; Sens. = Sensitivity.

Note that here demographic (age, sex, education), neuropsychiatric (from the NPI) and cognitive (Mattis Dementia Rating Scale subscores) variables were not significantly involved in predicting MCI/Controls classification or conversion from MCI to AD.

Discussion

The objective of this study was to test predictive models of MCI and conversion between MCI and AD using binary logistic regression models based on the association of depressive symptoms assessed by the Geriatric Depression Scale and brain glucose metabolism assessed with FDG-PET.

It was expected that more severe depressive symptoms and lower brain metabolism would increase the risk of having MCI or developing AD.

Classification of MCI compared with healthy controls was significantly improved by depression scores, and right and left middle orbital inferior temporal and frontal metabolism. These associations were broadly in the expected direction: more severe depression and lower metabolism increased risk of MCI, except for left orbitofrontal metabolism where higher metabolism increased risk.

Despite the lack of studies on discrimination or conversion from normal aging to MCI, some studies have been able to demonstrate metabolic differences in the hippocampal, parahippocampal, amygdala and insula regions, as well as interhemispheric metabolic asymmetries[341]. However, these markers are not always found: some authors showing instead lower metabolism in the precuneus and posterior cingulate in MCI compared to controls, others showing no difference[394,410].

On the other hand, depression showed associations with brain metabolism in addition to the associations shown in MCI. Considering its role in the risk of cognitive decline, it was expected that its association with metabolism would be involved in the discrimination between controls and MCI. In particular, it could be shown that MCI with depression had a lower metabolism in the right superior frontal gyrus, and that the importance of symptoms was negatively correlated with the metabolism of this region. Furthermore, while MCI showed hypometabolism in the right precuneus compared to controls, MCI with depression also showed hypometabolism in the precuneus, left postcentral, fusiform, and parahippocampal gyri, and right superior parietal[411]. Thus, while frontal regions appeared to be fairly well defined in depression in MCI, in our case the association between depression and orbitofrontal, right precuneus, and inferior temporal hypometabolism appear characteristic of MCI. It should also be noted that these differences between controls and MCI may also vary according to the amyloid status of the participants. Indeed, it could also be shown that MCI patients with depression presented temporo-parietal hypometabolism compared to controls if they were amyloid positive, and temporo-parietal and frontal hypometabolism if they were amyloid negative. Furthermore, MCI patients who were amyloid-positive with depression also showed right anterior cingulate and left orbitofrontal hypometabolism when compared to their amyloid-negative counterparts[412]. The authors

suggested that the metabolism of amyloid-positive MCI with depression were more similar to the metabolism found in AD.

Concerning the discrimination and conversion between MCI and AD, more studies tend to show lower metabolism in lateral parietal regions and precuneus in AD compared to MCI[410] or lower metabolism in inferior parietal in MCI converting to AD compared to non-converting[413] (36) in the posterior cingulate and precuneus[414], or in the bilateral temporo-parietal, frontal and posterior cingulate regions[415,416]. These data are also variable depending on the *APOE* status of the individuals: while individuals carrying an *APOE*-e4 mutation show temporo-parietal and posterior cingulate hypometabolism, carriers who convert to AD also show metabolic reductions in frontal, anterior cingulate, and inferior frontal regions[413].

Our results are in little agreement with previous data, showing a higher risk of conversion from MCI to AD in individuals with lower depressive symptoms, lower left angular (lateral parietal) metabolism, and higher left middle frontal metabolism.

More recently, other studies have demonstrated the value of FDG-PET in predicting MCI in AD, including the use of machine learning algorithms or regression analyses (including logistic)[414,417,418]. These studies already show good predictions of conversion up to 5 years of follow-up and sometimes use the combination of PET data for AD biomarkers, CSF protein data or neuropsychological data[418,419]. However, to our knowledge, this work is a pioneer in the joint use of neuropsychiatric symptoms and FDG-PET in control/MCI discrimination and in the prediction of MCI to AD conversion.

As elaborated previously, there are interactions between MCI status and *APOE*/Amyloid status on brain metabolism, including glucose metabolism. Failure to consider these factors is a limitation of this work. In addition, the sample size made it difficult to perform cross-validation to check the sensitivity of the predictions. The sometimes counterintuitive results also raise the question of metabolic asymmetries in the groups analyzed. Despite this, the sensitivity and specificity of the models remain relatively high and still underline the interest of these markers in the prediction of MCI and AD.

Part 2 : Prediction of cognitive decline in healthy aging based on neuropsychiatric symptoms and PET-biomarkers of Alzheimer's disease (in prep for Journal of Neurology)

Lucas Ronat [a,b,c], Alexandru Hanganu [b,d], Daphné Chylinski [c], Maxime Van Egroo [c], Justinas Narbutas [c,e], Gabriel Besson [c], Vincenzo Muto [c], Christina Schmidt [c,e], Mohamed Ali Bahri [c], Christophe Phillips [c], Eric Salmon [c,e,f], Pierre Maquet [c,f], Gilles Vandewalle [c,g], Fabienne Collette [c,e,g] & Christine Bastin[c,e,g]

Affiliations:

[a]Faculty of Medicine, Department of Medicine, University of Montreal, Montréal, Québec, Canada

[b]Research Centre of the University Institute of Geriatrics of Montreal, Neuroimaging of Emotions Laboratory, Montréal, Québec, Canada

[c]GIGA-Cyclotron Research Centre-In Vivo Imaging, University of Liège, Liège 4000, Belgium

[d]Faculty of Arts and Sciences, Department of Psychology, University of Montreal, Montréal, Québec, Canada

[e]Psychology and Neuroscience of Cognition Research Unit, Faculty of Psychology and Educational Sciences, University of Liège, Liège 4000, Belgium

[f]Department of Neurology, CHU Liège, Liège 4000, Belgium

[g]F.R.S.-Fonds National de la Recherche Scientifique, Bruxelles, Belgique

Corresponding author:

Christine Bastin

Bât. B30 GIGA CRC In vivo Imaging - Aging & Memory

Quartier Agora, allée du 6 Août 8, 4000 Liège, Belgium

Email: christine.Bastin@uliege.be

Phone: +32 4 3662369

Statements and Declarations

Funding

For this project, Lucas Ronat received a grant from the MITACS Globalink program. This work was supported by the Fonds National de la Recherche Scientifique (CS is a research associate, CB and GV are senior research associates, and FC and CP are research directors at the FRS-FNRS) and by the Wallonia-Brussels Federation (Concerted Research Actions – grant 17/21-09 SLEEPDEM).

Competing Interests

The authors have no competing interests to disclose.

Authors contributions

Conceptualization: Lucas Ronat, Christine Bastin, Gilles Vandewalle, Fabienne Collette, Alexandru Hanganu; **Methodology**: Lucas Ronat, Christine Bastin, Alexandru Hanganu; **Data acquisition & process**: Justinas Narbutas, Maxime Van Egroo, Daphne Chylinski, Gabriel Besson, Vincenzo Muto, Christina Schmidt, Mohamed Ali Bahri, Christophe Phillips, Eric Salmon, Pierre Maquet, Gilles Vandewalle, Fabienne Collette & Christine Bastin; **Formal analysis and investigation**: Lucas Ronat; **Writing - original draft preparation**: Lucas Ronat; **Writing - review and editing**: All authors; **Funding acquisition**: Lucas Ronat; **Supervision**: Christine Bastin, Alexandru Hanganu

Abstract

Neuropsychiatric symptoms (NPS) such as depression and anxiety have been associated with a risk of accelerated cognitive decline or conversion to dementia of the Alzheimer type, as well as with higher Alzheimer's Disease biomarkers (brain tau and amyloid burden) even in non-demented patients. This work aims to assess the relationship between longitudinal cognitive changes and NPS in association with AD biomarkers in healthy middle-aged to older participants. The cohort consisted of 101 healthy participants aged 50 to 70 years, 66 of whom had neuropsychological assessments of memory, executive functions, and global cognition at 2-year follow-up. At baseline, NPS were assessed using the Beck Depression and Anxiety Inventories while brain tau and amyloid loads were measured using positron emission topography scans. Participants whose cognition declined or remained stable at follow-up were categorized into groups for each cognitive domain. Group classification was investigated using binary logistic regressions based on combined AD biomarkers and NPS. The results showed that an association between anxiety and prefrontal amyloid burden significantly classified participants declining in episodic memory, while the classification of global cognitive decline involved temporal and occipital amyloid burden but not NPS. Moreover, depression together with prefrontal and hippocampal tau burden were associated to decline in memory. The classification of participants based on executive decline was related to depression and mainly prefrontal tau burden. These findings suggest that the combination of NPS and brain biomarkers of AD predicts the occurrence of cognitive decline in aging.

Keywords: Neuropsychiatric symptoms, Aging, Cognitive decline, Alzheimer's PET Biomarkers

Introduction

Neuropsychiatric symptoms (NPS) are present in the older population with and without cognitive impairment[7,97,184]. Among the most common symptoms are depression, apathy, and anxiety. When they manifest in mild cognitive impairment (MCI), they increase the risk of dementia[12]. When present in aging in the absence of cognitive impairment, they increase the risk of future cognitive impairment[8]. Notably, they have been associated with accelerated overall decline or decline in a specific cognitive domain, such as memory, executive functions, attention, language, praxis, and visuospatial functions[8,196].

In addition, several studies have focused on the relationships between NPS and Alzheimer disease (AD) biomarkers (i.e., β-amyloid and tau). Currently, the results are divergent. Notably, the use of anti-β-amyloid therapy was recently shown to increase depression, suicide attempts, anxiety, and sleep disturbances in individuals with AD[420]. The authors suggested that increased β-amyloid in the brain would contribute to attenuate or repair neuronal damage. Thus, sudden reduction of β-amyloid could worsen cognition and NPS. In contrast, other work with Positron Emission Tomography (PET) examination using radiotracers of β-amyloid has found greater amyloid burden in association with the severity of certain NPS. Mori et al. (2014) found more β-amyloid in bilateral frontal regions in AD patients with apathy[41]. Bensamoun et al. (2016) reported more whole-brain β-amyloid in patients exhibiting more severe anxiety or irritability. Both symptoms were also linked to higher β-amyloid burden in frontal and cingulate regions, while irritability also stood out with higher burden in parietal regions[57].

At the MCI stage, patients with amyloid-positive status have also been found to have a higher probability of NPS, including depression, anxiety, apathy, irritability, or disturbances in nocturnal behaviors[421]. Notably, amyloid-positive MCI patients with depression have a higher amyloid burden in insular and frontotemporal regions and have a higher rate of conversion to AD[398]. Some associations could also be demonstrated in older cognitively healthy individuals. While single NPS such as depression, apathy, and anxiety were positively correlated with global β-amyloid burden[167,422], the clinical state of mild behavioral disorder, as defined by Ismail et al. (2016, 2017), was also correlated with global and striatal burden[228,423,424]. Moreover, having higher depression

and anxiety scores increased the risk of having a positive amyloid PET scan in cognitively healthy individuals[421].

In addition to amyloid burden, tau burden measured with PET has also been associated with NPS in early AD. Different NPS were sometimes associated with the same burden locations. For example, affective (depression, anxiety) and hyperactive (agitation, aberrant motor behaviors) type symptoms were similarly associated with dorsolateral, entorhinal, inferior temporal, posterior cingulate, supramarginal, and precuneus tau burden[425]. Affective symptoms were also characterized by orbitofrontal tau burden[425]. Even in older cognitively healthy individuals, the probability of depression was associated with tau burden, but not with amyloid burden[426]. Similarly, total and affective NPS assessed with the NeuroPsychiatric Inventory were correlated with transentorhinal tau burden[427]. More recently, Tissot et al. (2021) undertook to analyze these relationships in a broad spectrum of NPS both in individuals without cognitive impairment, with MCI or AD[68]. In individuals without cognitive impairment, most NPS (agitation, depression, euphoria, hallucinations, motor disturbances and nocturnal behaviors) were associated with frontal and/or temporal tau burden. In cognitively impaired individuals, the overall severity of NPS was associated with temporal, medial frontal, precuneus and cuneus tau burden. Results were also broadly similar when corrected for β-amyloid status.

Considering the risk factors for decline represented by NPS and their associations with PET biomarkers of Alzheimer's disease, the objective of this work was to investigate the role of NPS associated with tau and β-amyloid burden in global and specific cognitive decline in cognitively healthy individuals. Moreover, given that a critical window to detect future decline due to Alzheimer pathology is in middle-age[428], we focus on middle-aged to young-old participants. We expected that the association between more severe NPS and higher amyloid and tau burden in different brain regions (frontal, temporal, parietal, cingulate) would be involved in predicting memory, executive or global cognitive decline.

Methods

Participants

This work relied on a cohort of 101 healthy French-speaking participants aged 50–70 years (68 women; M ± SD = 59.4 ± 5.3 years) who were enrolled between June 15, 2016, and October 2, 2019, for a multimodal cross-sectional study taking place at the University of Liège, Belgium (COFITAGE study; EudraCT: 2016-001436-35) [429]. They gave their written informed consent and received financial compensation. This research was approved by the ethical committee of the Faculty of Medicine at the University of Liège, Belgium.

Exclusion criteria were as follows: body mass index (BMI) < 18 and > 29; smoking; excessive alcohol consumption (>15 units/week); excessive caffeine consumption (>6 cups/day); clinical symptoms of cognitive impairment indicated by Dementia Rating Scale < 130[430] and/or Mini-Mental State Examination ≤ 27[431]; recent severe brain trauma; shift work in the past 6 months; transmeridian travel in the past 2 months; high levels of anxiety (21-item self-rated Beck Anxiety Inventory ≥ 17[432]) and depression (21-item self-rated Beck Depression Inventory ≥ 17[433]); recent psychiatry history; chronic medication affecting the central nervous system (stable treatment for more than 6 months for hypertension or hypothyroidism were included). Participants with sleep apnea (apnea–hypopnea index ≥ 15/hr) were screened and excluded during an in-lab screening night of polysomnography. Demographic characteristics of the final 99 participants are shown in Table 1.

Considering that this work is concerned with cognitive decline, the sample of interest was selected from participants with available neuropsychological data (N = 66). Among them, some participants had missing data that made it impossible to determine their scores for executive (final N = 65), memory (final N = 61) and global (final N = 59) decline. The demographic characteristics of the full sample are shown in Table 1.

Table appendix 2.1. Demographic characteristics of the sample (N = 66).

	Mean	± SD	Min	Max
Demographic				

Age	59.88	5.42	50	69
Education	14.89	3.28	9	25
Women %	66.2			
Neuropsychiatric				
BDI	4.43	4.37	0	16
BAI	2.40	2.55	0	9

Neuropsychiatric symptoms

Anxiety and depression were assessed respectively using the Beck Anxiety Inventory (BAI) and the Beck Depression Inventory (BDI). The BAI consists of a self-administered instrument with 21 items that covers the most frequent anxiety symptoms seen in clinical practice. Each item is scored 0, 1, 2 and 3 denoting increasing severity of symptoms. The BDI includes 21 self-rated items that covers a variety of depressive symptoms including feelings of sadness, concerns about the future, suicidal ideation, tearfulness, sleep, fatigue, interests, worries about health, sexual interest, appetite, weight loss and general enjoyment, with each response scored on a scale from 0 to 3. Higher total scores indicate more severe depressive symptoms.

Neuropsychological Data

Of all participants, 66 underwent neuropsychological assessments at baseline and at a 2-year follow-up visit. The battery included the Free and Cued Selective Reminding Test (FCSRT), the Logical Memory Test from the Wechsler Memory Scale III, a forced-choice reaction time test, the Mnemonic Similarity task, the Stroop test, the Digit Symbol Substitution Test, Digit Span test in direct and reversed order, phonemic and semantic Verbal Fluency, a n-back task, the Trail Making Test, the D2 test, and the Mattis Dementia Rating Scale[429,434]. For episodic memory performance, our analyses focused on the total recall score from the FCSRT due to its associations with medial temporal lobes in MCI and AD[435,436]. For executive functioning, we computed an executive composite score that included scores from verbal fluency, digit span in reverse order, Trail Making Test B, 3-back task, and Stroop by summing z-scores from tasks. Finally, a global composite score was obtained by the sum of z-scores from all tasks except the Mattis Dementia Rating Scale. For each of these scores, decline indices were established according to the formula: ($score_{T0}$–

$score_{T1}$)/$score_{T0}$. These indices were interpreted as follows: index = 0: performance was similar between baseline and follow-up, Index < 0: performance was improved at follow-up, Index > 0: performance was decreased at follow-up compared to baseline. It should be noted that in cases where performance decreases over time, it remains within the norms.

PET acquisition and processing

At baseline, Aβ-PET imaging was performed with radiotracers [18F]Flutemetamol (n = 63) or [18F]Florbetapir (n = 3), while tau/neuroinflammation-PET imaging was performed with radiotracer [18F]THK-5351 (n = 66), on an ECAT EXACT + HR scanner (Siemens, Erlangen, Germany). For all radiotracers, participants received a single dose of the respective radioligands in an antecubital vein (target dose app. 185 MBq). Aβ-PET image acquisitions started 85 min after injection, and 4 frames of 5 min were obtained, followed by a 10-minute transmission scan (with Germanium-68), with a total duration spent in the scanner of the app. 30 min. For [18F]THK-5351-PET, a 10-minute transmission scan was acquired first, and dynamic image acquisitions started immediately after injection, consisting of 32 frames (with increasing time duration), with a total duration spent in the scanner of approximately 100 min. All PET images were reconstructed using a filtered back-projection algorithm including corrections for measured attenuation, dead time, random events, and scatter using standard software (Siemens ECAT - HR + V7.1, Siemens/CTI, Knoxville, TN, USA). The preprocessing steps are detailed in Rizzolo et al. (2021)[429]. Standardized uptake value ratio (SUVR) was calculated using the whole cerebellum as the reference region for Aβ-PET[437], and cerebellum grey matter for [18F]THK-5351-PET[438]. Mean PET SUVr were extracted for regions from the Automated Anatomical Labelling atlas 3[439].

Statistical analysis

Statistical analyses were performed using SPSS version 26.0 software. Two analytic steps were performed. First, partial correlations between neuropsychiatric symptoms, decline indices and tau/amyloid burden values in AAL regions (with age, sex, and education as covariates) were performed as a validation step to check the potential associations between NPS and PET variables with cognition. In a second step, logistic regression models based on Wald statistic were applied to predict cognitive decline with the decline indices grouped into two categories (1 = positive

index indicating a decline in scores, 0 = zero or negative index) as dependent variable, and demographic (age, sex, education), NPS and tau/amyloid burden as predictive covariates. Separate models assessed the predictive value of NPS and amyloid burden on the one hand and NPS and tau burden on the other hand. The threshold of significance for all analyses was 0.05. A maximum of 20 iterations was set for each model. Each final model consisted of the one with the best classification characteristics (even in cases where the Wald statistics are not significant at $p<.05$ [type II error]).

Results

Correlational analyses

Partial correlations corrected for age, sex, and education are presented in Supplementary Table 1. Depression was positively correlated with anxiety. In terms of cognitive decline, depression and anxiety were not correlated with decline in any domain. In terms of amyloid burden, depression was negatively correlated with right pallidum and cerebellar (except for right cerebellum crus 2 for which correlation was positive), whereas anxiety was positively correlated with left temporal pole and vermis, and negatively correlated with cerebellar burdens. In terms of tau burden, depression was positively correlated with bilateral hippocampus and cuneus, cerebellar and vermis, whereas anxiety was negatively correlated with left anterior cingulate burdens.

Considering cognitive decline, executive decline was negatively correlated with left inferior temporal and cerebellar amyloid burdens and positively correlated with frontal, cingular, insular, temporal, occipital, parietal and striatal tau burdens at baseline; memory decline was negatively associated with frontal, left cingular and right temporal amyloid burden and positively with right orbitofrontal and bilateral rectus tau burdens at baseline; global decline was negatively correlated with precentral, rolandic operculum, supramarginal and cerebellar amyloid burdens, and positively with frontal, anterior cingular, parietal, occipital, and temporal tau burdens at baseline.

However, none of these correlations did survive Bonferroni correction for multiple comparisons.

Logistic regression predictive models

Overall, the combination of NPS and amyloid burden were significantly predictive of memory decline (Table 2). Prediction was improved by higher anxiety scores, lower amyloid burden in the right inferior frontal opercularis and triangularis regions and left and right cerebellar crus 1 and 3, as well as by higher amyloid burden in the left supplementary motor area, orbitofrontal cortex, superior parietal, and right inferior temporal regions. The model had a sensitivity of 86.4% and a specificity of 95.2% in predicting participants with a decline in memory performance (Table 3).

