Vers une meilleure compréhension des facteurs psychoaffectifs (anxiété et dépression) dans le vieillissement normal et pathologique : liens avec la cognition et la neuroimagerie multimodale

Inès Moulinet

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Normandie Université

THÈSE

Pour obtenir le diplôme de doctorat

Spécialité SCIENCES DE LA VIE ET DE LA SANTE

Préparée au sein de l'Université de Caen Normandie

Vers une meilleure compréhension des facteurs psychoaffectifs (anxiété et dépression) dans le vieillissement normal et pathologique : liens avec la cognition et la neuroimagerie multimodale

Présentée et soutenue par
Ines MOULINET

Thèse soutenue publiquement le 04/12/2020 devant le jury composé de		
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La science pour la santé
From science to health

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Zone de la pensée
Le cerveau
Schéma détaillé

Liste des abbréviations

Aβ = Peptide Bêta Amyloïde

APOE = Apolipoprotéine E

APP = *Amyloïd Protein Precursor*

CA1= Corne d'Ammon 1

CDS = *Cognitive Difficulties Scale*

DNF = Dégénérescences Neuro-Fibrillaires

DRS = *Mattis Dementia Rating Scale*

DSM = *Diagnostic and Statistical Manual of mental disorders*

ESR = Encodage, Stockage, Récupération

FDG = 18F-fluoro-2-deoxyglucose

IMAP = Imagerie Multimodale de la maladie d'Alzheimer à un stade Précoce

IWG = *International Working Group for New Research Criteria for the Diagnosis of Alzheimer's*

IRM = Imagerie par Résonnance Magnétique

LCR = Liquide Céphalo-Rachidien

MA = Maladie d'Alzheimer

MADRS = *Montgomery-Åsberg Depression Rating Scale*

MCI = *Mild Cognitive Impairment*

MMSE = *Mini Mental State Examination*

NIA-AA = *National Institute of Aging and Alzheimer Association*

NINCDS-ADRDA = *National Institute of Neurological and Communicative Disorders and Stroke – the Alzheimer's Disease and Related Disorders Association*

OMS = Organisation Mondiale de la Santé

PIB = *Pittsburg Compound B*

ROI = *Region of Interest*

SCD = *Subjective Cognitive Decline*

SG = Substance Grise

SNP = Symptômes Neuropsychiatriques

STAI = *Spielberger State-Trait Anxiety Inventory*

Tau = *Tubule Associated Unit*

- P-Tau = Protéine Tau phosphorylée
- T- Tau = Protéine Tau totale

TEP = Tomographie par Emission de Positons

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1. Introduction générale

Le vieillissement est défini par l'OMS comme « l'accumulation d'un vaste éventail de dommages moléculaires et cellulaires au fil du temps ». Ces changements ne sont pas linéaires et sont accompagnés d'une diminution des capacités physiques et mentales, et bien souvent d'une augmentation de la fréquence de certaines maladies. En effet, certaines personnes profitent encore d'une bonne santé physique et mentale jusqu'à 70 ans ou plus, tandis que d'autres développent des pathologies, telles que les démences, les rendant plus fragiles et dépendantes.

En effet, la démence est une des pathologies contribuant le plus largement à l'incapacité des personnes âgées, et toucherait 50 millions de personnes dans le monde, et au vu du vieillissement actuel de la population, ces chiffres ne cessent d'augmenter. La Maladie d'Azheimer est la plus fréquente de ces démences puisqu'elle concernerait 70% des cas, avec une incidence de 180 000 nouveaux cas par an en France. Au vu de son impact sur la santé mentale et physique des personnes atteintes et de leurs aidants, ainsi que du coût individuel et sociétal qui en résulte, prévenir cette maladie encore aujourd'hui incurable est un des enjeux de la recherche.

Plusieurs facteurs de risque modifiables ont été mis en évidence pour cette maladie. Parmi eux, on retrouve l'état émotionnel, notamment les symptômes anxieux et dépressifs, qui même à un niveau infra-clinique et donc non pris en charge, sont plus fréquents chez les personnes âgées, et sont associés à une augmentation du risque de déclin cognitif et de démence. Cependant, ils pourraient également être des symptômes associés à une démence, et pourraient constituer une manifestation clinique de la pathologie sous-jacente.

Dans ce contexte, l'objectif de cette thèse est de mieux comprendre les symptômes anxieux et dépressifs, à la fois dans le vieillissement normal et au cours de la maladie d'Alzheimer. Nous décrirons tout d'abord l'état des connaissances actuelles sur le vieillissement cérébral et la maladie d'Alzheimer, avec un focus particulier sur les symptômes anxieux et dépressifs dans ces populations. Nous présenterons ensuite les objectifs de cette thèse, ainsi que les travaux qui ont été menés. Pour finir,

nous discuterons des modifications, et des substrats cérébraux, des symptômes anxieux et dépressifs dans le continuum menant du vieillissement normal au vieillissement pathologique qu'est la MA.