Amyloid burden but not NPS was predictive of global cognitive decline (Table 4). Prediction was improved by lower amyloid burden in the right superior occipital region, left fusiform, right pallidum, and left cerebellar 7b lobule, as well as by higher amyloid burden in the right olfactory region, left hippocampus, right cuneus, left inferior occipital region, and right cerebellar 6 lobule. The model had a sensitivity of 89.7% and a specificity of 93.1% in predicting participants with global cognitive decline (Table 5).

No significant association with, or improved classification compared with the hazard threshold for, NPS and amyloid burden was found for executive decline. Also, for all models, age, sex, and education covariates were not significantly associated with classification.

Table appendix 2.2. Binary Logistic Regression for the mnesic decline prediction based on NPS and amyloïd burden.

	Coef.	**Wald**	**p-value**
BAI	1.635	4.856	0.028
Right Frontal pars opercularis	-129.461	6.196	0.013
Right Frontal pars triangularis	-160.272	5.572	0.018
Left Supplementary Motor Area	44.519	5.380	0.020
Right posterior Orbitofrontal Cortex	114.011	6.028	0.014
Right superior Parietal	54.241	3.953	0.047
Right inferior Temporal	51.883	3.911	0.048
Left Crus I of cerebellar hemisphere	-238.614	6.307	0.012
Right Lobule III of cerebellar hemisphere	-81.508	5.478	0.019
Constant	270.534	5.982	0.014

Legend: BAI = Beck Anxiety Inventory, R = Right, L = Left.

Table appendix 2.3. Psychometric characteristics for mnesic decline prediction based on NPS and amyloïd burden.

		Predicted		Correct %
	Groups	No decline	Decline	
Observed	No decline	40	2	95.24 (Spec.)
	Decline	3	19	86.36 (Sens.)
Accuracy				92.20
Youden Y				0.82
Yule Q Coefficient				0.98

Regarding global decline, prediction was improved by lower amyloid burden in the right parahippocampal, right superior occipital, left fusiform, right pallidum, and left cerebellar 7b lobule, as well as by higher amyloid burden in the right olfactory, left hippocampal, right cuneus, left inferior occipital, and right cerebellar 6 lobule. The model had a sensitivity and specificity of 96.6% in predicting participants with global cognitive decline (Table 5).

Table appendix 2.4. Binary Logistic Regression for the global cognitive decline prediction based on NPS and amyloïd burden.

	Coef.	Wald	p-value
R Olfactory Cortex	39.433	4.611	0.032
L Hippocampus	67.457	3.811	0.051
R ParaHippocampal	161.235	5.309	0.021
R Cuneus	-230.480	5.996	0.014
R superior Occipital	211.025	5.841	0.016
L inferior Occipital	-322.460	5.873	0.015
L Fusiform	-52.883	5.618	0.018
R Pallidum	229.353	5.165	0.023
R Lobule VI of cerebellar hemisphere	-223.493	5.219	0.022
L Lobule VIIb of cerebellar hemisphere	82.489	4.720	0.030
Constant	39.433	4.611	0.032

Legend: R = Right, L = Left.

Table appendix 2.5. Psychometric characteristics for global cognitive decline prediction based on NPS and amyloïd burden.

		Predicted		**Correct %**
	Groups	No decline	Decline	
Observed	No decline	26	2	93.1 (Spec.)
	Decline	3	27	89.7 (Sens.)
Accuracy				91.4
Youden Y				0.83
Yule Q Coefficient				0.98

Overall, the association of NPS and tau burden were significantly predictive of both memory (Table 6 and 7) and executive (Table 8 and 9) decline.

Regarding memory decline (Table 6), prediction was improved by higher depression scores, lower tau burden in the left hippocampal region, and higher burden in the right orbitofrontal cortex and right cerebellum 9. The model had a sensitivity and specificity of 91.7% in predicting participants with memory decline (Table 7).

Regarding executive decline (Table 8), prediction was improved by higher depression scores, lower tau burden in the right lateral orbitofrontal cortex, left lingual, and right precuneus regions, and higher burden in the right inferior opercularis frontal, right supplementary motor area, and left middle temporal regions. The model had a sensitivity of 96.4% and a specificity of 95% in predicting participants with declining executive performance (Table 9).

No significant association with, or improved classification compared with the hazard threshold for, NPS and tau burden was found for global cognitive decline. Also, for every model, age, sex, and education covariates were not significant.

Table appendix 2.6. Binary Logistic Regression for the mnesic decline prediction based on NPS and tau burden.

	Coef.	**Wald**	**p-value**
BDI	0.408	3.463	0.063
R medial Orbitofrontal Cortex	18.899	7.072	0.008

L Hippocampus	-17.350	7.695	0.006
R Lobule IX of cerebellar hemisphere	50.242	5.422	0.020
Constant	-58.810	4.708	0.030

Legend: BDI = Beck Depression Inventory, R = Right, L = Left.

Table appendix 2.7. Psychometric characteristics for mnesic decline prediction based on NPS and tau burden.

		Predicted		**Correct %**
	Groups	No decline	Decline	
Observed	No decline	33	3	91.7 (Spec.)
	Decline	1	11	91.7 (Sens.)
Accuracy				91.7
Youden Y				0.83
Yule Q Coefficient				0.98

Table appendix 2.8. Binary Logistic Regression for the executive decline prediction based on NPS and tau burden.

	Coef.	**Wald**	**p-value**
BDI	0.916	6.346	0.012
R Frontal pars opercularis	68.086	6.703	0.010
R Supplementary Motor Area	58.635	4.720	0.030
R lateral Orbitofrontal Cortex	-12.873	5.880	0.015
L Lingual	-107.474	6.697	0.010
R Precuneus	-51.189	4.346	0.037
L middle Temporal	49.983	5.659	0.017
Constant	-3.968	0.283	0.595

Legend: BDI = Beck Depression Inventory, R = Right, L = Left.

Table appendix 2.9. Psychometric characteristics for executive decline prediction based on NPS and tau burden.

		Predicted		**Correct %**
	Groups	No decline	Decline	
Observed	No decline	19	1	95 (Spec.)

	Decline	1	27	96.43 (Sens.)
Accuracy				95.80
Youden Y				0.91
Yule Q Coefficient				1.00

Discussion

The aim of this work was to investigate whether the association of neuropsychiatric factors (depression and anxiety) and Alzheimer's disease markers (brain β-amyloid and tau burden) predicts cognitive decline (global, memory, executive) in cognitively healthy middle-aged to older individuals. Based on previous work, it was expected that the association between more severe NPS and higher amyloid and tau burden in different brain regions (frontal, temporal, parietal, cingulate) would increase memory, executive or global cognitive decline, and could be predictive of the risk of decline.

Expectations regarding the hypotheses are partially supported by the results. NPS were involved in predicting memory decline when associated with amyloid and tau burden (anxiety and depression respectively), and in predicting executive decline when associated with tau burden (depression). The higher the NPS, the higher the probability of showing decline. Considering that NPS were below the clinical threshold thanks to inclusion criteria, this suggests that even subtle affective symptoms predict poorer cognitive performance two years later in memory and executive functions, the two domains which are the most sensitive to aging[440].

Concerning amyloid and tau burden, the results are diverse as there were both positive and negative associations with decline. The observation that more amyloid burden were linked to a stability of cognitive performance in some regions is not inline with the hypothesis raised by Panza et al. suggesting that an increase in amyloid burden, at the initial phase of rising levels, was an attempt by the brain to mitigate or repair neuronal damage[420]. Although this was work done with AD patients, whereas here participants were cognitively healthy, it raises the question of a possible protective role of amyloid and tau burden in small amounts. As Paracelsus said, "Everything is poison and nothing is without poison; the dose alone makes something not a poison". Other authors have demonstrated cognitive preservation in people with good cognitive

reserve even when developing high tau burden[441] or neuroinflammation in patients with early MCI. Amyloid deposits have been described as generating protective neuroinflammation while neuroinflammation would be toxic when generated by tau deposits[442]. Also, a positive association has been shown between executive functioning and tau loads[443]. The authors pointed out that tau loads begin in the entorhinal cortex and hippocampus, and that the association with better executive functioning could be due to a compensatory mechanism in executive function networks (such as the prefrontal cortex) which become more activated during the development of tau loads in medial temporal regions. The authors also point out the existing connections between the prefrontal cortex and the medial temporal lobe[444,445].

However, the observation that there was also a link between higher NPS and more amyloid/tau burden in some regions and cognitive decline supports the literature that showed higher tau and amyloid loads associated with higher NPS as risk factors for cognitive decline. For example, the association of depression with a positive amyloid status would increase the risk of MCI incidence by 3 times, while associated with anxiety, this status would increase the risk of MCI incidence by 5 times compared to amyloid-negative individuals without NPS[446]. Conversely, it has been shown that higher amyloid loads increase the emergence of NPS, notably anxiety and agitation[447]. Longitudinally, the amyloid positive status increases the severity of nocturnal and motor behaviors in early-onset AD[448]. Moreover, depression also appears to accelerate cognitive decline in amyloid-positive MCI patients. Interestingly, these participants had greater amyloid loads in frontotemporal and insular regions, as well as coincident hypermetabolism of glucose in frontal regions compared to patients without depression. Furthermore, the progression to AD was faster in amyloid-positive MCI with depression[398]. The current data suggests that such associations between NPS, AD biomarkers and cognitive decline already exist in middle-aged individuals who are cognitively healthy (notably, their scores at follow-up were still within the norms). A longer longitudinal follow-up should inform us about the potential emergence of MCI in some participants and one could predict that this would be more likely in those individuals who had the higher NPS score and the higher amyloid/tau burden. Additionally, within a larger cohort, it would therefore be appropriate to distinguish cognitive trajectories in cognitively healthy individuals

according to their protein burden divided into categories for example (1st vs. 4th quartile), or to define mixed models based on burden and allowing control of subjects as a random factor.

Despite limitations related to the sample size and the short duration of the follow-up, the findings of a link between NPS, AD biomarkers and cognitive decline in a cohort of cognitively healthy middle-aged to young-old individuals underline the importance of further investigations on the relationships between NPS and brain protein burden. Proportional hazard analyses in healthy individuals according to burden (amyloid positive or not, tau positive or not), genetic risk factor (ApoE-ε4 or not), and NPS (clinically significant or not) would help to understand the joint risk of the different factors in cognitive decline (normal or pathological). Also, it may be noted that the tau protein radiotracer [18F]THK5351 has been criticized for its off-binding to monoamine oxidase B (MAO-B) in vivo[449]. Thus, [18F]THK5351 is an important marker of neuroinflammatory elements such as reactive astrocytes, which increase along with tau pathology[450]. Finally, considering that inclusion of participants was based on BAI and BDI scores (<17), the results presented relate only to low levels of depression and anxiety and are therefore not generalizable to moderate/severe levels of these symptoms.

The generalizability of our results refers to the possibility of its implementation in a clinical setting and on an individual basis, to calculate the predictive value of the risk of cognitive decline after 2 years. After the corresponding parameters are being quantified, the probability of conversion can be calculated using the equation: $P(event) = 1/(1+e^{-[\beta1*X1+ \beta2*X2+ \beta3*X3+\ldots+ \beta n*Xn+constant)}$. The regression tables (Table 2-4-6-8) provide the β coefficients of each significant variable in the model and the X values are the individual-specific values quantified using corresponding NPS inventory and PET data. The data obtained from the calculation of each equation allows us to estimate, from the data of a given individual, the percentage risk of cognitive decline of this individual.

Supplementary Table 1. Partial correlations between NPS, decline scores and amyloid or tau burden.

	Amyloid (N = 55)					Tau (N = 40)				
	BDI	BAI	exec	mem	global	BDI	BAI	exec	mem	global
BDI	-	.468**	-.091	.197	.113	-	.510**	-.080	.197	.100
BAI	.468**	-	.062	.135	.066	.510**	-	-.010	.123	-.036
exec	-.091	.062	-	.028	.673**	-.080	-.010	-	.089	.672**
mem	.197	.135	.028	-	.609**	.197	.123	.089	-	.659**
global	.113	.066	.673**	.609**	-	.100	-.036	.672**	.659**	-
PreCentral L	-.017	.087	.001	-.214	-.203	.203	-.100	.281*	.128	.281*
PreCentral R	-.063	-.013	.041	-.314**	-.314**	.168	-.057	.419**	.063	.303*
Front Sup 2 L	-.112	.046	-.008	-.200	-.137	.048	-.196	.246	.083	.232
Front Sup 2 R	-.115	-.024	.009	-.280*	-.211	.122	-.132	.319*	.092	.259
Front Mid 2 L	-.076	-.024	-.104	-.113	-.155	.042	-.215	.234	.079	.209
Front Mid 2 R	-.044	-.017	.002	-.177	-.167	.087	-.166	.332*	.120	.276*
Front Inf Oper L	.054	.039	.058	-.124	.013	.140	-.158	.269*	.043	.205
Front Inf Oper R	-.146	-.106	.126	-.250*	-.114	.004	-.093	.521**	.061	.326*
Front Inf Tri L	.063	.025	-.114	-.128	-.114	.091	-.204	.239	.039	.171
Front Inf Tri R	.032	-.015	.056	-.145	-.082	.079	-.125	.431**	.035	.249
Front Inf Orb 2 L	.067	.111	-.044	-.081	-.046	.154	-.063	.271*	.059	.213
Front Inf Orb 2 R	.013	-.051	.043	-.033	-.037	.005	-.075	.453**	.020	.263
Rol Oper L	.092	.029	-.127	-.114	-.152	.244	-.105	.267*	.094	.272*
Rol Oper R	-.076	-.063	.012	-.228*	-.229*	.076	-.181	.416**	.044	.325*
SMA L	-.150	-.008	-.074	-.139	-.130	.118	-.141	.296*	-.013	.253
SMA R	-.132	.136	-.041	-.182	-.212	.174	-.137	.368**	.048	.315*
Olfactory L	.022	-.008	.021	.032	.106	.233	.022	.367**	.104	.348*
Olfactory R	.006	.127	-.041	.012	.023	.250	.073	.357*	.141	.393**
Front Sup Med L	-.084	-.046	.023	-.125	-.021	.033	-.252	.286*	.130	.306*
Front Sup Med R	-.157	-.068	.075	-.190	-.055	.051	-.200	.325*	.105	.292*
Front Med Orb L	-.087	-.023	-.026	-.015	-.005	.037	-.205	.310*	.250	.398**
Front Med Orb R	-.070	.062	.091	-.091	-.001	.119	-.062	.301*	.232	.336*
Rectus L	-.101	-.036	-.036	-.042	-.041	.115	-.076	.296*	.281*	.382**
Rectus R	-.095	.077	-.062	-.043	-.073	.076	.003	.302*	.310*	.383**
OFCmed L	-.023	.058	-.052	-.022	-.022	.021	.052	.247	.121	.182
OFCmed R	-.097	-.009	-.113	-.055	-.073	-.009	.144	.199	.241	.199
OFCant L	-.021	.013	-.004	.064	.080	.030	-.022	.208	.233	.272*
OFCant R	-.034	.074	-.125	.071	-.045	.058	.126	.190	.312*	.239
OFCpost L	.029	.049	-.016	.006	.028	.061	-.040	.204	.098	.187
OFCpost R	.030	.082	.001	-.074	-.021	.021	.062	.368**	.024	.288*
OFClat L	.070	.096	-.153	-.066	-.164	.047	.151	.099	.072	.070
OFClat R	.103	-.130	-.070	-.071	-.109	-.033	.118	.272*	-.118	.066
Insula L	.005	.061	-.010	.032	.030	.149	-.190	.273*	.052	.254
Insula R	-.123	-.032	.031	-.096	-.082	.096	-.167	.327*	-.006	.217

Cing Ant L	-.066	.026	.085	-.119	-.005	.041	-.267*	.270*	.140	.329*
Cing Ant R	.026	.090	.036	-.232*	-.108	.090	-.239	.307*	.106	.328*
Cing Mid L	-.045	-.009	.027	-.094	-.031	.099	-.213	.248	.003	.183
Cing Mid R	-.063	.097	.029	-.124	-.066	.122	-.229	.307*	.038	.251
Cing Post L	-.040	.053	.117	-.151	.020	.196	-.141	.239	-.053	.143
Cing Post R	.055	.137	.216	-.222	-.035	.175	-.104	.318*	.059	.260
Hippocampus L	.068	.084	.049	-.092	.064	.312*	-.118	.173	-.058	.130
Hippocampus R	.183	.169	.122	-.069	.004	.280*	-.133	.204	-.024	.159
Parahippocampal L	.001	.201	-.053	-.079	-.050	.255	-.079	.235	-.011	.189
Parahippocampal R	-.064	.179	.068	-.068	-.038	.248	-.103	.217	.054	.259
Amygdala L	-.170	.065	-.142	.028	-.035	.246	-.118	.189	-.031	.154
Amygdala R	-.184	.167	-.141	-.090	-.174	.225	-.088	.219	-.076	.152
Calcarine L	.036	.018	.014	-.074	-.077	.211	-.075	.220	.087	.216
Calcarine R	.008	.115	.100	-.140	-.071	.247	-.094	.300*	.108	.273*
Cuneus L	.105	.086	-.037	.034	-.066	.319*	-.006	.196	.102	.228
Cuneus R	.030	.112	.045	-.113	-.094	.299*	.012	.341*	.195	.336*
Lingual L	-.079	-.112	.088	-.184	-.038	.194	-.180	.182	-.004	.164
Lingual R	-.063	-.058	.205	-.132	.014	.159	-.181	.256	-.028	.168
Occ Sup L	.205	.085	.026	.022	-.067	.231	-.071	.247	.192	.319*
Occ Sup R	.082	.054	.008	-.146	-.200	.179	.001	.389**	.153	.320*
Occ Mid L	.099	-.055	.003	.031	-.015	.215	-.080	.324*	.173	.345*
Occ Mid R	.096	.073	-.059	-.044	-.171	.151	-.076	.293*	.194	.315*
Occ Inf L	-.026	-.205	.078	-.137	.032	.152	-.191	.220	.028	.199
Occ Inf R	.084	-.069	.093	-.028	-.007	.155	-.188	.161	.038	.153
Fusiform L	-.059	-.056	-.091	-.164	-.133	.192	-.132	.154	.044	.159
Fusiform R	-.018	.015	-.092	-.094	-.170	.216	-.137	.202	.090	.230
PostCentral L	-.024	.012	.043	-.060	-.103	.176	-.066	.291*	.160	.278*
PostCentral R	-.060	-.019	.080	-.193	-.210	.041	-.153	.412**	.098	.302*
Par Sup L	.055	.004	-.201	-.018	-.154	.226	-.052	.247	.158	.284*
Par Sup R	-.041	-.049	-.039	-.202	-.216	.052	-.065	.345*	.094	.250
Par Inf L	-.017	.010	-.014	-.006	-.022	.128	-.041	.268*	.171	.281*
Par Inf R	-.038	-.011	-.015	-.149	-.180	.011	-.115	.334*	.063	.227
SupMar L	.052	.119	-.053	-.103	-.104	.211	-.042	.219	.172	.246
SupMar R	-.013	.003	-.004	-.216	-.239*	.074	-.132	.367**	.105	.301*
Angular L	-.020	-.070	-.087	-.092	-.131	.110	-.129	.231	.145	.249
Angular R	.016	.008	-.096	-.098	-.202	.057	-.152	.297*	.061	.214
Precuneus L	-.067	-.012	-.106	-.051	-.117	.172	-.125	.257	.099	.264*
Precuneus R	-.105	.053	-.037	-.145	-.142	.158	-.127	.314*	.127	.285*
Paracentral L	-.199	-.059	.088	-.087	-.061	.172	-.019	.328*	.150	.346*
Paracentral R	-.090	.102	.044	-.093	-.103	.164	-.027	.349*	.020	.227
Caudate L	.072	-.016	.057	-.182	-.007	.123	-.092	.311*	-.100	.128
Caudate R	.027	.045	.052	-.205	-.027	.118	-.101	.286*	-.063	.155
Putamen L	-.068	-.017	-.117	.090	.032	.129	-.138	.267*	.027	.225
Putamen R	-.153	.017	-.038	.032	-.009	.154	-.144	.268*	.020	.208
Pallidum L	-.161	.149	.015	.063	.132	.160	-.131	.184	.017	.146

Pallidum R	-.311*	-.039	.107	.032	.108	.251	-.121	.186	.013	.118
Thalamus L	-.222	-.118	.066	-.031	.118	.195	-.090	.200	-.099	.049
Thalamus R	-.209	-.099	.175	.031	.186	.167	-.111	.189	-.076	.067
Heschl L	.081	-.010	-.057	-.093	-.047	.096	-.155	.241	.126	.238
Heschl R	.026	-.003	-.007	-.194	-.152	.043	-.248	.287*	.019	.238
Temp Sup L	.006	.042	-.035	-.114	-.065	.136	-.148	.239	.074	.214
Temp Sup R	.019	.032	.035	-.216	-.166	.099	-.189	.340*	.058	.257
Temp Pole Sup L	.136	.035	.161	-.098	.066	.138	-.060	.234	-.042	.087
Temp Pole Sup R	-.015	-.078	.180	-.205	-.081	.020	-.045	.387**	-.031	.188
Temp Mid L	.019	-.074	-.124	-.039	-.099	.175	-.107	.257	.139	.269*
Temp Mid R	-.063	-.060	-.002	-.158	-.176	.093	-.193	.384**	.099	.328*
Temp Pole Mid L	.180	.243*	.040	-.068	-.013	.175	.186	.316*	.075	.230
Temp Pole Mid R	.137	.122	-.029	-.228*	-.178	.008	.022	.436**	-.039	.261
Temp Inf L	.052	.040	-.298*	.009	-.180	.254	-.068	.228	.191	.289*
Temp Inf R	.011	-.030	-.121	-.071	-.171	.175	-.124	.359*	.193	.377**
Cereb Crus1 L	-.024	-.116	-.252*	-.135	-.178	.099	-.040	.271*	.002	.228
Cereb Crus1 R	.197	.009	-.236*	-.055	-.114	.267*	.021	.186	.000	.243
Cereb Crus2 L	.160	-.157	-.231*	-.130	-.181	-.203	.142	-.231	.042	-.215
Cereb Crus2 R	.312*	.017	-.250*	-.058	-.218	-.106	.009	-.015	.018	-.065
Cereb 3 L	-.030	.051	.092	.110	.099	.380**	.050	-.085	.061	.012
Cereb 3 R	.068	-.028	.076	-.079	-.066	.300*	.015	.083	.010	.106
Cereb 4 5 L	-.032	-.160	-.013	-.107	-.003	.279*	-.061	.163	-.028	.162
Cereb 4 5 R	-.127	-.269*	.083	-.082	.086	.274*	-.079	.218	-.133	.107
Cereb 6 L	.043	-.151	-.085	-.038	-.004	.176	-.137	.257	.015	.240
Cereb 6 R	-.065	-.215	-.067	.071	.032	.185	-.130	.245	-.079	.161
Cereb 7b L	-.159	-.270*	-.367**	-.151	-.319**	-.275*	.094	-.267*	.021	-.275*
Cereb 7b R	.100	-.047	-.352**	-.089	-.333**	-.224	.069	-.164	.003	-.187
Cereb 8 L	-.282*	-.145	-.325**	-.087	-.299*	-.145	.116	-.270*	.031	-.232
Cereb 8 R	-.175	-.021	-.269*	.017	-.262*	-.215	.056	-.212	-.013	-.173
Cereb 9 L	-.288*	.152	-.063	-.066	-.181	-.126	.083	-.262	.009	-.259
Cereb 9 R	-.312*	.002	.045	-.097	-.110	.087	.151	-.098	-.064	-.127
Cereb 10 L	.043	.033	-.038	-.160	-.071	.257	.080	.268*	-.148	.169
Cereb 10 R	.113	.134	.020	-.214	-.057	.353*	.126	.096	-.167	-.112
Vermis 1 2	.009	.214	.016	.190	.077	.313*	.026	.221	-.062	.151
Vermis 3	-.047	-.109	.035	-.013	.060	.288*	.029	.094	-.030	.126
Vermis 4 5	-.153	-.075	.091	-.137	.026	.192	-.040	.168	-.069	.105
Vermis 6	.089	.040	-.016	-.040	-.027	.119	-.095	.258	-.127	.111
Vermis 7	.065	.038	-.074	.127	.039	.114	.124	.182	-.017	.029
Vermis 8	.064	-.065	-.025	.174	.086	.257	.109	.306*	-.032	.171
Vermis 9	-.081	.161	.073	.084	.046	.233	.098	.217	-.086	.071
Vermis 10	.059	.317**	.097	.117	.144	.171	.004	.190	.014	.177

Legend: BDI = Beck Depression Inventory, BAI = Beck Anxiety Inventory, exec = executive decline score, mem = memory decline score, global = global cognitive decline score, L = Left, R = Right, PreC =Precentral, Front = Frontal, Cing = Cingulate, Occ = Occipital, Par = Parietal, Temp =

Temporal, Cereb = Cerebellum, Sup = Superior, Mid = Middle, Inf = Inferior, Rol = Rolandic, Oper = Opercularis, Tri = Triangularis, Orb = Orbitalis, SMA = Supplementary Motor Area, Med = Medial, OFC = OrbitoFrontal Cortex, ant = anterior, post = posterior, lat = lateral, SupMar = Supramarginal. *p<.05, ** p<.01

Références bibliographiques

1. Alzheimer A. Uber einen eigenartigen schweren Er Krankungsprozeb der Hirnrinde. *Neurologisches Centralblatt*. 1906;23:1129-1136.

2. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44(12):2308-2308. doi:10.1212/WNL.44.12.2308

3. Turvey CL, Schultz SK, Arndt S, Ellingrod V, Wallace R, Herzog R. Caregiver Report of Hallucinations and Paranoid Delusions in Elders Aged 70 or Older. *International Psychogeriatrics*. 2001;13(2):241-249. doi:10.1017/S1041610201007621

4. Östling S, Skoog I. Psychotic Symptoms and Paranoid Ideation in a Nondemented Population–Based Sample of the Very Old. *Archives of General Psychiatry*. 2002;59(1):53-59. doi:10.1001/archpsyc.59.1.53

5. Assal F, Cummings JL. Neuropsychiatric symptoms in the dementias. *Current Opinion in Neurology*. 2002;15(4):445-450.

6. Hwang TJ, Masterman DL, Ortiz F, Fairbanks LA, Cummings JL. Mild Cognitive Impairment is Associated With Characteristic Neuropsychiatric Symptoms. *Alzheimer Disease & Associated Disorders*. 2004;18(1):17.

7. Geda YE, Roberts RO, Knopman DS, et al. Prevalence of Neuropsychiatric Symptoms in Mild Cognitive Impairment and Normal Cognitive Aging: Population-Based Study. *Archives of General Psychiatry*. 2008;65(10):1193-1198. doi:10.1001/archpsyc.65.10.1193

8. Burhanullah MH, Tschanz JT, Peters ME, et al. Neuropsychiatric Symptoms as Risk Factors for Cognitive Decline in Clinically Normal Older Adults: The Cache County Study. *The American Journal of Geriatric Psychiatry*. 2020;28(1):64-71. doi:10.1016/j.jagp.2019.03.023

9. Fernandez-Martinez M, Molano A, Castro J, J. Zarranz J. Prevalence of Neuropsychiatric Symptoms in Mild Cognitive Impairment and Alzheimer's Disease, and its Relationship with Cognitive Impairment. *Current Alzheimer Research*. 2010;7(6):517-526. doi:10.2174/156720510792231748

10. Krell-Roesch J, Ruider H, Lowe VJ, et al. FDG-PET and Neuropsychiatric Symptoms among Cognitively Normal Elderly Persons: The Mayo Clinic Study of Aging. *Journal of Alzheimer's Disease*. 2016;53(4):1609-1616. doi:10.3233/JAD-160326

11. Liew TM. Neuropsychiatric symptoms in cognitively normal older persons, and the association with Alzheimer's and non-Alzheimer's dementia. *Alz Res Therapy*. 2020;12(1):35. doi:10.1186/s13195-020-00604-7

12. Rosenberg PB, Mielke MM, Appleby BS, Oh ES, Geda YE, Lyketsos CG. The Association of Neuropsychiatric Symptoms in MCI with Incident Dementia and Alzheimer Disease. *The American Journal of Geriatric Psychiatry*. 2013;21(7):685-695. doi:10.1016/j.jagp.2013.01.006

13. Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. *The Lancet*. 2005;366(9503):2112-2117. doi:10.1016/S0140-6736(05)67889-0

14. Reitz C, Mayeux R. Alzheimer disease: Epidemiology, diagnostic criteria, risk factors and biomarkers. *Biochemical Pharmacology*. 2014;88(4):640-651. doi:10.1016/j.bcp.2013.12.024

15. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34(7):939-939. doi:10.1212/WNL.34.7.939

16. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*. 2011;7(3):280-292. doi:10.1016/j.jalz.2011.03.003

17. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*. 2011;7(3):270-279. doi:10.1016/j.jalz.2011.03.008

18. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*. 2011;7(3):263-269. doi:10.1016/j.jalz.2011.03.005

19. Zhao QF, Tan L, Wang HF, et al. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. *Journal of Affective Disorders*. 2016;190:264-271. doi:10.1016/j.jad.2015.09.069

20. Martin E, Velayudhan L. Neuropsychiatric Symptoms in Mild Cognitive Impairment: A Literature Review. *DEM*. 2020;49(2):146-155. doi:10.1159/000507078

21. Brodaty H, Heffernan M, Draper B, et al. Neuropsychiatric Symptoms in Older People with and without Cognitive Impairment. *Journal of Alzheimer's Disease*. 2012;31(2):411-420. doi:10.3233/JAD-2012-120169

22. Forrester SN, Gallo JJ, Smith GS, Leoutsakos JMS. Patterns of Neuropsychiatric Symptoms in Mild Cognitive Impairment and Risk of Dementia. *The American Journal of Geriatric Psychiatry*. 2016;24(2):117-125. doi:10.1016/j.jagp.2015.05.007

23. Geda YE, Roberts RO, Mielke MM, et al. Baseline Neuropsychiatric Symptoms and the Risk of Incident Mild Cognitive Impairment: A Population-Based Study. *AJP*. 2014;171(5):572-581. doi:10.1176/appi.ajp.2014.13060821

24. Ferretti L, McCurry SM, Logsdon R, Gibbons L, Teri L. Anxiety and Alzheimer's Disease. *J Geriatr Psychiatry Neurol*. 2001;14(1):52-58. doi:10.1177/089198870101400111

25. Somme J, Fernandez-Martínez M, Molano A, Jose Zarranz J. Neuropsychiatric Symptoms in Amnestic Mild Cognitive Impairment: Increased Risk and Faster Progression to Dementia. *Current Alzheimer Research*. 2013;10(1):86-94. doi:10.2174/156720513804871453

26. Mega MS, Cummings JL, Fiorello T, Gornbein J. The spectrum of behavioral changes in Alzheimer's disease. *Neurology*. 1996;46(1):130-135. doi:10.1212/WNL.46.1.130

27. Palmer K, Di Iulio F, Varsi AE, et al. Neuropsychiatric Predictors of Progression from Amnestic-Mild Cognitive Impairment to Alzheimer's Disease: The Role of Depression and Apathy. *Journal of Alzheimer's Disease*. 2010;20(1):175-183. doi:10.3233/JAD-2010-1352

28. Bayard S, Jacus JP, Raffard S, Gely-Nargeot MC. Apathy and Emotion-Based Decision-Making in Amnesic Mild Cognitive Impairment and Alzheimer's Disease. *Behavioural Neurology*. 2014;2014:e231469. doi:10.1155/2014/231469

29. Purandare N, Burns A, Craig S, Faragher B, Scott K. Depressive symptoms in patients with Alzheimer's disease. *International Journal of Geriatric Psychiatry*. 2001;16(10):960-964. doi:10.1002/gps.449

30. Modrego PJ, Ferrández J. Depression in Patients With Mild Cognitive Impairment Increases the Risk of Developing Dementia of Alzheimer Type: A Prospective Cohort Study. *Archives of Neurology*. 2004;61(8):1290-1293. doi:10.1001/archneur.61.8.1290

31. Ismail Z, Agüera-Ortiz L, Brodaty H, et al. The Mild Behavioral Impairment Checklist (MBI-C): A rating scale for neuropsychiatric symptoms in pre-dementia populations. *J Alzheimers Dis*. 2017;56(3):929-938. doi:10.3233/JAD-160979

32. Ismail Z, Elbayoumi H, Fischer CE, et al. Prevalence of Depression in Patients With Mild Cognitive Impairment: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. 2017;74(1):58-67. doi:10.1001/jamapsychiatry.2016.3162

33. Peters ME, Rosenberg PB, Steinberg M, et al. Neuropsychiatric Symptoms as Risk Factors for Progression From CIND to Dementia: The Cache County Study. *The American Journal of Geriatric Psychiatry*. 2013;21(11):1116-1124. doi:10.1016/j.jagp.2013.01.049

34. Martin JL, Ancoli-Israel S. Sleep Disturbances in Long-Term Care. *Clinics in Geriatric Medicine*. 2008;24(1):39-50. doi:10.1016/j.cger.2007.08.001

35. Leoutsakos JMS, Forrester SN, Lyketsos CG, Smith GS. Latent Classes of Neuropsychiatric Symptoms in NACC Controls and Conversion to Mild Cognitive Impairment or Dementia. *Journal of Alzheimer's Disease*. 2015;48(2):483-493. doi:10.3233/JAD-150421

36. Teng E, Lu PH, Cummings JL. Neuropsychiatric Symptoms Are Associated with Progression from Mild Cognitive Impairment to Alzheimer's Disease. *DEM*. 2007;24(4):253-259. doi:10.1159/000107100

37. Gill S, Mouches P, Hu S, et al. Using Machine Learning to Predict Dementia from Neuropsychiatric Symptom and Neuroimaging Data. *Journal of Alzheimer's Disease*. 2020;75(1):277-288. doi:10.3233/JAD-191169

38. Chen Y, Dang M, Zhang Z. Brain mechanisms underlying neuropsychiatric symptoms in Alzheimer's disease: a systematic review of symptom-general and –specific lesion patterns. *Mol Neurodegeneration*. 2021;16(1):38. doi:10.1186/s13024-021-00456-1

39. Apostolova LG, Akopyan GG, Partiali N, et al. Structural Correlates of Apathy in Alzheimer's Disease. *Dement Geriatr Cogn Disord*. 2007;24(2):91-97. doi:10.1159/000103914

40. Marshall GA, Monserratt L, Harwood D, Mandelkern M, Cummings JL, Sultzer DL. Positron Emission Tomography Metabolic Correlates of Apathy in Alzheimer Disease. *Archives of Neurology*. 2007;64(7):1015-1020. doi:10.1001/archneur.64.7.1015

41. Mori T, Shimada H, Shinotoh H, et al. Apathy correlates with prefrontal amyloid β deposition in Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2014;85(4):449-455. doi:10.1136/jnnp-2013-306110

42. Tighe SK, Oishi K, Mori S, et al. Diffusion Tensor Imaging of Neuropsychiatric Symptoms in Mild Cognitive Impairment and Alzheimer's Dementia. *JNP*. 2012;24(4):484-488. doi:10.1176/appi.neuropsych.11120375

43. Marshall GA, Fairbanks LA, Tekin S, Vinters HV, Cummings JL. Neuropathologic Correlates of Apathy in Alzheimer's Disease. *DEM*. 2006;21(3):144-147. doi:10.1159/000090674

44. Mohamed Nour A elazeim A, Jiao Y, Teng GJ, For the Alzheimer's Disease Neuroimaging Initiative. Neuroanatomical associations of depression, anxiety and apathy neuropsychiatric symptoms in patients with Alzheimer's disease. *Acta Neurologica Belgica*. 2021;121(6):1469-1480. doi:10.1007/s13760-020-01349-8

45. Tunnard C, Whitehead D, Hurt C, et al. Apathy and cortical atrophy in Alzheimer's disease. *International Journal of Geriatric Psychiatry*. 2011;26(7):741-748. doi:10.1002/gps.2603

46. Hirono N, Mori E, Ishii K, et al. Frontal lobe hypometabolism and depression in Alzheimer's disease. *Neurology*. 1998;50(2):380-383. doi:10.1212/WNL.50.2.380

47. Holthoff VA, Beuthien-Baumann B, Kalbe E, et al. Regional cerebral metabolism in early Alzheimer's disease with clinically significant apathy or depression. *Biol Psychiatry*. 2005;57(4):412-421. doi:10.1016/j.biopsych.2004.11.035

48. Lebedev AV, Beyer MK, Fritze F, Westman E, Ballard C, Aarsland D. Cortical Changes Associated with Depression and Antidepressant Use in Alzheimer and Lewy Body Dementia: An MRI Surface-based Morphometric Study. *The American Journal of Geriatric Psychiatry*. 2014;22(1):4-13.e1. doi:10.1016/j.jagp.2013.02.004

49. Lebedeva A, Westman E, Lebedev AV, et al. Structural brain changes associated with depressive symptoms in the elderly with Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2014;85(8):930-935. doi:10.1136/jnnp-2013-307110

50. Lee HS, Choo IH, Lee DY, et al. Frontal Dysfunction Underlies Depression in Mild Cognitive Impairment: A FDG-PET Study. *Psychiatry Investig*. 2010;7(3):208-214. doi:10.4306/pi.2010.7.3.208

51. Morra JH, Tu Z, Apostolova LG, et al. Automated 3D mapping of hippocampal atrophy and its clinical correlates in 400 subjects with Alzheimer's disease, mild cognitive impairment, and elderly controls. *Hum Brain Mapp*. 2009;30(9):2766-2788. doi:10.1002/hbm.20708

52. Son JH, Han DH, Min KJ, Kee BS. Correlation between gray matter volume in the temporal lobe and depressive symptoms in patients with Alzheimer's disease. *Neurosci Lett*. 2013;548:15-20. doi:10.1016/j.neulet.2013.05.021

53. Zahodne LB, Gongvatana A, Cohen RA, Ott BR, Tremont G. Are Apathy and Depression Independently Associated with Longitudinal Trajectories of Cortical Atrophy in Mild Cognitive Impairment? *The American Journal of Geriatric Psychiatry*. 2013;21(11):1098-1106. doi:10.1016/j.jagp.2013.01.043

54. Mah L, Binns MA, Steffens DC. Anxiety Symptoms in Amnestic Mild Cognitive Impairment Are Associated with Medial Temporal Atrophy and Predict Conversion to Alzheimer Disease. *The American Journal of Geriatric Psychiatry*. 2015;23(5):466-476. doi:10.1016/j.jagp.2014.10.005

55. Poulin SP, Dautoff R, Morris JC, Barrett LF, Dickerson BC. Amygdala atrophy is prominent in early Alzheimer's disease and relates to symptom severity. *Psychiatry Research: Neuroimaging*. 2011;194(1):7-13. doi:10.1016/j.pscychresns.2011.06.014

56. Hashimoto H, Monserratt L, Nguyen P, et al. Anxiety and Regional Cortical Glucose Metabolism in Patients With Alzheimer's Disease. *JNP*. 2006;18(4):521-528. doi:10.1176/jnp.2006.18.4.521

57. Bensamoun D, Guignard R, Furst AJ, et al. Associations between Neuropsychiatric Symptoms and Cerebral Amyloid Deposition in Cognitively Impaired Elderly People. *Journal of Alzheimer's Disease*. 2016;49(2):387-398. doi:10.3233/JAD-150181

58. Aalten P, Verhey FRJ, Boziki M, et al. Neuropsychiatric syndromes in dementia. Results from the European Alzheimer Disease Consortium: part I. *Dement Geriatr Cogn Disord*. 2007;24(6):457-463. doi:10.1159/000110738

59. Balthazar MLF, Pereira FRS, Lopes TM, et al. Neuropsychiatric symptoms in Alzheimer's disease are related to functional connectivity alterations in the salience network. *Hum Brain Mapp*. 2014;35(4):1237-1246. doi:10.1002/hbm.22248

60. Meguro K, Yamaguchi S, Itoh M, Fujiwara T, Yamadori A. Striatal dopamine metabolism correlated with frontotemporal glucose utilization in Alzheimer's disease: a double-tracer PET study. *Neurology*. 1997;49(4):941-945. doi:10.1212/wnl.49.4.941

61. Reilly TJ, Staff RT, Ahearn TS, Bentham P, Wischik CM, Murray AD. Regional cerebral blood flow and aberrant motor behaviour in Alzheimer's disease. *Behavioural Brain Research*. 2011;222(2):375-379. doi:10.1016/j.bbr.2011.04.003