2. Cadre théorique

2.1. La maladie d'Alzheimer (MA)

2.1.1. Généralités

2.1.1.1. Historique

La démence de type Alzheimer est une maladie neurodégénérative décrite pour la première fois en 1906 par le neurologue allemand Aloïs Alzheimer, suite à l'autopsie d'une de ses patientes, Auguste Deter (Figure 1). Celle-ci fut hospitalisée en 1901 à Francfort, alors âgée de 51 ans, avec des symptômes démentiels évolutifs tels que des troubles de mémoire, de compréhension, du langage et une désorientation, ainsi que des comportements imprévisibles et des signes psychiatriques (paranoïa, hallucinations). Dans son article de 1907, le Dr. Alzheimer met en lien ces symptômes cliniques avec les modifications cérébrales observées *post mortem*, telles que l'atrophie cérébrale, mais surtout les principales lésions neuropathologiques qui définissent la maladie, les plaques amyloïdes et les dégénérescences neurofibrillaires. Plus de 110 ans plus tard, bien que ces modifications soient relativement bien connues, l'autopsie est toujours le seul moyen de poser un diagnostic avéré de la maladie, et aucun traitement curatif n'a encore été développé.

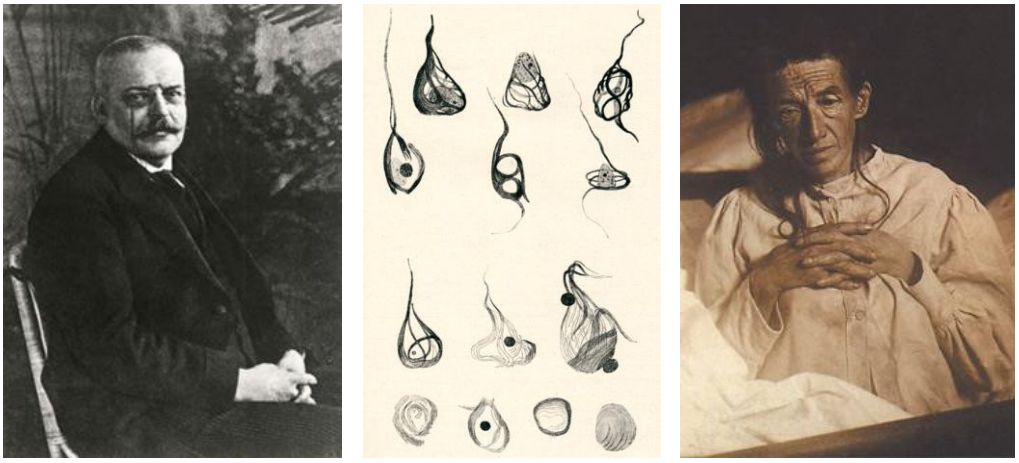

Figure 1 : Portraits d'Alois Alzheimer (gauche) et d'Auguste Deter (droite), accompagné d'un dessin représentant les observations histopathologiques du neurologue lors de l'autopsie de sa patiente (centre).

2.1.1.2. Incidence et prévalence

La démence est une pathologie liée à l'âge, qui contribue notamment le plus à l'incapacité des personnes âgées. Selon l'OMS, elle concerne plus de 50 millions de personnes dans le monde, et pourrait même tripler d'ici 2050 pour atteindre plus de 131 millions. Au vu du vieillissement de la population et de son impact sur la société, c'est donc aujourd'hui un enjeu majeur de santé publique. La MA apparaît comme la principale cause de démence du sujet âgé, puisqu'une étude épidémiologique sur des personnes âgées suivies depuis 1988 dans le sud-ouest de la France montre que près de 80% des patients déments présenteraient un diagnostic clinique de MA (Ramaroson et al., 2003). En France, la démence concernerait entre 1 000 000 et 1 500 000 (Dementia in Europe Yearbook, 2016) et son incidence est estimée à 225 000 nouveaux cas par an (Helmer et al., 2006), soit environ 180 000 cas de MA. Si l'on inclut l'entourage familial, ce sont ainsi près de trois millions de personnes qui sont directement touchées par la maladie. De plus, celle-ci augmenterait fortement avec l'âge, doublant tous les 5 à 6 ans après l'âge de 65 ans (Querfurth & LaFerla, 2010) et ce dans le monde entier (Ziegler-Graham et al., 2008). Il est à noter que la MA reste cependant sous-diagnostiquée, puisque à « déclaration non obligatoire » et selon le rapport d'expertise Inserm réalisé en 2007, seule la moitié des patients MA français seraient effectivement diagnostiqués, ce qui complique l'estimation de la prévalence et de l'évolution de l'incidence de la maladie.

Malgré ce constat alarmant, on observe une légère diminution des taux d'incidence de la MA, notamment aux Etats-Unis, au cours de ces 10-20 dernières années (Grasset et al., 2016; Matthews et al., 2013; Schrijvers et al., 2012), qui pourrait être liée à une meilleure prévention, notamment cardiovasculaire. Pour finir, l'OMS estime que les prévisions d'augmentation d'incidence de la démence concernent principalement les pays à revenu faible ou intermédiaire.

2.1.1.3. Facteurs de risque et de protection

La maladie d'Alzheimer est toujours pour l'instant incurable et ses origines sont encore mal comprises. C'est pourquoi identifier les facteurs de risque qui amènent à développer la MA est si important à cette étape de compréhension de la maladie, afin d'identifier les sujets les plus à risque, facilitant ainsi l'étude des stades précoces de la maladie. De plus, la mise en évidence de facteurs de risque modifiables ou de facteurs de protection, pourrait permettre de retarder l'apparition ou l'évolution de la maladie. Pour le moment, plusieurs facteurs de risque de démence ont été identifiés (Figure 2) et on estime que près de la moitié des cas de démences sont associés à des facteurs modifiables (Ashby-Mitchell et al., 2017; Norton et al., 2014; pour revue Serrano-Pozo & Growdon, 2019). Si ces cas étaient pris en charge en termes de prévention, une réduction de 10 à 20% de ces facteurs pourrait éviter entre 1,1 et 3,0 millions de cas (Barnes & Yaffe, 2011).

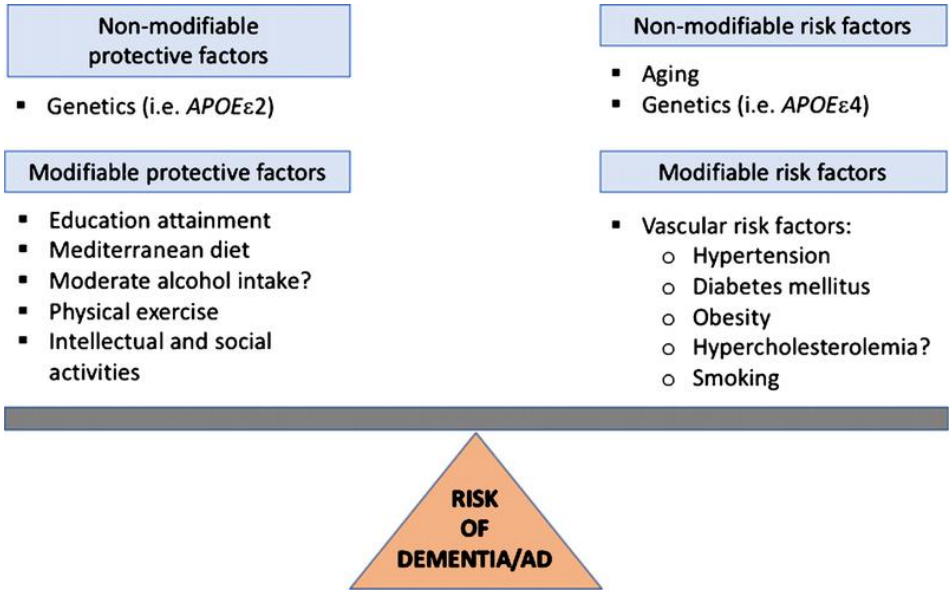

Figure 2 : Schéma représentant le risque de démence et de maladie d'Alzheimer comme un équilibre entre les facteurs de protection et de risque modifiables et non modifiables, *d'après Serrano-Pozo et Growdon, 2019*.

2.1.1.3.1. Non modifiables

Comme nous l'avons vu précédemment, le facteur de risque principal dit « non modifiable » de développement d'une démence est l'avancée en âge (Winblad et al., 2016). Le sexe est également déterminant puisqu'on observe une prévalence plus élevée de démence chez les femmes, principalement après 80 ans (Hebert et al., 2001; Letenneur et al., 1999; Miech et al., 2002). Cependant, cette différence pourrait être expliquée par la plus grande longévité des femmes (Helmer et al., 2006; Letenneur et al., 1999) ou par des différences hormonales ou culturelles (pour revues Grimm et al., 2016; Mielke et al., 2014).