62. Trzepacz PT, Yu P, Bhamidipati PK, et al. Frontolimbic atrophy is associated with agitation and aggression in mild cognitive impairment and Alzheimer's disease. *Alzheimer's & Dementia*. 2013;9(5, Supplement):S95-S104.e1. doi:10.1016/j.jalz.2012.10.005

63. Holth J, Patel T, Holtzman DM. Sleep in Alzheimer's Disease - Beyond Amyloid. *Neurobiol Sleep Circadian Rhythms*. 2017;2:4-14. doi:10.1016/j.nbscr.2016.08.002

64. Ju YES, Lucey BP, Holtzman DM. Sleep and Alzheimer disease pathology--a bidirectional relationship. *Nat Rev Neurol*. 2014;10(2):115-119. doi:10.1038/nrneurol.2013.269

65. Shokri-Kojori E, Wang GJ, Wiers CE, et al. β-Amyloid accumulation in the human brain after one night of sleep deprivation. *Proc Natl Acad Sci U S A*. 2018;115(17):4483-4488. doi:10.1073/pnas.1721694115

66. Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. *J Neuropathol Exp Neurol*. 2011;70(11):960-969. doi:10.1097/NEN.0b013e318232a379

67. Siafarikas N, Alnæs D, Monereo-Sanchez J, et al. Neuropsychiatric symptoms and brain morphology in patients with mild cognitive impairment and Alzheimer's disease with dementia. *International Psychogeriatrics*. 2021;33(11):1217-1228. doi:10.1017/S1041610221000934

68. Tissot C, Therriault J, Pascoal TA, et al. Association between regional tau pathology and neuropsychiatric symptoms in aging and dementia due to Alzheimer's disease. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*. 2021;7(1). doi:10.1002/trc2.12154

69. Chien LY, Chu H, Guo JL, et al. Caregiver support groups in patients with dementia: a meta-analysis. *International Journal of Geriatric Psychiatry*. 2011;26(10):1089-1098. doi:10.1002/gps.2660

70. Khoo SA, Chen TY, Ang YH, Yap P. The impact of neuropsychiatric symptoms on caregiver distress and quality of life in persons with dementia in an Asian tertiary hospital memory clinic. *International Psychogeriatrics*. 2013;25(12):1991-1999. doi:10.1017/S1041610213001518

71. George LK, Gwyther LP. Caregiver well-being: a multidimensional examination of family caregivers of demented adults. *Gerontologist*. 1986;26(3):253-259. doi:10.1093/geront/26.3.253

72. Clipp EC, George LK. Psychotropic drug use among caregivers of patients with dementia. *J Am Geriatr Soc*. 1990;38(3):227-235. doi:10.1111/j.1532-5415.1990.tb03496.x

73. Schulz R, O'Brien AT, Bookwala J, Fleissner K. Psychiatric and physical morbidity effects of dementia caregiving: prevalence, correlates, and causes. *Gerontologist*. 1995;35(6):771-791. doi:10.1093/geront/35.6.771

74. Schulz R, Beach SR. Caregiving as a risk factor for mortality: the Caregiver Health Effects Study. *JAMA*. 1999;282(23):2215-2219. doi:10.1001/jama.282.23.2215

75. Vitaliano PP, Zhang J, Scanlan JM. Is caregiving hazardous to one's physical health? A meta-analysis. *Psychol Bull*. 2003;129(6):946-972. doi:10.1037/0033-2909.129.6.946

76. Achterberg W, Pot AM, Kerkstra A, Ribbe M. Depressive symptoms in newly admitted nursing home residents. *Int J Geriatr Psychiatry*. 2006;21(12):1156-1162. doi:10.1002/gps.1623

77. Drageset J, Natvig GK, Eide GE, et al. Differences in health-related quality of life between older nursing home residents without cognitive impairment and the general population of Norway. *J Clin Nurs*. 2008;17(9):1227-1236. doi:10.1111/j.1365-2702.2007.02132.x

78. Fahey T, Montgomery AA, Barnes J, Protheroe J. Quality of care for elderly residents in nursing homes and elderly people living at home: controlled observational study. *BMJ*. 2003;326(7389):580. doi:10.1136/bmj.326.7389.580

79. Teresi J, Abrams R, Holmes D, Ramirez M, Eimicke J. Prevalence of depression and depression recognition in nursing homes. *Soc Psychiatry Psychiatr Epidemiol*. 2001;36(12):613-620. doi:10.1007/s127-001-8202-7

80. Bergvall N, Brinck P, Eek D, et al. Relative importance of patient disease indicators on informal care and caregiver burden in Alzheimer's disease. *Int Psychogeriatr*. 2011;23(1):73-85. doi:10.1017/S1041610210000785

81. Fischer CE, Ismail Z, Schweizer TA. Impact of neuropsychiatric symptoms on caregiver burden in patients with Alzheimer's disease. *Neurodegenerative Disease Management*. 2012;2(3):269-277. doi:10.2217/nmt.12.19

82. Torrisi M, De Cola MC, Marra A, De Luca R, Bramanti P, Calabrò RS. Neuropsychiatric symptoms in dementia may predict caregiver burden: a Sicilian exploratory study. *Psychogeriatrics*. 2017;17(2):103-107. doi:10.1111/psyg.12197

83. Isik AT, Soysal P, Solmi M, Veronese N. Bidirectional relationship between caregiver burden and neuropsychiatric symptoms in patients with Alzheimer's disease: A narrative review. *International Journal of Geriatric Psychiatry*. 2019;34(9):1326-1334. doi:10.1002/gps.4965

84. García-Alberca JM, Lara JP, Garrido V, Gris E, González-Herero V, Lara A. Neuropsychiatric Symptoms in Patients With Alzheimer's Disease: The Role of Caregiver Burden and Coping Strategies. *Am J Alzheimers Dis Other Demen*. 2014;29(4):354-361. doi:10.1177/1533317513518649

85. Pinyopornpanish M, Pinyopornpanish K, Soontornpun A, et al. Perceived stress and depressive symptoms not neuropsychiatric symptoms predict caregiver burden in Alzheimer's disease: a cross-sectional study. *BMC Geriatr*. 2021;21(1):180. doi:10.1186/s12877-021-02136-7

86. Sink KM, Covinsky KE, Barnes DE, Newcomer RJ, Yaffe K. Caregiver Characteristics Are Associated with Neuropsychiatric Symptoms of Dementia. *Journal of the American Geriatrics Society*. 2006;54(5):796-803. doi:10.1111/j.1532-5415.2006.00697.x

87. Allegri RF, Sarasola D, Serrano CM, et al. Neuropsychiatric symptoms as a predictor of caregiver burden in Alzheimer's disease. *Neuropsychiatric Disease and Treatment*. 2006;2(1):105-110. doi:10.2147/ndt.s12160165

88. Ryan KA, Weldon A, Persad C, Heidebrink JL, Barbas N, Giordani B. Neuropsychiatric Symptoms and Executive Functioning in Patients with Mild Cognitive Impairment: Relationship to Caregiver Burden. *DEM*. 2012;34(3-4):206-215. doi:10.1159/000339955

89. Aarsland D, Larsen JP, Lim NG, et al. Range of neuropsychiatric disturbances in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1999;67(4):492-496. doi:10.1136/jnnp.67.4.492

90. Mueller C, Rajkumar AP, Wan YM, et al. Assessment and Management of Neuropsychiatric Symptoms in Parkinson's Disease. *CNS Drugs*. 2018;32(7):621-635. doi:10.1007/s40263-018-0540-6

91. Pachana NA, Egan SJ, Laidlaw K, et al. Clinical issues in the treatment of anxiety and depression in older adults with Parkinson's disease. *Movement Disorders*. 2013;28(14):1930-1934. doi:10.1002/mds.25689

92. de Frias CM, Nilsson LG, Herlitz A. Sex Differences in Cognition are Stable Over a 10-Year Period in Adulthood and Old Age. *Aging, Neuropsychology, and Cognition*. 2006;13(3-4):574-587. doi:10.1080/13825580600678418

93. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. *Neurology*. 2013;80(19):1778-1783. doi:10.1212/WNL.0b013e31828726f5

94. Gao S, Hendrie HC, Hall KS, Hui S. The Relationships Between Age, Sex, and the Incidence of Dementia and Alzheimer Disease: A Meta-analysis. *Archives of General Psychiatry*. 1998;55(9):809-815. doi:10.1001/archpsyc.55.9.809

95. Niu H, Álvarez-Álvarez I, Guillén-Grima F, Aguinaga-Ontoso I. Prevalence and incidence of Alzheimer's disease in Europe: A meta-analysis. *Neurología (English Edition)*. 2017;32(8):523-532. doi:10.1016/j.nrleng.2016.02.009

96. Koran MEI, Wagener M, Hohman TJ. Sex Differences in the Association between AD Biomarkers and Cognitive Decline. *Brain Imaging Behav*. 2017;11(1):205-213. doi:10.1007/s11682-016-9523-8

97. Mortby ME, Ismail Z, Anstey KJ. Prevalence estimates of mild behavioral impairment in a population-based sample of pre-dementia states and cognitively healthy older adults. *International Psychogeriatrics*. 2018;30(2):221-232. doi:10.1017/S1041610217001909

98. Fernández M, Gobartt AL, Balañá M, the COOPERA Study Group. Behavioural symptoms in patients with Alzheimer's disease and their association with cognitive impairment. *BMC Neurology*. 2010;10(1):87. doi:10.1186/1471-2377-10-87

99. Van der Mussele S, Le Bastard N, Vermeiren Y, et al. Behavioral symptoms in mild cognitive impairment as compared with Alzheimer's disease and healthy older adults. *International Journal of Geriatric Psychiatry*. 2013;28(3):265-275. doi:10.1002/gps.3820

100. David ND, Lin F, Porsteinsson AP. Trajectories of Neuropsychiatric Symptoms and Cognitive Decline in Mild Cognitive Impairment. *The American Journal of Geriatric Psychiatry*. 2016;24(1):70-80. doi:10.1016/j.jagp.2015.06.001

101. Gulpers B, Ramakers I, Hamel R, Köhler S, Oude Voshaar R, Verhey F. Anxiety as a Predictor for Cognitive Decline and Dementia: A Systematic Review and Meta-Analysis. *The American Journal of Geriatric Psychiatry*. 2016;24(10):823-842. doi:10.1016/j.jagp.2016.05.015

102. Quaranta D, Vita MG, Bizzarro A, et al. Cognitive and Behavioral Determinants of Psychotic Symptoms in Alzheimer's Disease. *DEM*. 2015;39(3-4):194-206. doi:10.1159/000369161

103. Ready RE, Ott BR, Grace J, Cahn-Weiner DA. Apathy and Executive Dysfunction in Mild Cognitive Impairment and Alzheimer Disease. *The American Journal of Geriatric Psychiatry*. 2003;11(2):222-228. doi:10.1097/00019442-200303000-00013

104. Robert PH, Berr C, Volteau M, et al. Neuropsychological Performance in Mild Cognitive Impairment with and without Apathy. *DEM*. 2006;21(3):192-197. doi:10.1159/000090766

105. Wilson RS, Gilley DW, Bennett DA, Beckett LA, Evans DA. Hallucinations, delusions, and cognitive decline in Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry*. 2000;69(2):172-177. doi:10.1136/jnnp.69.2.172

106. Inamura K, Shinagawa S, Tsuneizumi Y, et al. Sex differences in the severity of neuropsychiatric symptoms and their relationship with clinico-demographic and psychosocial factors in patients with amnestic mild cognitive impairment and mild Alzheimer's disease. *Aging & Mental Health*. 2020;24(3):431-438. doi:10.1080/13607863.2018.1539834

107. Spalletta G, Musicco M, Padovani A, et al. Neuropsychiatric Symptoms and Syndromes in a Large Cohort of Newly Diagnosed, Untreated Patients With Alzheimer Disease. *The American Journal of Geriatric Psychiatry*. 2010;18(11):1026-1035. doi:10.1097/JGP.0b013e3181d6b68d

108. Tao Y, Peters ME, Drye LT, et al. Sex Differences in the Neuropsychiatric Symptoms of Patients With Alzheimer's Disease. *Am J Alzheimers Dis Other Demen*. 2018;33(7):450-457. doi:10.1177/1533317518783278

109. Xing Y, Tang Y, Jia J. Sex Differences in Neuropsychiatric Symptoms of Alzheimer's Disease: The Modifying Effect of Apolipoprotein E ε4 Status. *Behavioural Neurology*. 2015;2015:e275256. doi:10.1155/2015/275256

110. Kassem AM, Ganguli M, Yaffe K, et al. Anxiety symptoms and risk of dementia and mild cognitive impairment in the oldest old women. *Aging & Mental Health*. 2018;22(4):474-482. doi:10.1080/13607863.2016.1274370

111. Kassem AM, Ganguli M, Yaffe K, et al. Anxiety symptoms and risk of cognitive decline in older community-dwelling men. *International Psychogeriatrics*. 2017;29(7):1137-1145. doi:10.1017/S104161021700045X

112. Ng TP, Niti M, Zaw MH, Kua EH. Depressive Symptoms and Incident Cognitive Impairment in Cognitively Well-Functioning Older Men and Women. *Journal of the American Geriatrics Society*. 2009;57(6):1058-1063. doi:10.1111/j.1532-5415.2009.02262.x

113. Mueller SG, Weiner MW, Thal LJ, et al. Ways toward an early diagnosis in Alzheimer's disease: The Alzheimer's Disease Neuroimaging Initiative (ADNI). *Alzheimer's & Dementia*. 2005;1(1):55-66. doi:10.1016/j.jalz.2005.06.003

114. Shaw LM, Korecka M, Clark CM, Lee VMY, Trojanowski JQ. Biomarkers of neurodegeneration for diagnosis and monitoring therapeutics. *Nat Rev Drug Discov*. 2007;6(4):295-303. doi:10.1038/nrd2176

115. ADNI | Alzheimer's Disease Neuroimaging Initiative. Accessed April 22, 2022. https://adni.loni.usc.edu/

116. Albert MS, DeKosky ST, Dickson D, et al. The Diagnosis of Mild Cognitive Impairment due to Alzheimer's Disease: Recommendations from the National Institute on Aging-Alzheimer's Association Workgroups on Diagnostic Guidelines for Alzheimer's Disease. *FOC*. 2013;11(1):96-106. doi:10.1176/appi.focus.11.1.96

117. Cummings JL. The Neuropsychiatric Inventory: Assessing psychopathology in dementia patients. *Neurology*. 1997;48(5 Suppl 6):10S-16S. doi:10.1212/WNL.48.5_Suppl_6.10S

118. Cummings JL, McPherson S. Neuropsychiatric assessment of Alzheimer's disease and related dementias. *Aging Clin Exp Res*. 2001;13(3):240-246. doi:10.1007/BF03351482

119. Zuidema SU, de Jonghe JFM, Verhey FRJ, Koopmans RTCM. Predictors of neuropsychiatric symptoms in nursing home patients: influence of gender and dementia severity. *International Journal of Geriatric Psychiatry*. 2009;24(10):1079-1086. doi:10.1002/gps.2225

120. Kyomen HH, Satlin A, Hennen J, Wei JY. Estrogen Therapy and Aggressive Behavior in Elderly Patients With Moderate-to-Severe Dementia: Results From a Short-Term, Randomized, Double-Blind Trial. *The American Journal of Geriatric Psychiatry*. 1999;7(4):339-348. doi:10.1097/00019442-199911000-00011

121. Mielke MM. Sex and Gender Differences in Alzheimer's Disease Dementia. *Psychiatr Times*. 2018;35(11):14-17.

122. Sukonick DL, Pollock BG, Sweet RA, et al. The 5-HTTPR*S/*L Polymorphism and Aggressive Behavior in Alzheimer Disease. *Archives of Neurology*. 2001;58(9):1425-1428. doi:10.1001/archneur.58.9.1425

123. Xing Y, Qin W, Li F, Jia XF, Jia J. Apolipoprotein E ε4 Status Modifies the Effects of Sex Hormones on Neuropsychiatric Symptoms of Alzheimer's Disease. *DEM*. 2012;33(1):35-42. doi:10.1159/000336600

124. McCarrey AC, An Y, Kitner-Triolo MH, Ferrucci L, Resnick SM. Sex differences in cognitive trajectories in clinically normal older adults. *Psychology and Aging*. 2016;31(2):166-175. doi:10.1037/pag0000070

125. Reas ET, Hagler DJ, Zhong AJ, Lee RR, Dale AM, McEvoy LK. Brain microstructure mediates sex-specific patterns of cognitive aging. *Aging (Albany NY)*. 2021;13(3):3218-3238. doi:10.18632/aging.202561

126. Levy R, Dubois B. Apathy and the Functional Anatomy of the Prefrontal Cortex–Basal Ganglia Circuits. *Cerebral Cortex*. 2006;16(7):916-928. doi:10.1093/cercor/bhj043

127. Radakovic R, Abrahams S. Multidimensional apathy: evidence from neurodegenerative disease. *Current Opinion in Behavioral Sciences*. 2018;22:42-49. doi:10.1016/j.cobeha.2017.12.022

128. Drijgers RL, Verhey FRJ, Leentjens AFG, Köhler S, Aalten P. Neuropsychological correlates of apathy in mild cognitive impairment and Alzheimer's disease: the role of executive functioning. *International Psychogeriatrics*. 2011;23(8):1327-1333. doi:10.1017/S1041610211001037

129. Montoya-Murillo G, Ibarretxe-Bilbao N, Peña J, Ojeda N. The impact of apathy on cognitive performance in the elderly. *International Journal of Geriatric Psychiatry*. 2019;34(5):657-665. doi:10.1002/gps.5062

130. van Dyck CH, Arnsten AFT, Padala PR, et al. Neurobiologic Rationale for Treatment of Apathy in Alzheimer's Disease With Methylphenidate. *The American Journal of Geriatric Psychiatry*. 2021;29(1):51-62. doi:10.1016/j.jagp.2020.04.026

131. Nakaaki S, Murata Y, Sato J, et al. Association between apathy/depression and executive function in patients with Alzheimer's disease. *International Psychogeriatrics*. 2008;20(5):964-975. doi:10.1017/S1041610208007308

132. Sun X, Steffens DC, Au R, et al. Amyloid-Associated Depression: A Prodromal Depression of Alzheimer Disease? *Archives of General Psychiatry*. 2008;65(5):542-550. doi:10.1001/archpsyc.65.5.542

133. Kuzis G, Sabe L, Tiberti C, Dorrego F, Starkstein SE. Neuropsychological correlates of apathy and depression in patients with dementia. *Neurology*. 1999;52(7):1403-1403. doi:10.1212/WNL.52.7.1403

134. Lai CK. The merits and problems of Neuropsychiatric Inventory as an assessment tool in people with dementia and other neurological disorders. *Clin Interv Aging*. 2014;9:1051-1061. doi:10.2147/CIA.S63504

135. Cummings J. The Neuropsychiatric Inventory: Development and Applications. *J Geriatr Psychiatry Neurol*. 2020;33(2):73-84. doi:10.1177/0891988719882102

136. Orengo CA, Kunik ME, Ghusn H, Yudofsky SC. Correlation of Testosterone with Aggression in Demented Elderly Men. *The Journal of Nervous and Mental Disease*. 1997;185(5):349-351.

137. Fillit H. Estrogens in the Pathogenesis and Treatment of Alzheimer's Disease in Postmenopausal Women. *Annals of the New York Academy of Sciences*. 1994;743(1):233-238. doi:10.1111/j.1749-6632.1994.tb55795.x

138. Ott BR, Tate CA, Gordon NM, Heindel WC. Gender Differences in the Behavioral Manifestations of Alzheimer's Disease. *Journal of the American Geriatrics Society*. 1996;44(5):583-587. doi:10.1111/j.1532-5415.1996.tb01447.x

139. Gilley DW, Bienias JL, Wilson RS, Bennett DA, Beck TL, Evans DA. Influence of behavioral symptoms on rates of institutionalization for persons with Alzheimer's disease. *Psychological Medicine*. 2004;34(6):1129-1135. doi:10.1017/S0033291703001831

140. Craig D, Mirakhur A, Hart DJ, McIlroy SP, Passmore AP. A Cross-Sectional Study of Neuropsychiatric Symptoms in 435 Patients With Alzheimer's Disease. *The American Journal of Geriatric Psychiatry*. 2005;13(6):460-468. doi:10.1097/00019442-200506000-00004

141. Aalten P, de Vugt ME, Jaspers N, Jolles J, Verhey FRJ. The course of neuropsychiatric symptoms in dementia. Part I: findings from the two-year longitudinal Maasbed study. *International Journal of Geriatric Psychiatry*. 2005;20(6):523-530. doi:10.1002/gps.1316

142. Lyketsos CG, Sheppard JME, Steinberg M, et al. Neuropsychiatric disturbance in Alzheimer's disease clusters into three groups: the Cache County study. *International Journal of Geriatric Psychiatry*. 2001;16(11):1043-1053. doi:10.1002/gps.448

143. Steinberg M, Shao H, Zandi P, et al. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. *International Journal of Geriatric Psychiatry*. 2008;23(2):170-177. doi:10.1002/gps.1858

144. Lanctôt KL, Agüera-Ortiz L, Brodaty H, et al. Apathy associated with neurocognitive disorders: Recent progress and future directions. *Alzheimer's & Dementia*. 2017;13(1):84-100. doi:10.1016/j.jalz.2016.05.008

145. Lyketsos CG, Carrillo MC, Ryan JM, et al. Neuropsychiatric symptoms in Alzheimer's disease. *Alzheimer's & Dementia*. 2011;7(5):532-539. doi:10.1016/j.jalz.2011.05.2410

146. Ng KP, Pascoal TA, Mathotaarachchi S, et al. Neuropsychiatric symptoms predict hypometabolism in preclinical Alzheimer disease. *Neurology*. 2017;88(19):1814-1821. doi:10.1212/WNL.0000000000003916

147. Bruen PD, McGeown WJ, Shanks MF, Venneri A. Neuroanatomical correlates of neuropsychiatric symptoms in Alzheimer's disease. *Brain*. 2008;131(9):2455-2463. doi:10.1093/brain/awn151

148. Ota M, Sato N, Nakata Y, Arima K, Uno M. Relationship between apathy and diffusion tensor imaging metrics of the brain in Alzheimer's disease. *International Journal of Geriatric Psychiatry*. 2012;27(7):722-726. doi:10.1002/gps.2779

149. Brommelhoff JA, Spann BM, Go JL, Mack WJ, Gatz M. Striatal Hypodensities, Not White Matter Hypodensities on CT, Are Associated with Late-Onset Depression in Alzheimer's Disease. *Journal of Aging Research*. 2011;2011:e187219. doi:10.4061/2011/187219

150. Tagai K, Nagata T, Shinagawa S, et al. Correlation between both Morphologic and Functional Changes and Anxiety in Alzheimer's Disease. *DEM*. 2014;38(3-4):153-160. doi:10.1159/000358822

151. Kim HG, Kong EJ, Cheon EJ, Kim HW, Koo BH. Association between Cerebral Amyloid Deposition and Clinical Factors Including Cognitive Function in Geriatric Depression: Pilot Study Using Amyloid Positron Emission Tomography. *Clin Psychopharmacol Neurosci*. 2016;14(4):378-382. doi:10.9758/cpn.2016.14.4.378

152. Branger P, Arenaza-Urquijo EM, Tomadesso C, et al. Relationships between sleep quality and brain volume, metabolism, and amyloid deposition in late adulthood. *Neurobiology of Aging*. 2016;41:107-114. doi:10.1016/j.neurobiolaging.2016.02.009

153. Joo EY, Kim H, Suh S, Hong SB. Hippocampal Substructural Vulnerability to Sleep Disturbance and Cognitive Impairment in Patients with Chronic Primary Insomnia: Magnetic Resonance Imaging Morphometry. *Sleep*. 2014;37(7):1189-1198. doi:10.5665/sleep.3836

154. Neylan TC, Mueller SG, Wang Z, et al. Insomnia Severity Is Associated with a Decreased Volume of the CA3/Dentate Gyrus Hippocampal Subfield. *Biological Psychiatry*. 2010;68(5):494-496. doi:10.1016/j.biopsych.2010.04.035

155. Sexton CE, Storsve AB, Walhovd KB, Johansen-Berg H, Fjell AM. Poor sleep quality is associated with increased cortical atrophy in community-dwelling adults. *Neurology*. 2014;83(11):967-973. doi:10.1212/WNL.0000000000000774

156. Liu Y shou, Wang Y ming, Zha D jun. Brain Functional and Structural Changes in Alzheimer's Disease With Sleep Disorders: A Systematic Review. *Frontiers in Psychiatry*. 2021;12. Accessed April 7, 2023. https://www.frontiersin.org/articles/10.3389/fpsyt.2021.772068

157. Panizzon MS, Fennema-Notestine C, Eyler LT, et al. Distinct Genetic Influences on Cortical Surface Area and Cortical Thickness. *Cerebral Cortex*. 2009;19(11):2728-2735. doi:10.1093/cercor/bhp026

158. Zhang Y, Liu S. Analysis of structural brain MRI and multi-parameter classification for Alzheimer's disease. *Biomedical Engineering / Biomedizinische Technik*. 2018;63(4):427-437. doi:10.1515/bmt-2016-0239

159. Fischl B, Salat DH, Busa E, et al. Whole Brain Segmentation: Automated Labeling of Neuroanatomical Structures in the Human Brain. *Neuron*. 2002;33(3):341-355. doi:10.1016/S0896-6273(02)00569-X

160. Desikan RS, Ségonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*. 2006;31(3):968-980. doi:10.1016/j.neuroimage.2006.01.021

161. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences*. 2000;97(20):11050-11055. doi:10.1073/pnas.200033797

162. Winkler AM, Sabuncu MR, Yeo BTT, et al. Measuring and comparing brain cortical surface area and other areal quantities. *NeuroImage*. 2012;61(4):1428-1443. doi:10.1016/j.neuroimage.2012.03.026

163. Winkler AM, Greve DN, Bjuland KJ, et al. Joint Analysis of Cortical Area and Thickness as a Replacement for the Analysis of the Volume of the Cerebral Cortex. *Cerebral Cortex*. 2018;28(2):738-749. doi:10.1093/cercor/bhx308

164. Jack CR, Petersen RC, Xu Y, et al. Rate of medial temporal lobe atrophy in typical aging and Alzheimer's disease. *Neurology*. 1998;51(4):993-999. doi:10.1212/WNL.51.4.993

165. Whelan CD, Mattsson N, Nagle MW, et al. Multiplex proteomics identifies novel CSF and plasma biomarkers of early Alzheimer's disease. *Acta Neuropathologica Communications*. 2019;7(1):169. doi:10.1186/s40478-019-0795-2

166. Cotta Ramusino M, Perini G, Vaghi G, et al. Correlation of Frontal Atrophy and CSF Tau Levels With Neuropsychiatric Symptoms in Patients With Cognitive Impairment: A Memory Clinic Experience. *Frontiers in Aging Neuroscience*. 2021;13. Accessed April 13, 2023. https://www.frontiersin.org/articles/10.3389/fnagi.2021.595758

167. Johansson M, Stomrud E, Lindberg O, et al. Apathy and anxiety are early markers of Alzheimer's disease. *Neurobiology of Aging*. 2020;85:74-82. doi:10.1016/j.neurobiolaging.2019.10.008

168. Wang ZT, Shen XN, Ma YH, et al. Associations of the Rate of Change in Geriatric Depression Scale with Amyloid and Cerebral Glucose Metabolism in Cognitively Normal Older Adults: A Longitudinal Study. *Journal of Affective Disorders*. 2021;280:77-84. doi:10.1016/j.jad.2020.10.078

169. Donovan NJ, Wadsworth LP, Lorius N, et al. Regional Cortical Thinning Predicts Worsening Apathy and Hallucinations Across the Alzheimer Disease Spectrum. *The American Journal of Geriatric Psychiatry*. 2014;22(11):1168-1179. doi:10.1016/j.jagp.2013.03.006

170. Hayata TT, Bergo FPG, Rezende TJ, et al. Cortical correlates of affective syndrome in dementia due to Alzheimer's disease. *Arq Neuro-Psiquiatr*. 2015;73:553-560. doi:10.1590/0004-282X20150068

171. Binnewijzend MAA, Schoonheim MM, Sanz-Arigita E, et al. Resting-state fMRI changes in Alzheimer's disease and mild cognitive impairment. *Neurobiology of Aging*. 2012;33(9):2018-2028. doi:10.1016/j.neurobiolaging.2011.07.003

172. Sheline YI, Barch DM, Price JL, et al. The default mode network and self-referential processes in depression. *Proceedings of the National Academy of Sciences*. 2009;106(6):1942-1947. doi:10.1073/pnas.0812686106

173. Rosenberg PB, Nowrangi MA, Lyketsos CG. Neuropsychiatric symptoms in Alzheimer's disease: What might be associated brain circuits? *Molecular Aspects of Medicine*. 2015;43-44:25-37. doi:10.1016/j.mam.2015.05.005

174. Theleritis C, Politis A, Siarkos K, Lyketsos CG. A review of neuroimaging findings of apathy in Alzheimer's disease. *International Psychogeriatrics*. 2014;26(2):195-207. doi:10.1017/S1041610213001725

175. Guercio B, Donovan NJ, Ward A, et al. Apathy is associated with lower inferior temporal cortical thickness in mild cognitive impairment and normal elderly. *J Neuropsychiatry Clin Neurosci*. 2015;27(1):e22-e27. doi:10.1176/appi.neuropsych.13060141

176. Le Heron C, Apps. MAJ, Husain M. The anatomy of apathy: A neurocognitive framework for amotivated behaviour. *Neuropsychologia*. 2018;118:54-67. doi:10.1016/j.neuropsychologia.2017.07.003

177. Redlich R, Grotegerd D, Opel N, et al. Are you gonna leave me? Separation anxiety is associated with increased amygdala responsiveness and volume. *Social Cognitive and Affective Neuroscience*. 2015;10(2):278-284. doi:10.1093/scan/nsu055

178. Horˇínek D, Petrovický P, Hort J, et al. Amygdalar volume and psychiatric symptoms in Alzheimer's disease: an MRI analysis. *Acta Neurologica Scandinavica*. 2006;113(1):40-45. doi:10.1111/j.1600-0404.2006.00540.x

179. American Psychiatric Association, ed. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. 5th ed. American Psychiatric Association; 2013.

180. Jak AJ, Bondi MW, Delano-Wood L, et al. Quantification of Five Neuropsychological Approaches to Defining Mild Cognitive Impairment. *The American Journal of Geriatric Psychiatry*. 2009;17(5):368-375. doi:10.1097/JGP.0b013e31819431d5

181. Heidebrink JL. Is Dementia with Lewy Bodies the Second Most Common Cause of Dementia? *J Geriatr Psychiatry Neurol*. 2002;15(4):182-187. doi:10.1177/089198870201500402

182. Bednarek A, Mojs E, Krawczyk-Wasielewska A, et al. Correlation between depression and burden observed in informal caregivers of people suffering from dementia with time spent on caregiving and dementia severity. 2016;20:59-63.

183. Schulz R, McGinnis KA, Zhang S, et al. Dementia Patient Suffering and Caregiver Depression. *Alzheimer Dis Assoc Disord*. 2008;22(2):170-176. doi:10.1097/WAD.0b013e31816653cc

184. Geda YE, Smith GE, Knopman DS, et al. De novo genesis of neuropsychiatric symptoms in Mild Cognitive Impairment (MCI). *International Psychogeriatrics*. 2004;16(1):51-60. doi:10.1017/S1041610204000067

185. Lee GJ, Lu PH, Hua X, et al. Depressive Symptoms in Mild Cognitive Impairment Predict Greater Atrophy in Alzheimer's Disease-Related Regions. *Biological Psychiatry*. 2012;71(9):814-821. doi:10.1016/j.biopsych.2011.12.024

186. Steenland K, Karnes C, Seals R, Carnevale C, Hermida A, Levey A. Late-Life Depression as a Risk Factor for Mild Cognitive Impairment or Alzheimer's Disease in 30 US Alzheimer's Disease Centers. *Journal of Alzheimer's Disease*. 2012;31(2):265-275. doi:10.3233/JAD-2012-111922

187. van Dalen JW, van Wanrooij LL, Moll van Charante EP, Brayne C, van Gool WA, Richard E. Association of Apathy With Risk of Incident Dementia: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. 2018;75(10):1012-1021. doi:10.1001/jamapsychiatry.2018.1877

188. Gallagher D, Coen R, Kilroy D, et al. Anxiety and behavioural disturbance as markers of prodromal Alzheimer's disease in patients with mild cognitive impairment. *International Journal of Geriatric Psychiatry*. 2011;26(2):166-172. doi:10.1002/gps.2509

189. Ma L. Depression, Anxiety, and Apathy in Mild Cognitive Impairment: Current Perspectives. *Frontiers in Aging Neuroscience*. 2020;12:9. doi:10.3389/fnagi.2020.00009

190. Rozzini L, Chilovi BV, Peli M, et al. Anxiety symptoms in mild cognitive impairment. *International Journal of Geriatric Psychiatry*. 2009;24(3):300-305. doi:10.1002/gps.2106

191. Devier DJ, Pelton GH, Tabert MH, et al. The impact of anxiety on conversion from mild cognitive impairment to Alzheimer's disease. *International Journal of Geriatric Psychiatry*. 2009;24(12):1335-1342. doi:10.1002/gps.2263

192. Robert PH, Berr C, Volteau M, et al. Importance of Lack of Interest in Patients With Mild Cognitive Impairment. *The American Journal of Geriatric Psychiatry*. 2008;16(9):770-776. doi:10.1097/JGP.0b013e31817e73db

193. Lee JS, Cho SK, Kim HJ, et al. Prediction Models of Cognitive Trajectories in Patients with Nonamnestic Mild Cognitive Impairment. *Sci Rep*. 2018;8(1):10468. doi:10.1038/s41598-018-28881-1

194. Moon B, Kim S, Park YH, et al. Depressive Symptoms are Associated with Progression to Dementia in Patients with Amyloid-Positive Mild Cognitive Impairment. *Journal of Alzheimer's Disease*. 2017;58(4):1255-1264. doi:10.3233/JAD-170225

195. Creese B, Brooker H, Ismail Z, et al. Mild Behavioral Impairment as a Marker of Cognitive Decline in Cognitively Normal Older Adults. *The American Journal of Geriatric Psychiatry*. 2019;27(8):823-834. doi:10.1016/j.jagp.2019.01.215

196. Krell-Roesch J, Syrjanen JA, Machulda MM, et al. Neuropsychiatric symptoms and the outcome of cognitive trajectories in older adults free of dementia: The Mayo Clinic Study of Aging. *International Journal of Geriatric Psychiatry*. 2021;36(9):1362-1369. doi:10.1002/gps.5528

197. Davatzikos C, Bhatt P, Shaw LM, Batmanghelich KN, Trojanowski JQ. Prediction of MCI to AD conversion, via MRI, CSF biomarkers, and pattern classification. *Neurobiology of Aging*. 2011;32(12):2322.e19-2322.e27. doi:10.1016/j.neurobiolaging.2010.05.023

198. deToledo-Morrell L, Stoub TR, Bulgakova M, et al. MRI-derived entorhinal volume is a good predictor of conversion from MCI to AD. *Neurobiology of Aging*. 2004;25(9):1197-1203. doi:10.1016/j.neurobiolaging.2003.12.007

199. Risacher SL, Saykin AJ, Wes JD, Shen L, Firpi HA, McDonald BC. Baseline MRI Predictors of Conversion from MCI to Probable AD in the ADNI Cohort. *Current Alzheimer Research*. 2009;6(4):347-361. doi:10.2174/156720509788929273

200. Destrieux C, Fischl B, Dale A, Halgren E. Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *NeuroImage*. 2010;53(1):1-15. doi:10.1016/j.neuroimage.2010.06.010

201. Iglesias JE, Insausti R, Lerma-Usabiaga G, et al. A probabilistic atlas of the human thalamic nuclei combining ex vivo MRI and histology. *NeuroImage*. 2018;183:314-326. doi:10.1016/j.neuroimage.2018.08.012

202. Saygin ZM, Kliemann D, Iglesias JE, et al. High-resolution magnetic resonance imaging reveals nuclei of the human amygdala: manual segmentation to automatic atlas. *NeuroImage*. 2017;155:370-382. doi:10.1016/j.neuroimage.2017.04.046

203. Iglesias JE, Augustinack JC, Nguyen K, et al. A computational atlas of the hippocampal formation using ex vivo, ultra-high resolution MRI: Application to adaptive segmentation of in vivo MRI. *NeuroImage*. 2015;115:117-137. doi:10.1016/j.neuroimage.2015.04.042

204. Sanfilipo MP, Benedict RHB, Zivadinov R, Bakshi R. Correction for intracranial volume in analysis of whole brain atrophy in multiple sclerosis: the proportion vs. residual method. *NeuroImage*. 2004;22(4):1732-1743. doi:10.1016/j.neuroimage.2004.03.037

205. Orso B, Mattei C, Arnaldi D, et al. Clinical and MRI Predictors of Conversion From Mild Behavioural Impairment to Dementia. *The American Journal of Geriatric Psychiatry*. 2020;28(7):755-763. doi:10.1016/j.jagp.2019.12.007

206. Gallagher D, Fischer CE, Iaboni A. Neuropsychiatric Symptoms in Mild Cognitive Impairment: An Update on Prevalence, Mechanisms, and Clinical Significance. *Can J Psychiatry*. 2017;62(3):161-169. doi:10.1177/0706743716648296

207. Lü W, Duan J, Zhang W, Yang W, Yu W. Relationship between neuropsychiatric symptoms and cognitive functions in patients with cognitive impairment. *Psychogeriatrics*. 2021;21(5):773-782. doi:10.1111/psyg.12738

208. Grober E, Hall CB, Lipton RB, Zonderman AB, Resnick SM, Kawas C. Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer's disease. *Journal of the International Neuropsychological Society*. 2008;14(2):266-278. doi:10.1017/S1355617708080302

209. Edmonds EC, Delano-Wood L, Galasko DR, Salmon DP, Bondi MW. Subjective Cognitive Complaints Contribute to Misdiagnosis of Mild Cognitive Impairment. *Journal of the International Neuropsychological Society*. 2014;20(8):836-847. doi:10.1017/S135561771400068X

210. Mitchell AJ, Beaumont H, Ferguson D, Yadegarfar M, Stubbs B. Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: meta-analysis. *Acta Psychiatrica Scandinavica*. 2014;130(6):439-451. doi:10.1111/acps.12336

211. van Oijen M, de Jong FJ, Hofman A, Koudstaal PJ, Breteler MMB. Subjective memory complaints, education, and risk of Alzheimer's disease. *Alzheimer's & Dementia*. 2007;3(2):92-97. doi:10.1016/j.jalz.2007.01.011

212. Baerresen KM, Miller KJ, Hanson ER, et al. Neuropsychological tests for predicting cognitive decline in older adults. *Neurodegener Dis Manag*. 2015;5(3):191-201. doi:10.2217/nmt.15.7

213. Chen PH, Cheng FY, Cheng SJ, Shaw JS. Predicting Cognitive Decline in Parkinson's Disease with Mild Cognitive Impairment: A One-Year Observational Study. *Parkinson’s Disease*. 2020;2020:e8983960. doi:10.1155/2020/8983960

214. Eijlers AJC, van Geest Q, Dekker I, et al. Predicting cognitive decline in multiple sclerosis: a 5-year follow-up study. *Brain*. 2018;141(9):2605-2618. doi:10.1093/brain/awy202

215. Singh V, Chertkow H, Lerch JP, Evans AC, Dorr AE, Kabani NJ. Spatial patterns of cortical thinning in mild cognitive impairment and Alzheimer's disease. *Brain*. 2006;129(11):2885-2893. doi:10.1093/brain/awl256

216. Wang L, Goldstein FC, Veledar E, et al. Alterations in Cortical Thickness and White Matter Integrity in Mild Cognitive Impairment Measured by Whole-Brain Cortical Thickness Mapping and Diffusion Tensor Imaging. *American Journal of Neuroradiology*. 2009;30(5):893-899. doi:10.3174/ajnr.A1484

217. Hsu JL, Lee WJ, Liao YC, Lirng JF, Wang SJ, Fuh JL. Posterior Atrophy and Medial Temporal Atrophy Scores Are Associated with Different Symptoms in Patients with Alzheimer's Disease and Mild Cognitive Impairment. *PLOS ONE*. 2015;10(9):e0137121. doi:10.1371/journal.pone.0137121

218. Hu X, Meiberth D, Newport B, Jessen F, the Alzheimer's Disease Neuroimaging Initiative. Anatomical Correlates of the Neuropsychiatric Symptoms in Alzheimer's Disease. *Current Alzheimer Research*. 2015;12(3):266-277.

219. Bateman DR, Gill S, Hu S, et al. Agitation and impulsivity in mid and late life as possible risk markers for incident dementia. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*. 2020;6(1):e12016. doi:10.1002/trc2.12016

220. Isella V, Villa G, Mapelli C, Ferri F, Appollonio IM, Ferrarese C. The Neuropsychiatric Profile of Posterior Cortical Atrophy. *J Geriatr Psychiatry Neurol*. 2015;28(2):136-144. doi:10.1177/0891988714554713

221. Ismail Z, Herrmann N, Rothenburg LS, et al. A functional neuroimaging study of appetite loss in Alzheimer's disease. *Journal of the Neurological Sciences*. 2008;271(1):97-103. doi:10.1016/j.jns.2008.03.023

222. Suma S, Watanabe Y, Hirano H, et al. Factors affecting the appetites of persons with Alzheimer's disease and mild cognitive impairment. *Geriatrics & Gerontology International*. 2018;18(8):1236-1243. doi:10.1111/ggi.13455

223. Jessen F, Feyen L, Freymann K, et al. Volume reduction of the entorhinal cortex in subjective memory impairment. *Neurobiology of Aging*. 2006;27(12):1751-1756. doi:10.1016/j.neurobiolaging.2005.10.010

224. Saykin AJ, Wishart HA, Rabin LA, et al. Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI. *Neurology*. 2006;67(5):834-842. doi:10.1212/01.wnl.0000234032.77541.a2

225. Schultz SA, Oh JM, Koscik RL, et al. Subjective memory complaints, cortical thinning, and cognitive dysfunction in middle-age adults at risk of AD. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*. 2015;1(1):33-40. doi:10.1016/j.dadm.2014.11.010

226. Stewart R, Dufouil C, Godin O, et al. Neuroimaging correlates of subjective memory deficits in a community population. *Neurology*. 2008;70(18):1601-1607. doi:10.1212/01.wnl.0000310982.99438.54

227. Stewart R, Godin O, Crivello F, et al. Longitudinal neuroimaging correlates of subjective memory impairment: 4-year prospective community study. *The British Journal of Psychiatry*. 2011;198(3):199-205. doi:10.1192/bjp.bp.110.078683

228. Ismail Z, Smith EE, Geda Y, et al. Neuropsychiatric symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment. *Alzheimer's & Dementia*. 2016;12(2):195-202. doi:10.1016/j.jalz.2015.05.017

229. Nagata T, Shinagawa S, Nakajima S, Mimura M, Shigeta M. Association between Neuropsychiatric Improvement and Neurocognitive Change in Alzheimer's Disease: Analysis of the CATIE-AD Study. *Journal of Alzheimer's Disease*. 2018;66(1):139-148. doi:10.3233/JAD-180304

230. Nagata T, Nakajima S, Shinagawa S, et al. Psychosocial or clinico-demographic factors related to neuropsychiatric symptoms in patients with Alzheimer's disease needing interventional treatment: analysis of the CATIE-AD study. *International Journal of Geriatric Psychiatry*. 2017;32(12):1264-1271. doi:10.1002/gps.4607

231. Rouch I, Pongan E, Trombert B, et al. One-Year Evolution of Behavioral and Psychological Symptoms of Dementia in Patients Initially Hospitalized in Cognitive Behavioral Units: The EVITAL Prospective Cohort. *Journal of Alzheimer's Disease*. 2017;57:1-9. doi:10.3233/JAD-161023

232. Marazziti D, Consoli G, Picchetti M, Carlini M, Faravelli L. Cognitive impairment in major depression. *European Journal of Pharmacology*. 2010;626(1):83-86. doi:10.1016/j.ejphar.2009.08.046

233. Lee JS, Potter GG, Wagner HR, Welsh-Bohmer KA, Steffens DC. Persistent mild cognitive impairment in geriatric depression. *International Psychogeriatrics*. 2007;19(1):125-135. doi:10.1017/S1041610206003607

234. Butters MA, Becker JT, Nebes RD, et al. Changes in Cognitive Functioning Following Treatment of Late-Life Depression. *AJP*. 2000;157(12):1949-1954. doi:10.1176/appi.ajp.157.12.1949

235. Wilson RS, Barnes LL, Leon CFM de, et al. Depressive symptoms, cognitive decline, and risk of AD in older persons. *Neurology*. 2002;59(3):364-370. doi:10.1212/WNL.59.3.364

236. Köhler S, van Boxtel MPJ, van Os J, et al. Depressive Symptoms and Cognitive Decline in Community-Dwelling Older Adults. *Journal of the American Geriatrics Society*. 2010;58(5):873-879. doi:10.1111/j.1532-5415.2010.02807.x

237. Oh DJ, Han JW, Bae JB, et al. Chronic subsyndromal depression and risk of dementia in older adults. *Aust N Z J Psychiatry*. 2021;55(8):809-816. doi:10.1177/0004867420972763

238. Singh-Manoux A, Dugravot A, Fournier A, et al. Trajectories of Depressive Symptoms Before Diagnosis of Dementia: A 28-Year Follow-up Study. *JAMA Psychiatry*. 2017;74(7):712-718. doi:10.1001/jamapsychiatry.2017.0660

239. Kiosses DN, Klimstra S, Murphy C, Alexopoulos GS. Executive Dysfunction and Disability in Elderly Patients With Major Depression. *The American Journal of Geriatric Psychiatry*. 2001;9(3):269-274. doi:10.1097/00019442-200108000-00011

240. Gildengers AG, Butters MA, Chisholm D, et al. Cognition in older adults with bipolar disorder versus major depressive disorder. *Bipolar Disorders*. 2012;14(2):198-205. doi:10.1111/j.1399-5618.2012.00995.x

241. Forsell Y, Palmer K, Fratiglioni L. Psychiatric symptoms/syndromes in elderly persons with mild cognitive impairment. Data from a cross-sectional study. *Acta Neurologica Scandinavica*. 2003;107(s179):25-28. doi:10.1034/j.1600-0404.107.s179.4.x

242. Gabryelewicz T, Styczynska M, Pfeffer A, et al. Prevalence of major and minor depression in elderly persons with mild cognitive impairment—MADRS factor analysis. *International Journal of Geriatric Psychiatry*. 2004;19(12):1168-1172. doi:10.1002/gps.1235

243. Lopez OL, Becker JT, Sweet RA, et al. Psychiatric Symptoms Vary With the Severity of Dementia in Probable Alzheimer's Disease. *JNP*. 2003;15(3):346-353. doi:10.1176/jnp.15.3.346

244. Liew TM. Symptom Clusters of Neuropsychiatric Symptoms in Mild Cognitive Impairment and Their Comparative Risks of Dementia: A Cohort Study of 8530 Older Persons. *Journal of the American Medical Directors Association*. 2019;20(8):1054.e1-1054.e9. doi:10.1016/j.jamda.2019.02.012

245. Hek K, Tiemeier H, Newson RS, Luijendijk HJ, Hofman A, Mulder CL. Anxiety disorders and comorbid depression in community dwelling older adults. *International Journal of Methods in Psychiatric Research*. 2011;20(3):157-168. doi:10.1002/mpr.344

246. Beaudreau SA, O'Hara R. The association of anxiety and depressive symptoms with cognitive performance in community-dwelling older adults. *Psychology and Aging*. 2009;24(2):507-512. doi:10.1037/a0016035

247. Korten NCM, Penninx BWJH, Kok RM, et al. Heterogeneity of late-life depression: relationship with cognitive functioning. *International Psychogeriatrics*. 2014;26(6):953-963. doi:10.1017/S1041610214000155

248. Zuidema SU, Jonghe JFM de, Verhey FRJ, Koopmans RTCM. Neuropsychiatric Symptoms in Nursing Home Patients: Factor Structure Invariance of the Dutch Nursing Home Version of the Neuropsychiatric Inventory in Different Stages of Dementia. *DEM*. 2007;24(3):169-176. doi:10.1159/000105603

249. Ismail Z, Gatchel J, Bateman DR, et al. Affective and emotional dysregulation as pre-dementia risk markers: exploring the mild behavioral impairment symptoms of depression, anxiety, irritability, and euphoria. *International Psychogeriatrics*. 2018;30(2):185-196. doi:10.1017/S1041610217001880

250. Almeida OP, McCaul K, Hankey GJ, Yeap BB, Golledge J, Flicker L. Risk of dementia and death in community-dwelling older men with bipolar disorder. *The British Journal of Psychiatry*. 2016;209(2):121-126. doi:10.1192/bjp.bp.115.180059

251. Van der Mussele S, Bekelaar K, Le Bastard N, et al. Prevalence and associated behavioral symptoms of depression in mild cognitive impairment and dementia due to Alzheimer's disease. *International Journal of Geriatric Psychiatry*. 2013;28(9):947-958. doi:10.1002/gps.3909

252. Van der Mussele S, Fransen E, Struyfs H, et al. Depression in Mild Cognitive Impairment is associated with Progression to Alzheimer's Disease: A Longitudinal Study. *Journal of Alzheimer's Disease*. 2014;42(4):1239-1250. doi:10.3233/JAD-140405

253. Van der Mussele S, Le Bastard N, Saerens J, et al. Agitation-associated behavioral symptoms in mild cognitive impairment and Alzheimer's dementia. *Aging & Mental Health*. 2015;19(3):247-257. doi:10.1080/13607863.2014.924900

254. Mintzer JE, Brawman-Mintzer O. Agitation as a possible expression of generalized anxiety disorder in demented elderly patients: toward a treatment approach. *J Clin Psychiatry*. 1996;57 Suppl 7:55-63; discussion 73-5.

255. Liu KY, Costello H, Reeves S, Howard R, Initiative for the ADN. The Relationship Between Anxiety and Incident Agitation in Alzheimer's Disease. *Journal of Alzheimer's Disease*. 2020;78(3):1119-1127. doi:10.3233/JAD-200516

256. El Haj M, Roche J, Jardri R, Kapogiannis D, Gallouj K, Antoine P. Clinical and neurocognitive aspects of hallucinations in Alzheimer's disease. *Neuroscience & Biobehavioral Reviews*. 2017;83:713-720. doi:10.1016/j.neubiorev.2017.02.021

257. El Haj M, Larøi F, Gély-Nargeot MC, Raffard S. Inhibitory deterioration may contribute to hallucinations in Alzheimer's disease. *Cognitive Neuropsychiatry*. 2015;20(4):281-295. doi:10.1080/13546805.2015.1023392

258. Haj ME, Larøi F. Olfactory hallucinations in Alzheimer's disease. *Acta Neuropsychiatrica*. 2021;33(1):37-42. doi:10.1017/neu.2020.33

259. El Haj M, Jardri R, Larøi F, Antoine P. Hallucinations, loneliness, and social isolation in Alzheimer's disease. *Cognitive Neuropsychiatry*. 2016;21(1):1-13. doi:10.1080/13546805.2015.1121139

260. Reichmann FF. Loneliness. *Psychiatry*. 1959;22(1):1-15. doi:10.1080/00332747.1959.11023153

261. Launay G, Slade P. The measurement of hallucinatory predisposition in male and female prisoners. *Personality and Individual Differences*. 1981;2(3):221-234. doi:10.1016/0191-8869(81)90027-1

262. Apostolova LG, Di LJ, Duffy EL, et al. Risk Factors for Behavioral Abnormalities in Mild Cognitive Impairment and Mild Alzheimer's Disease. *DEM*. 2014;37(5-6):315-326. doi:10.1159/000351009

263. Angst J, Gamma A, Gerber-Werder R, Zarate CA, Manji HK. Does long-term medication with lithium, clozapine or antidepressants prevent or attenuate dementia in bipolar and depressed patients? *International Journal of Psychiatry in Clinical Practice*. 2007;11(1):2-8. doi:10.1080/13651500600810133

264. Lee CWS, Lin CL, Sung FC, Liang JA, Kao CH. Antidepressant Treatment and Risk of Dementia: A Population-Based, Retrospective Case-Control Study. *J Clin Psychiatry*. 2016;77(1):961. doi:10.4088/JCP.14m09580

265. Leng Y, Diem SJ, Stone KL, Yaffe K. Antidepressant Use and Cognitive Outcomes in Very Old Women. *The Journals of Gerontology: Series A*. 2018;73(10):1390-1395. doi:10.1093/gerona/glx226

266. Chan JYC, Yiu KKL, Kwok TCY, Wong SYS, Tsoi KKF. Depression and Antidepressants as Potential Risk Factors in Dementia: A Systematic Review and Meta-analysis of 18 Longitudinal Studies. *Journal of the American Medical Directors Association*. 2019;20(3):279-286.e1. doi:10.1016/j.jamda.2018.12.004

267. Yatawara C, Lim L, Chander R, Zhou J, Kandiah N. Depressive symptoms influence global cognitive impairment indirectly by reducing memory and executive function in patients with mild cognitive impairment. *J Neurol Neurosurg Psychiatry*. 2016;87(12):1375-1383. doi:10.1136/jnnp-2016-314191

268. Marshall GA, Rentz DM, Frey MT, Locascio JJ, Johnson KA, Sperling RA. Executive function and instrumental activities of daily living in mild cognitive impairment and Alzheimer's disease. *Alzheimer's & Dementia*. 2011;7(3):300-308. doi:10.1016/j.jalz.2010.04.005

269. Paula JJ de, Malloy-Diniz LF. Funções executivas como preditores do desempenho funcional em idosos com demência de Alzheimer em fase inicial e comprometimento cognitivo leve. *Estudos de Psicologia (Natal)*. 2013;18(1):117-124. doi:10.1590/S1413-294X2013000100019

270. Brandt J, Aretouli E, Neijstrom E, et al. SELECTIVITY OF EXECUTIVE FUNCTION DEFICITS IN MILD COGNITIVE IMPAIRMENT. *Neuropsychology*. 2009;23(5):607-618. doi:10.1037/a0015851

271. Cloninger R, Przybeck T, Svrakic D, Wetzel R. The Temperament and Character Inventory (TCI): A guide to its development and use. Published online 1994.

272. Dell'Orco S, Sperandeo R, Moretto E, Maldonato NM. Revision on Psychometric Properties of the Temperament and Character Inventory in a Clinical Sample. *Frontiers in Psychology*.

2018;9. Accessed November 21, 2022. https://www.frontiersin.org/articles/10.3389/fpsyg.2018.01951

273. Low LF, Harrison F, Lackersteen SM. Does Personality Affect Risk for Dementia? A Systematic Review and Meta-Analysis. *The American Journal of Geriatric Psychiatry*. 2013;21(8):713-728. doi:10.1016/j.jagp.2012.08.004

274. Terracciano A, Sutin AR, An Y, et al. Personality and risk of Alzheimer's disease: New data and meta-analysis. *Alzheimer's & Dementia*. 2014;10(2):179-186. doi:10.1016/j.jalz.2013.03.002

275. Terracciano A, Stephan Y, Luchetti M, Albanese E, Sutin AR. Personality traits and risk of cognitive impairment and dementia. *Journal of Psychiatric Research*. 2017;89:22-27. doi:10.1016/j.jpsychires.2017.01.011

276. Caselli RJ, Dueck AC, Locke DEC, et al. Impact of Personality on Cognitive Aging: A Prospective Cohort Study. *J Int Neuropsychol Soc*. 2016;22(7):765-776. doi:10.1017/S1355617716000527

277. Crowe M, Andel R, Pedersen NL, Fratiglioni L, Gatz M. Personality and risk of cognitive impairment 25 years later. *Psychology and Aging*. 2006;21(3):573. doi:10.1037/0882-7974.21.3.573

278. Krasuski JS, Alexander GE, Horwitz B, et al. Volumes of Medial Temporal Lobe Structures in Patients with Alzheimer's Disease and Mild Cognitive Impairment (and in Healthy Controls). *Biological Psychiatry*. 1998;43(1):60-68. doi:10.1016/S0006-3223(97)00013-9

279. Zufferey V, Donati A, Popp J, et al. Neuroticism, depression, and anxiety traits exacerbate the state of cognitive impairment and hippocampal vulnerability to Alzheimer's disease. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*. 2017;7:107-114. doi:10.1016/j.dadm.2017.05.002

280. Giannakopoulos P, Rodriguez C, Montandon ML, Garibotto V, Haller S, Herrmann FR. Personality Factors' Impact on the Structural Integrity of Mentalizing Network in Old Age: A Combined PET-MRI Study. *Frontiers in Psychiatry*. 2020;11. Accessed November 1, 2022. https://www.frontiersin.org/articles/10.3389/fpsyt.2020.552037

281. Giannakopoulos P, Rodriguez C, Montandon ML, Garibotto V, Haller S, Herrmann FR. Personality Impact on Alzheimer's Disease — Signature and Vascular Imaging Markers: A PET-MRI Study. *Journal of Alzheimer's Disease*. 2022;85(4):1807-1817. doi:10.3233/JAD-215062

282. Taki Y, Thyreau B, Kinomura S, et al. A longitudinal study of the relationship between personality traits and the annual rate of volume changes in regional gray matter in healthy adults. *Human Brain Mapping*. 2013;34(12):3347-3353. doi:10.1002/hbm.22145

283. Benedict RHB, Schwartz CE, Duberstein P, et al. Influence of Personality on the Relationship Between Gray Matter Volume and Neuropsychiatric Symptoms in Multiple Sclerosis. *Psychosomatic Medicine*. 2013;75(3):253-261. doi:10.1097/PSY.0b013e31828837cc

284. Capuron L, Castanon N. Role of Inflammation in the Development of Neuropsychiatric Symptom Domains: Evidence and Mechanisms. In: Dantzer R, Capuron L, eds. *Inflammation-Associated Depression: Evidence, Mechanisms and Implications*. Current Topics in Behavioral Neurosciences. Springer International Publishing; 2017:31-44. doi:10.1007/7854_2016_14

285. Delgado-Alonso C, Valles-Salgado M, Delgado-Álvarez A, et al. Examining Association of Personality Characteristics and Neuropsychiatric Symptoms in Post-COVID Syndrome. *Brain Sciences*. 2022;12(2):265. doi:10.3390/brainsci12020265

286. Greenop KR, Almeida OP, Hankey GJ, Bockxmeer F van, Lautenschlager NT. Premorbid personality traits are associated with post-stroke behavioral and psychological symptoms: a three-month follow-up study in Perth, Western Australia. *International Psychogeriatrics*. 2009;21(6):1063-1071. doi:10.1017/S1041610209990457

287. Lautenschlager NT, Förstl H. Personality change in old age. *Current Opinion in Psychiatry*. 2007;20(1):62. doi:10.1097/YCO.0b013e3280113d09

288. Archer N, Brown RG, Reeves SJ, et al. Premorbid Personality and Behavioral and Psychological Symptoms in Probable Alzheimer Disease. *The American Journal of Geriatric Psychiatry*. 2007;15(3):202-213. doi:10.1097/01.JGP.0000232510.77213.10

289. Pocnet C, Rossier J, Antonietti JP, von Gunten A. Personality traits and behavioral and psychological symptoms in patients at an early stage of Alzheimer's disease. *International Journal of Geriatric Psychiatry*. 2013;28(3):276-283. doi:10.1002/gps.3822

290. McCrae RR, Costa PT. Validation of the five-factor model of personality across instruments and observers. *Journal of Personality and Social Psychology*. 1987;52:81-90. doi:10.1037/0022-3514.52.1.81

291. Capanna C, Struglia F, Riccardi I, Daneluzzo E, Stratta P, Rossi A. Temperament and Character Inventory—R (TCI—R) and Big Five Questionnaire (BFQ): Convergence and Divergence. *Psychol Rep*. 2012;110(3):1002-1006. doi:10.2466/02.03.09.PR0.110.3.1002-1006

292. De Fruyt F, Van De Wiele L, Van Heeringen C. Cloninger's Psychobiological Model of Temperament and Character and the Five-Factor Model of Personality. *Personality and Individual Differences*. 2000;29(3):441-452. doi:10.1016/S0191-8869(99)00204-4

293. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. *Journal of General Internal Medicine*. 2001;16(9):606-613. doi:10.1046/j.1525-1497.2001.016009606.x

294. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Applied Psychological Measurement*. 1977;1(3):385-401. doi:10.1177/014662167700100306

295. Levenstein S, Prantera C, Varvo V, et al. Development of the perceived stress questionnaire: A new tool for psychosomatic research. *Journal of Psychosomatic Research*. 1993;37(1):19-32. doi:10.1016/0022-3999(93)90120-5

296. Kecklund G, Åkerstedt T. The psychometric properties of the Karolinska Sleep Questionnaire. *J Sleep Res*. 1992;1(Suppl 1):113.

297. Dureman I. SRB: 1. *Psykologiförlaget, Stockholm*. Published online 1960.

298. Reuter M, Schmansky NJ, Rosas HD, Fischl B. Within-subject template estimation for unbiased longitudinal image analysis. *NeuroImage*. 2012;61(4):1402-1418. doi:10.1016/j.neuroimage.2012.02.084

299. Bauer IE, Wu MJ, Meyer TD, et al. The role of white matter in personality traits and affective processing in bipolar disorder. *Journal of Psychiatric Research*. 2016;80:64-72. doi:10.1016/j.jpsychires.2016.06.003

300. Coutinho JF, Sampaio A, Ferreira M, Soares JM, Gonçalves OF. Brain correlates of pro-social personality traits: a voxel-based morphometry study. *Brain Imaging and Behavior*. 2013;7(3):293-299. doi:10.1007/s11682-013-9227-2

301. DeYoung CG, Hirsh JB, Shane MS, Papademetris X, Rajeevan N, Gray JR. Testing Predictions From Personality Neuroscience: Brain Structure and the Big Five. *Psychol Sci*. 2010;21(6):820-828. doi:10.1177/0956797610370159

302. Gardini S, Cloninger CR, Venneri A. Individual differences in personality traits reflect structural variance in specific brain regions. *Brain Research Bulletin*. 2009;79(5):265-270. doi:10.1016/j.brainresbull.2009.03.005

303. Giannakopoulos P, Rodriguez C, Montandon ML, Garibotto V, Haller S, Herrmann FR. Less agreeable, better preserved? A PET amyloid and MRI study in a community-based cohort. *Neurobiology of Aging*. 2020;89:24-31. doi:10.1016/j.neurobiolaging.2020.02.004

304. Jackson J, Balota DA, Head D. Exploring the relationship between personality and regional brain volume in healthy aging. *Neurobiology of Aging*. 2011;32(12):2162-2171. doi:10.1016/j.neurobiolaging.2009.12.009

305. Kaasinen V, Maguire RP, Kurki T, Brück A, Rinne JO. Mapping brain structure and personality in late adulthood. *NeuroImage*. 2005;24(2):315-322. doi:10.1016/j.neuroimage.2004.09.017

306. Li T, Yan X, Li Y, et al. Neuronal Correlates of Individual Differences in the Big Five Personality Traits: Evidences from Cortical Morphology and Functional Homogeneity. *Frontiers in Neuroscience*. 2017;11. Accessed November 1, 2022. https://www.frontiersin.org/articles/10.3389/fnins.2017.00414

307. Liu WY, Weber B, Reuter M, Markett S, Chu WC, Montag C. The Big Five of Personality and structural imaging revisited: a VBM – DARTEL study. *NeuroReport*. 2013;24(7):375-380. doi:10.1097/WNR.0b013e328360dad7

308. Lu F, Huo Y, Li M, et al. Relationship between Personality and Gray Matter Volume in Healthy Young Adults: A Voxel-Based Morphometric Study. *PLOS ONE*. 2014;9(2):e88763. doi:10.1371/journal.pone.0088763

309. Prillwitz CC, Rüber T, Reuter M, et al. The salience network and human personality: Integrity of white matter tracts within anterior and posterior salience network relates to the self-directedness character trait. *Brain Research*. 2018;1692:66-73. doi:10.1016/j.brainres.2018.04.035

310. Sanjari Moghaddam H, Mehrabinejad MM, Mohebi F, et al. Microstructural white matter alterations and personality traits: A diffusion MRI study. *Journal of Research in Personality*. 2020;88:104010. doi:10.1016/j.jrp.2020.104010

311. Xu J, Potenza MN. White matter integrity and five-factor personality measures in healthy adults. *NeuroImage*. 2012;59(1):800-807. doi:10.1016/j.neuroimage.2011.07.040

312. Sundström A, Marklund P, Nilsson LG, et al. APOE influences on neuropsychological function after mild head injury: Within-person comparisons. *Neurology*. 2004;62(11):1963-1966. doi:10.1212/01.WNL.0000129268.83927.A8

313. Schielzeth H, Dingemanse NJ, Nakagawa S, et al. Robustness of linear mixed-effects models to violations of distributional assumptions. *Methods in Ecology and Evolution*. 2020;11(9):1141-1152. doi:10.1111/2041-210X.13434

314. Brändström S, Sigvardsson S, Nylander PO, Richter J. The Swedish version of the Temperament and Character Inventory (TCI): A cross-validation of age and gender influences. *European Journal of Psychological Assessment*. 2008;24:14-21. doi:10.1027/1015-5759.24.1.14

315. Rubio MM, Antonietti JP, Donati A, Rossier J, Gunten A von. Personality Traits and Behavioural and Psychological Symptoms in Patients with Mild Cognitive Impairment. *DEM*. 2013;35(1-2):87-97. doi:10.1159/000346129

316. Aschwanden D, Strickhouser JE, Luchetti M, Stephan Y, Sutin AR, Terracciano A. Is personality associated with dementia risk? A meta-analytic investigation. *Ageing Research Reviews*. 2021;67:101269. doi:10.1016/j.arr.2021.101269

317. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. *Brain*. 1995;118(1):279-306. doi:10.1093/brain/118.1.279

318. Gorbach T, Pudas S, Lundquist A, et al. Longitudinal association between hippocampus atrophy and episodic-memory decline. *Neurobiology of Aging*. 2017;51:167-176. doi:10.1016/j.neurobiolaging.2016.12.002

319. Gorbach T, Pudas S, Bartrés-Faz D, et al. Longitudinal association between hippocampus atrophy and episodic-memory decline in non-demented APOE ε4 carriers. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*. 2020;12(1):e12110. doi:10.1002/dad2.12110

320. Holroyd CB, Yeung N. Motivation of extended behaviors by anterior cingulate cortex. *Trends in Cognitive Sciences*. 2012;16(2):122-128. doi:10.1016/j.tics.2011.12.008

321. Srinivasan L, Asaad WF, Ginat DT, et al. Action Initiation in the Human Dorsal Anterior Cingulate Cortex. *PLOS ONE*. 2013;8(2):e55247. doi:10.1371/journal.pone.0055247

322. Kapogiannis D, Sutin A, Davatzikos C, Costa Jr. P, Resnick S. The five factors of personality and regional cortical variability in the baltimore longitudinal study of aging. *Human Brain Mapping*. 2013;34(11):2829-2840. doi:10.1002/hbm.22108

323. Duron E, Vidal JS, Bounatiro S, et al. Relationships between Personality Traits, Medial Temporal Lobe Atrophy, and White Matter Lesion in Subjects Suffering from Mild Cognitive Impairment. *Frontiers in Aging Neuroscience*. 2014;6. Accessed November 1, 2022. https://www.frontiersin.org/articles/10.3389/fnagi.2014.00195

324. Terracciano A, Iacono D, O'Brien RJ, et al. Personality and resilience to Alzheimer's disease neuropathology: a prospective autopsy study. *Neurobiology of Aging*. 2013;34(4):1045-1050. doi:10.1016/j.neurobiolaging.2012.08.008

325. Sapkota S, Wiebe SA, Small BJ, Dixon RA. Apolipoprotein E and Clusterin can magnify effects of personality vulnerability on declarative memory performance in non-demented older adults. *International Journal of Geriatric Psychiatry*. 2016;31(5):502-509. doi:10.1002/gps.4355

326. Johansson L, Guo X, Duberstein PR, et al. Midlife personality and risk of Alzheimer disease and distress: A 38-year follow-up. *Neurology*. 2014;83(17):1538-1544. doi:10.1212/WNL.0000000000000907

327. Gurvich C, Hoy K, Thomas N, Kulkarni J. Sex Differences and the Influence of Sex Hormones on Cognition through Adulthood and the Aging Process. *Brain Sciences*. 2018;8(9):163. doi:10.3390/brainsci8090163

328. Rodrigues MA, Verdile G, Foster JK, et al. Gonadotropins and Cognition in Older Women. *Journal of Alzheimer's Disease*. 2008;13(3):267-274. doi:10.3233/JAD-2008-13304

329. Verdile G, Yeap BB, Clarnette RM, et al. Luteinizing Hormone Levels Are Positively Correlated with Plasma Amyloid-β Protein Levels in Elderly Men. *Journal of Alzheimer's Disease*. 2008;14(2):201-208. doi:10.3233/JAD-2008-14208

330. Lee JH, Byun MS, Yi D, et al. Sex-specific association of sex hormones and gonadotropins, with brain amyloid and hippocampal neurodegeneration. *Neurobiology of Aging*. 2017;58:34-40. doi:10.1016/j.neurobiolaging.2017.06.005

331. Verdile G, Laws SM, Henley D, et al. Associations between gonadotropins, testosterone and β amyloid in men at risk of Alzheimer's disease. *Mol Psychiatry*. 2014;19(1):69-75. doi:10.1038/mp.2012.147

332. Buckley RF, Mormino EC, Amariglio RE, et al. Sex, amyloid, and *APOE* ε4 and risk of cognitive decline in preclinical Alzheimer's disease: Findings from three well-characterized cohorts. *Alzheimer's & Dementia*. 2018;14(9):1193-1203. doi:10.1016/j.jalz.2018.04.010

333. Goveas JS, Espeland MA, Woods NF, Wassertheil-Smoller S, Kotchen JM. Depressive Symptoms and Incidence of Mild Cognitive Impairment and Probable Dementia in Elderly Women: The Women's Health Initiative Memory Study. *J Am Geriatr Soc*. 2011;59(1):57-66. doi:10.1111/j.1532-5415.2010.03233.x

334. Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. *J Affect Disord*. 1993;29(2-3):85-96. doi:10.1016/0165-0327(93)90026-g

335. Lim ASP, Kowgier M, Yu L, Buchman AS, Bennett DA. Sleep Fragmentation and the Risk of Incident Alzheimer's Disease and Cognitive Decline in Older Persons. *Sleep*. 2013;36(7):1027-1032. doi:10.5665/sleep.2802

336. Bixler EO, Vgontzas AN, Lin HM, et al. Prevalence of sleep-disordered breathing in women: effects of gender. *Am J Respir Crit Care Med*. 2001;163(3 Pt 1):608-613. doi:10.1164/ajrccm.163.3.9911064

337. Saari T, Hallikainen I, Hintsa T, Koivisto AM. Neuropsychiatric symptoms and activities of daily living in Alzheimer's disease: ALSOVA 5-year follow-up study. *International Psychogeriatrics*. 2020;32(6):741-751. doi:10.1017/S1041610219001571

338. Rog LA, Park LQ, Harvey DJ, Huang CJ, Mackin S, Farias ST. The independent contributions of cognitive impairment and neuropsychiatric symptoms to everyday function in older adults. *Clin Neuropsychol*. 2014;28(2):215-236. doi:10.1080/13854046.2013.876101

339. Long X, Jiang C, Zhang L. Morphological Biomarker Differentiating MCI Converters from Nonconverters: Longitudinal Evidence Based on Hemispheric Asymmetry. *Behavioural Neurology*. 2018;2018:e3954101. doi:10.1155/2018/3954101

340. Long X, Liao W, Jiang C, Qiu B, Liu Y, Zhang L. Multivariate analysis on hemispheric asymmetry alterations in differentiating mild cognitive impairment and Alzheimer's disease from healthy aging. *Proc Intl Soc Mag Reson Med*. Published online 2012.

341. Pagani M, De Carli F, Morbelli S, et al. Volume of interest-based [18F]fluorodeoxyglucose PET discriminates MCI converting to Alzheimer's disease from healthy controls. A European Alzheimer's Disease Consortium (EADC) study. *NeuroImage: Clinical*. 2015;7:34-42. doi:10.1016/j.nicl.2014.11.007

342. Gray KR, Wolz R, Heckemann RA, Aljabar P, Hammers A, Rueckert D. Multi-region analysis of longitudinal FDG-PET for the classification of Alzheimer's disease. *Neuroimage*. 2012;60(1):221-229. doi:10.1016/j.neuroimage.2011.12.071

343. Derflinger S, Sorg C, Gaser C, et al. Grey-Matter Atrophy in Alzheimer's Disease is Asymmetric but not Lateralized. *Journal of Alzheimer's Disease*. 2011;25(2):347-357. doi:10.3233/JAD-2011-110041

344. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134(9):2456-2477. doi:10.1093/brain/awr179

345. Salloway SP, Malloy PF, Duffy JD. *The Frontal Lobes and Neuropsychiatric Illness*. American Psychiatric Pub; 2008.

346. Gillespie NA, Cloninger CR, Heath AC, Martin NG. The genetic and environmental relationship between Cloninger's dimensions of temperament and character. *Pers Individ Dif*. 2003;35(8):1931-1946. doi:10.1016/S0191-8869(03)00042-4

347. Comings D, Gade-Andavolu R, Gonzalez N, et al. A multivariate analysis of 59 candidate genes in personality traits: the temperament and character inventory. *Clinical Genetics*. 2000;58(5):375-385. doi:10.1034/j.1399-0004.2000.580508.x

348. Ando J, Suzuki A, Yamagata S, et al. Genetic and Environmental Structure of Cloninger's Temperament and Character Dimensions. *Journal of Personality Disorders*. 2004;18(4):379-393. doi:10.1521/pedi.2004.18.4.379

349. Samochowiec J, Rybakowski F, Czerski P, et al. Polymorphisms in the Dopamine, Serotonin, and Norepinephrine Transporter Genes and Their Relationship to Temperamental Dimensions Measured by the Temperament and Character Inventory in Healthy Volunteers. *Neuropsychobiology*. 2001;43(4):248-253. doi:10.1159/000054898

350. Herbst JH, Zonderman AB, McCrae RR, Costa PT. Do the Dimensions of the Temperament and Character Inventory Map a Simple Genetic Architecture? Evidence From Molecular Genetics and Factor Analysis. *AJP*. 2000;157(8):1285-1290. doi:10.1176/appi.ajp.157.8.1285

351. Wrosch C, Scheier MF. Personality and quality of life: The importance of optimism and goal adjustment. *Qual Life Res*. 2003;12(1):59-72. doi:10.1023/A:1023529606137

352. Huang IC, Lee JL, Ketheeswaran P, Jones CM, Revicki DA, Wu AW. Does personality affect health-related quality of life? A systematic review. *PLOS ONE*. 2017;12(3):e0173806. doi:10.1371/journal.pone.0173806

353. Denollet J, Vaes J, Brutsaert DL. Inadequate response to treatment in coronary heart disease : adverse effects of type D personality and younger age on 5-year prognosis and quality of life. *Circulation*. 2000;102(6):630-635. doi:10.1161/01.cir.102.6.630

354. Perkins DO, Davidson EJ, Leserman J, Liao D, Evans DL. Personality disorder in patients infected with HIV: a controlled study with implications for clinical care. *Am J Psychiatry*. 1993;150(2):309-315. doi:10.1176/ajp.150.2.309

355. Erlen JA, Stilley CS, Bender A, et al. Personality Traits and Chronic Illness: A Comparison of Individuals with Psychiatric, Coronary Heart Disease, and HIV/AIDS Diagnoses. *Appl Nurs Res*. 2011;24(2):74-81. doi:10.1016/j.apnr.2009.04.006

356. Brickman AL, Yount SE, Blaney NT, Rothberg ST, De-Nour AK. Personality traits and long-term health status. The influence of neuroticism and conscientiousness on renal deterioration in type-1 diabetes. *Psychosomatics*. 1996;37(5):459-468. doi:10.1016/S0033-3182(96)71534-7

357. Allen MT, Stoney CM, Owens JF, Matthews KA. Hemodynamic adjustments to laboratory stress: the influence of gender and personality. *Psychosom Med*. 1993;55(6):505-517. doi:10.1097/00006842-199311000-00006

358. Peters R, Booth A, Rockwood K, Peters J, D'Este C, Anstey KJ. Combining modifiable risk factors and risk of dementia: a systematic review and meta-analysis. *BMJ Open*. 2019;9(1):e022846. doi:10.1136/bmjopen-2018-022846

359. Zhang J, Chen C, Hua S, et al. An updated meta-analysis of cohort studies: Diabetes and risk of Alzheimer's disease. *Diabetes Research and Clinical Practice*. 2017;124:41-47. doi:10.1016/j.diabres.2016.10.024

360. Power MC, Weuve J, Gagne JJ, McQueen MB, Viswanathan A, Blacker D. The association between blood pressure and incident Alzheimer disease: a systematic review and meta-analysis. *Epidemiology*. 2011;22(5):646-659. doi:10.1097/EDE.0b013e31822708b5

361. Mortby ME, Burns R, Eramudugolla R, Ismail Z, Anstey KJ. Neuropsychiatric Symptoms and Cognitive Impairment: Understanding the Importance of Co-Morbid Symptoms. *J Alzheimers Dis*. 2017;59(1):141-153. doi:10.3233/JAD-170050

362. Choudhury A, Renjilian E, Asan O. Use of machine learning in geriatric clinical care for chronic diseases: a systematic literature review. *JAMIA Open*. 2020;3(3):459-471. doi:10.1093/jamiaopen/ooaa034

363. Myszczynska MA, Ojamies PN, Lacoste AMB, et al. Applications of machine learning to diagnosis and treatment of neurodegenerative diseases. *Nat Rev Neurol*. 2020;16(8):440-456. doi:10.1038/s41582-020-0377-8

364. Nusinovici S, Tham YC, Chak Yan MY, et al. Logistic regression was as good as machine learning for predicting major chronic diseases. *Journal of Clinical Epidemiology*. 2020;122:56-69. doi:10.1016/j.jclinepi.2020.03.002

365. Baecker L, Garcia-Dias R, Vieira S, Scarpazza C, Mechelli A. Machine learning for brain age prediction: Introduction to methods and clinical applications. *eBioMedicine*. 2021;72:103600. doi:10.1016/j.ebiom.2021.103600

366. Rutledge RB, Chekroud AM, Huys QJ. Machine learning and big data in psychiatry: toward clinical applications. *Current Opinion in Neurobiology*. 2019;55:152-159. doi:10.1016/j.conb.2019.02.006

367. Watson DS, Krutzinna J, Bruce IN, et al. Clinical applications of machine learning algorithms: beyond the black box. *BMJ*. 2019;364:l886. doi:10.1136/bmj.l886

368. Lee CS, Lee AY. Clinical applications of continual learning machine learning. *The Lancet Digital Health*. 2020;2(6):e279-e281. doi:10.1016/S2589-7500(20)30102-3

369. Pfeffer RI, Kurosaki TT, Harrah CH Jr, Chance JM, Filos S. Measurement of Functional Activities in Older Adults in the Community1. *Journal of Gerontology*. 1982;37(3):323-329. doi:10.1093/geronj/37.3.323

370. Dutra MC, Ribeiro R dos S, Pinheiro SB, Melo GF de, Carvalho G de A. Accuracy and reliability of the Pfeffer Questionnaire for the Brazilian elderly population. *Dement neuropsychol*. 2015;9:176-183. doi:10.1590/1980-57642015DN92000012

371. Hunsberger J, Austin DR, Henter ID, Chen G. The neurotrophic and neuroprotective effects of psychotropic agents. *Dialogues in Clinical Neuroscience*. 2009;11(3):333-348. doi:10.31887/DCNS.2009.11.3/jhunsberger

372. Hovorka M, Ewing D, Middlemas DS. Chronic SSRI Treatment, but Not Norepinephrine Reuptake Inhibitor Treatment, Increases Neurogenesis in Juvenile Rats. *International Journal of Molecular Sciences*. 2022;23(13):6919. doi:10.3390/ijms23136919

373. Boldrini M, Hen R, Underwood MD, et al. HIPPOCAMPAL ANGIOGENESIS AND PROGENITOR CELL PROLIFERATION ARE INCREASED WITH ANTIDEPRESSANT USE IN MAJOR DEPRESSION. *Biol Psychiatry*. 2012;72(7):562-571. doi:10.1016/j.biopsych.2012.04.024

374. Caminiti SP, Ballarini T, Sala A, et al. FDG-PET and CSF biomarker accuracy in prediction of conversion to different dementias in a large multicentre MCI cohort. *NeuroImage: Clinical*. 2018;18:167-177. doi:10.1016/j.nicl.2018.01.019

375. Bron EE, Klein S, Papma JM, et al. Cross-cohort generalizability of deep and conventional machine learning for MRI-based diagnosis and prediction of Alzheimer's disease. *NeuroImage: Clinical*. 2021;31:102712. doi:10.1016/j.nicl.2021.102712

376. Jack CR Jr, Wiste HJ, Vemuri P, et al. Brain beta-amyloid measures and magnetic resonance imaging atrophy both predict time-to-progression from mild cognitive impairment to Alzheimer's disease. *Brain*. 2010;133(11):3336-3348. doi:10.1093/brain/awq277

377. Nasrallah IM, Wolk DA. Multimodality Imaging of Alzheimer Disease and Other Neurodegenerative Dementias. *Journal of Nuclear Medicine*. 2014;55(12):2003-2011. doi:10.2967/jnumed.114.141416

378. Noor MBT, Zenia NZ, Kaiser MS, Mahmud M, Al Mamun S. Detecting Neurodegenerative Disease from MRI: A Brief Review on a Deep Learning Perspective. In: Liang P, Goel V, Shan C, eds. *Brain Informatics*. Lecture Notes in Computer Science. Springer International Publishing; 2019:115-125. doi:10.1007/978-3-030-37078-7_12

379. Pérez-Grijalba V, Arbizu J, Romero J, et al. Plasma Aβ42/40 ratio alone or combined with FDG-PET can accurately predict amyloid-PET positivity: a cross-sectional analysis from the AB255 Study. *Alz Res Therapy*. 2019;11(1):96. doi:10.1186/s13195-019-0549-1

380. Karikari TK, Pascoal TA, Ashton NJ, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. *The Lancet Neurology*. 2020;19(5):422-433. doi:10.1016/S1474-4422(20)30071-5

381. Planche V, Bouteloup V, Pellegrin I, et al. Validity and Performance of Blood Biomarkers for Alzheimer Disease to Predict Dementia Risk in a Large Clinic-Based Cohort. *Neurology*. 2023;100(5):e473-e484. doi:10.1212/WNL.0000000000201479

382. Shen XN, Li JQ, Wang HF, et al. Plasma amyloid, tau, and neurodegeneration biomarker profiles predict Alzheimer's disease pathology and clinical progression in older adults without dementia. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*. 2020;12(1):e12104. doi:10.1002/dad2.12104

383. Lin CH, Chiu SI, Chen TF, Jang JSR, Chiu MJ. Classifications of Neurodegenerative Disorders Using a Multiplex Blood Biomarkers-Based Machine Learning Model. *International Journal of Molecular Sciences*. 2020;21(18):6914. doi:10.3390/ijms21186914

384. Thomas KR, Bangen KJ, Weigand AJ, et al. Objective subtle cognitive difficulties predict future amyloid accumulation and neurodegeneration. *Neurology*. 2020;94(4):e397-e406. doi:10.1212/WNL.0000000000008838

385. Leon MJ de, Ferris SH, George AE, et al. Positron emission tomographic studies of aging and Alzheimer disease. *American Journal of Neuroradiology*. 1983;4(3):568-571.

386. Small GW, Ercoli LM, Silverman DHS, et al. Cerebral metabolic and cognitive decline in persons at genetic risk for Alzheimer's disease. *Proceedings of the National Academy of Sciences*. 2000;97(11):6037-6042. doi:10.1073/pnas.090106797

387. Mosconi L, Brys M, Glodzik-Sobanska L, De Santi S, Rusinek H, de Leon MJ. Early detection of Alzheimer's disease using neuroimaging. *Experimental Gerontology*. 2007;42(1):129-138. doi:10.1016/j.exger.2006.05.016

388. Mosconi L, De Santi S, Rusinek H, Convit A, de Leon MJ. Magnetic resonance and PET studies in the early diagnosis of Alzheimer's disease. *Expert Review of Neurotherapeutics*. 2004;4(5):831-849. doi:10.1586/14737175.4.5.831

389. Phelps ME, Mazziotta J, Schelbert HR. Positron emission tomography and autoradiography: Principles and applications for the brain and heart. Published online January 1, 1985. Accessed April 25, 2023. https://www.osti.gov/biblio/5688647

390. Convit A, de Leon MJ, Tarshish C, et al. Hippocampal volume losses in minimally impaired elderly. *Lancet*. 1995;345(8944):266. doi:10.1016/s0140-6736(95)90265-1

391. Convit A, de Asis J, de Leon MJ, Tarshish CY, De Santi S, Rusinek H. Atrophy of the medial occipitotemporal, inferior, and middle temporal gyri in non-demented elderly predict decline to Alzheimer's disease☆. *Neurobiology of Aging*. 2000;21(1):19-26. doi:10.1016/S0197-4580(99)00107-4

392. Killiany RJ, Moss MB, Albert MS, Sandor T, Tieman J, Jolesz F. Temporal Lobe Regions on Magnetic Resonance Imaging Identify Patients With Early Alzheimer's Disease. *Archives of Neurology*. 1993;50(9):949-954. doi:10.1001/archneur.1993.00540090052010

393. Nestor PJ, Fryer TD, Smielewski P, Hodges JR. Limbic hypometabolism in Alzheimer's disease and mild cognitive impairment. *Annals of Neurology*. 2003;54(3):343-351. doi:10.1002/ana.10669

394. Bailly M, Destrieux C, Hommet C, et al. Precuneus and Cingulate Cortex Atrophy and Hypometabolism in Patients with Alzheimer's Disease and Mild Cognitive Impairment: MRI and ^{18}F-FDG PET Quantitative Analysis Using FreeSurfer. *BioMed Research International*. 2015;2015:e583931. doi:10.1155/2015/583931

395. Nestor PJ, Fryer TD, Ikeda M, Hodges JR. Retrosplenial cortex (BA 29/30) hypometabolism in mild cognitive impairment (prodromal Alzheimer's disease). *European Journal of Neuroscience*. 2003;18(9):2663-2667. doi:10.1046/j.1460-9568.2003.02999.x

396. Wise EA, Rosenberg PB, Lyketsos CG, Leoutsakos JM. Time course of neuropsychiatric symptoms and cognitive diagnosis in National Alzheimer's Coordinating Centers

volunteers. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*. 2019;11:333-339. doi:10.1016/j.dadm.2019.02.006

397. Weissberger GH, Melrose RJ, Narvaez TA, Harwood D, Mandelkern MA, Sultzer DL. 18F-Fluorodeoxyglucose Positron Emission Tomography Cortical Metabolic Activity Associated with Distinct Agitation Behaviors in Alzheimer Disease. *The American Journal of Geriatric Psychiatry*. 2017;25(6):569-579. doi:10.1016/j.jagp.2017.01.017

398. Brendel M, Pogarell O, Xiong G, et al. Depressive symptoms accelerate cognitive decline in amyloid-positive MCI patients. *Eur J Nucl Med Mol Imaging*. 2015;42(5):716-724. doi:10.1007/s00259-014-2975-4

399. Ballarini T, Iaccarino L, Magnani G, et al. Neuropsychiatric subsyndromes and brain metabolic network dysfunctions in early onset Alzheimer's disease: Behavior, Brain Metabolism in Early Onset AD. *Hum Brain Mapp*. 2016;37(12):4234-4247. doi:10.1002/hbm.23305

400. Smith GS, Kramer E, Ma Y, et al. The functional neuroanatomy of geriatric depression. *International Journal of Geriatric Psychiatry*. 2009;24(8):798-808. doi:10.1002/gps.2185

401. Ng KP, Chiew HJ, Rosa-Neto P, Kandiah N, Ismail Z, Gauthier S. Brain Metabolic Dysfunction in Early Neuropsychiatric Symptoms of Dementia. *Front Pharmacol*. 2019;10:1398. doi:10.3389/fphar.2019.01398

402. Caselli RJ, Chen K, Lee W, Alexander GE, Reiman EM. Correlating Cerebral Hypometabolism With Future Memory Decline in Subsequent Converters to Amnestic Pre–Mild Cognitive Impairment. *Archives of Neurology*. 2008;65(9):1231-1236. doi:10.1001/archneurol.2008.1

403. Choi H, Jin KH. Predicting cognitive decline with deep learning of brain metabolism and amyloid imaging. *Behavioural Brain Research*. 2018;344:103-109. doi:10.1016/j.bbr.2018.02.017

404. Walhovd KB, Fjell AM, Dale AM, et al. Multi-modal imaging predicts memory performance in normal aging and cognitive decline. *Neurobiology of Aging*. 2010;31(7):1107-1121. doi:10.1016/j.neurobiolaging.2008.08.013

405. Petersen RC, Roberts RO, Knopman DS, et al. Prevalence of mild cognitive impairment is higher in men: The Mayo Clinic Study of Aging. *Neurology*. 2010;75(10):889-897. doi:10.1212/WNL.0b013e3181f11d85

406. Morris JC. Clinical Dementia Rating: A Reliable and Valid Diagnostic and Staging Measure for Dementia of the Alzheimer Type. *International Psychogeriatrics*. 1997;9(S1):173-176. doi:10.1017/S1041610297004870

407. Lemaire C, Damhaut Ph, Lauricella B, et al. Fast [18F]FDG synthesis by alkaline hydrolysis on a low polarity solid phase support. *Journal of Labelled Compounds and Radiopharmaceuticals*. 2002;45(5):435-447. doi:10.1002/jlcr.572

408. Yakushev I, Landvogt C, Buchholz HG, et al. Choice of reference area in studies of Alzheimer's disease using positron emission tomography with fluorodeoxyglucose-F18. *Psychiatry Res*. 2008;164(2):143-153. doi:10.1016/j.pscychresns.2007.11.004

409. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al. Automated Anatomical Labeling of Activations in SPM Using a Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain. *NeuroImage*. 2002;15(1):273-289. doi:10.1006/nimg.2001.0978

410. Devanand DP, Mikhno A, Pelton GH, et al. Pittsburgh Compound B (11C-PIB) and Fluorodeoxyglucose (18 F-FDG) PET in Patients With Alzheimer Disease, Mild Cognitive Impairment, and Healthy Controls. *J Geriatr Psychiatry Neurol*. 2010;23(3):185-198. doi:10.1177/0891988710363715

411. Lee HS, Choo IH, Lee DY, et al. Frontal Dysfunction Underlies Depression in Mild Cognitive Impairment: A FDG-PET Study. *Psychiatry Investig*. 2010;7(3):208-214. doi:10.4306/pi.2010.7.3.208

412. Youn H, Lee ES, Lee S, Suh S, Jeong HG, Eo JS. Regional glucose metabolism due to the presence of cerebral amyloidopathy in older adults with depression and mild cognitive impairment. *Journal of Affective Disorders*. 2018;239:30-36. doi:10.1016/j.jad.2018.06.029

413. Mosconi L, Perani D, Sorbi S, et al. MCI conversion to dementia and the APOE genotype: A prediction study with FDG-PET. *Neurology*. 2004;63(12):2332-2340. doi:10.1212/01.WNL.0000147469.18313.3B

414. Cabral C, Morgado PM, Campos Costa D, Silveira M. Predicting conversion from MCI to AD with FDG-PET brain images at different prodromal stages. *Computers in Biology and Medicine*. 2015;58:101-109. doi:10.1016/j.compbiomed.2015.01.003

415. Drzezga A, Grimmer T, Riemenschneider M, et al. Prediction of Individual Clinical Outcome in MCI by Means of Genetic Assessment and 18F-FDG PET. *Journal of Nuclear Medicine*. 2005;46(10):1625-1632.

416. Pagani M, Nobili F, Morbelli S, et al. Early identification of MCI converting to AD: a FDG PET study. *Eur J Nucl Med Mol Imaging*. 2017;44(12):2042-2052. doi:10.1007/s00259-017-3761-x

417. Inui Y, Ito K, Kato T, Group SJS. Longer-Term Investigation of the Value of 18F-FDG-PET and Magnetic Resonance Imaging for Predicting the Conversion of Mild Cognitive Impairment to Alzheimer's Disease: A Multicenter Study. *Journal of Alzheimer's Disease*. 2017;60(3):877-887. doi:10.3233/JAD-170395

418. Ottoy J, Niemantsverdriet E, Verhaeghe J, et al. Association of short-term cognitive decline and MCI-to-AD dementia conversion with CSF, MRI, amyloid- and 18F-FDG-PET imaging. *NeuroImage: Clinical*. 2019;22:101771. doi:10.1016/j.nicl.2019.101771

419. Teng L, Li Y, Zhao Y, et al. Predicting MCI progression with FDG-PET and cognitive scores: a longitudinal study. *BMC Neurol*. 2020;20(1):148. doi:10.1186/s12883-020-01728-x

420. Panza F, Lozupone M, Bellomo A, Imbimbo BP. Do anti-amyloid-β drugs affect neuropsychiatric status in Alzheimer's disease patients? *Ageing Research Reviews*. 2019;55:100948. doi:10.1016/j.arr.2019.100948

421. Krell-Roesch J, Lowe VJ, Neureiter J, et al. Depressive and anxiety symptoms and cortical amyloid deposition among cognitively normal elderly persons: the Mayo Clinic Study of Aging. *Int Psychogeriatr*. 2018;30(2):245-251. doi:10.1017/S1041610217002368

422. Yasuno F, Kazui H, Morita N, et al. High amyloid-β deposition related to depressive symptoms in older individuals with normal cognition: a pilot study. *International Journal of Geriatric Psychiatry*. 2016;31(8):920-928. doi:10.1002/gps.4409

423. Ismail Z, Agüera-Ortiz L, Brodaty H, et al. The Mild Behavioral Impairment Checklist (MBI-C): A Rating Scale for Neuropsychiatric Symptoms in Pre-Dementia Populations. *Journal of Alzheimer's Disease*. 2017;56(3):929-938. doi:10.3233/JAD-160979

424. Lussier FZ, Pascoal TA, Chamoun M, et al. Mild behavioral impairment is associated with β-amyloid but not tau or neurodegeneration in cognitively intact elderly individuals. *Alzheimer's & Dementia*. 2020;16(1):192-199. doi:10.1002/alz.12007

425. Tommasi NS, Gonzalez C, Briggs D, et al. Affective symptoms and regional cerebral tau burden in early-stage Alzheimer's disease. *International Journal of Geriatric Psychiatry*. 2021;36(7):1050-1058. doi:10.1002/gps.5530

426. Babulal GM, Roe CM, Stout SH, et al. Depression is Associated with Tau and Not Amyloid Positron Emission Tomography in Cognitively Normal Adults. Published online 2021:19.

427. Yasuno F, Minami H, Hattori H, for the Alzheimer's Disease Neuroimaging Initiative. Relationship between neuropsychiatric symptoms and Alzheimer's disease pathology: An in vivo positron emission tomography study. *Int J Geriatr Psychiatry*. 2021;36(4):598-605. doi:10.1002/gps.5459

428. Jack CR, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *The Lancet Neurology*. 2013;12(2):207-216. doi:10.1016/S1474-4422(12)70291-0

429. Rizzolo L, Narbutas J, Van Egroo M, et al. Relationship between brain AD biomarkers and episodic memory performance in healthy aging. *Brain and Cognition*. 2021;148:105680. doi:10.1016/j.bandc.2020.105680

430. Mattis S. Dementia rating scale. Professional manual. Published online 1988.

431. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." *Journal of Psychiatric Research*. 1975;12(3):189-198. doi:10.1016/0022-3956(75)90026-6

432. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology*. 1988;56:893-897. doi:10.1037/0022-006X.56.6.893

433. Beck AT, Steer RA, Carbin MG. Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review*. 1988;8(1):77-100. doi:10.1016/0272-7358(88)90050-5

434. Narbutas J, Van Egroo M, Chylinski D, et al. Associations Between Cognitive Complaints, Memory Performance, Mood, and Amyloid-β Accumulation in Healthy Amyloid Negative Late-Midlife Individuals. *Journal of Alzheimer's Disease*. 2021;83(1):127-141. doi:10.3233/JAD-210332

435. Sarazin M, Chauviré V, Gerardin E, et al. The Amnestic Syndrome of Hippocampal type in Alzheimer's Disease: An MRI Study. *JAD*. 2010;22(1):285-294. doi:10.3233/JAD-2010-091150

436. Sánchez-Benavides G, Gómez-Ansón B, Molinuevo JL, et al. Medial Temporal Lobe Correlates of Memory Screening Measures in Normal Aging, MCI, and AD. *J Geriatr Psychiatry Neurol*. 2010;23(2):100-108. doi:10.1177/0891988709355271

437. Klunk WE, Koeppe RA, Price JC, et al. The Centiloid Project: Standardizing quantitative amyloid plaque estimation by PET. *Alzheimer's & Dementia*. 2015;11(1):1-15.e4. doi:10.1016/j.jalz.2014.07.003

438. Ishiki A, Harada R, Kai H, et al. Neuroimaging-pathological correlations of [18F]THK5351 PET in progressive supranuclear palsy. *Acta Neuropathologica Communications*. 2018;6(1):53. doi:10.1186/s40478-018-0556-7

439. Rolls ET, Huang CC, Lin CP, Feng J, Joliot M. Automated anatomical labelling atlas 3. *NeuroImage*. 2020;206:116189. doi:10.1016/j.neuroimage.2019.116189

440. Craik FIM, Salthouse TA. *The Handbook of Aging and Cognition: Third Edition*. Psychology Press; 2011.

441. Rentz DM, Mormino EC, Papp KV, Betensky RA, Sperling RA, Johnson KA. Cognitive resilience in clinical and preclinical Alzheimer's disease: the Association of Amyloid and Tau

Burden on cognitive performance. *Brain Imaging and Behavior*. 2017;11(2):383-390. doi:10.1007/s11682-016-9640-4

442. Ismail R, Parbo P, Madsen LS, et al. The relationships between neuroinflammation, beta-amyloid and tau deposition in Alzheimer's disease: a longitudinal PET study. *J Neuroinflammation*. 2020;17(1):151. doi:10.1186/s12974-020-01820-6

443. Narbutas J, Chylinski D, Van Egroo M, et al. Positive Effect of Cognitive Reserve on Episodic Memory, Executive and Attentional Functions Taking Into Account Amyloid-Beta, Tau, and Apolipoprotein E Status. *Frontiers in Aging Neuroscience*. 2021;13. Accessed August 7, 2023. https://www.frontiersin.org/articles/10.3389/fnagi.2021.666181

444. Folloni D, Sallet J, Khrapitchev AA, Sibson N, Verhagen L, Mars RB. Dichotomous organization of amygdala/temporal-prefrontal bundles in both humans and monkeys. Heilbronner S, Gold JI, Thiebaut de Schotten M, eds. *eLife*. 2019;8:e47175. doi:10.7554/eLife.47175

445. Ketz NA, Jensen O, O'Reilly RC. Thalamic pathways underlying prefrontal cortex-medial temporal lobe oscillatory interactions. *Trends Neurosci*. 2015;38(1):3-12. doi:10.1016/j.tins.2014.09.007

446. Neureiter J, Krell-Roesch J, Pink A, et al. Amyloid-β, Neuropsychiatric Symptoms and the Risk of Incident Mild Cognitive Impairment: A Prospective Cohort Study (S35.003). *Neurology*. 2016;86(16 Supplement). Accessed December 7, 2021. https://n.neurology.org/content/86/16_Supplement/S35.003

447. Apostolova L, Goukasian N, Do T, Grotts J, Ringman J, Elashoff D. Effect of Brain Amyloidosis on the Emergence of Neuropsychiatric Behaviors in MCI over Time (I12.012). *Neurology*. 2016;86(16 Supplement). Accessed December 7, 2021. https://n.neurology.org/content/86/16_Supplement/I12.012

448. Martínez NF, Allen IE, Kramer J, et al. Neuropsychiatric symptoms in early and late onset Alzheimer's Disease (2452). *Neurology*. 2021;96(15 Supplement). Accessed December 7, 2021. https://n.neurology.org/content/96/15_Supplement/2452

449. Murugan NA, Chiotis K, Rodriguez-Vieitez E, Lemoine L, Ågren H, Nordberg A. Cross-interaction of tau PET tracers with monoamine oxidase B: evidence from in silico modelling and in vivo imaging. *Eur J Nucl Med Mol Imaging*. 2019;46(6):1369-1382. doi:10.1007/s00259-019-04305-8

450. Harada R, Ishiki A, Kai H, et al. Correlations of 18F-THK5351 PET with Postmortem Burden of Tau and Astrogliosis in Alzheimer Disease. *Journal of Nuclear Medicine*. 2018;59(4):671-674. doi:10.2967/jnumed.117.197426