Il a été établi que les antécédents familiaux de MA constituent un risque important de développer la pathologie (Fratiglioni et al., 1993; Green et al., 2002; Mayeux et al., 1991), particulièrement si c'est un parent au premier degré et si les deux parents sont concernés (Lautenschlager et al., 1996). Ces résultats suggèrent donc l'existence de mécanismes génétiques de vulnérabilité à la MA.

En effet, bien que cette maladie soit en grande majorité sporadique et non héréditaire (la forme héréditaire ne sera pas discutée dans cette thèse), le polymorphisme du gène de l'apolipoprotéine E (APOE) a été identifié comme le principal facteur de susceptibilité génétique de la MA. Ce gène, situé sur le chromosome 19, peut présenter 3 allèles, qui portent chacun un degré de risque ou de protection différent. La forme ε3 de l'allèle, la plus courante (présent chez 75 à 80 % de la population générale), est considérée comme « neutre », tandis que la forme ε4 (présent chez environ 15 % de la population générale) est le facteur de risque génétique le plus important de la MA sporadique (Cedazo-Mínguez & Cowburn, 2001; Corder et al., 1993; Farrer et al., 1997; Genin et al., 2011; Zannis & Breslow, 1982), et le risque est d'autant plus important que cet allèle est présent de manière homozygote (Farrer et al., 1997). La forme ε2 quant à elle, présente chez 7 à 8 % de la population générale (Cedazo-Mínguez & Cowburn, 2001; Zannis & Breslow, 1982), est un facteur protecteur de développement de la MA (Corder et al., 1994). Plus récemment, d'autres gènes ont été identifiés, notamment impliqués dans le système immunitaire (PLD3 et PICALM), dans la production ou l'élimination de l'amyloïde (TREM2,

SORL1 et ABCA7)(Cruchaga et al., 2014; Guerreiro et al., 2013; Lambert et al., 2013, 2015; Le Guennec et al., 2016; Vardarajan et al., 2015; Winblad et al., 2016).

2.1.1.3.2. Modifiables

Les autres facteurs sont dits « modifiables » car ils peuvent être influencés, pharmacologiquement ou non, dans un cadre de prévention. On retrouve parmi ceux-ci des facteurs liés à la santé, notamment les facteurs de risque cardio-vasculaires tels que l'hypertension (Kennelly et al., 2009; Kloppenborg et al., 2008; Purnell et al., 2009; Qiu et al., 2005), le diabète (Biessels et al., 2006; Kloppenborg et al., 2008; Kopf & Frölich, 2009; Profenno et al., 2010), l'obésité (Beydoun et al., 2008), ou la présence de troubles du sommeil (Branger et al., 2016; Peter-Derex et al., 2015) ou de troubles psychoaffectifs anxieux ou dépressifs (Burke et al., 2018; Chan et al., 2011; Gulpers et al., 2016; Palmer et al., 2007; Petkus et al., 2016; Santabárbara et al., 2020; Steck et al., 2018; Wilson et al., 2002). On peut également citer des facteurs de vie tels que le tabagisme (Barnes et al., 2010; Cataldo et al., 2010; Chen, 2012; Peters et al., 2008; Zhong et al., 2015), le régime alimentaire (Barberger-Gateau et al., 2007; Barnard et al., 2014; Morris et al., 2015; Panza et al., 2010; Solfrizzi et al., 2010), et l'activité physique (Barnes & Yaffe, 2011; Beydoun et al., 2014; Blondell et al., 2014; Stephen et al., 2017) ou cognitive (Barnes & Yaffe, 2011; Caamaño-Isorna et al., 2006; Fratiglioni et al., 2004; Imtiaz et al., 2014; Valenzuela, 2008; Valenzuela et al., 2008). De façon intéressante plusieurs de ces facteurs sont liés entre eux et pourraient donc être cible de prévention efficace.

2.1.2. Modifications neuropsychologiques

2.1.2.1. Dans le vieillissement

Le vieillissement normal est associé à un déclin graduel des capacités cognitives. Il touche des domaines spécifiques comprenant la vitesse de traitement, les fonctions exécutives, la mémoire de travail, et la mémoire épisodique (Buckner, 2004; Nyberg et al., 2012; Park & Reuter-Lorenz, 2008; Rabbitt et al., 2001; Salthouse & Czaja, 2000; Salthouse, 2003; Schretlen et al., 2000; Tulving et al., 2004), tandis que d'autres fonctions telles que les capacités verbales, la connaissance des mots et la

mémoire procédurale sont relativement préservées (Park & Reuter-Lorenz, 2008; Tulving et al., 2004). Concernant certains de ces processus, tels que la recollection et le fonctionnement exécutif.

De plus, le déclin n'est pas toujours linéaire. En effet, le déclin de la mémoire épisodique débute à partir de 50–60 ans (Nyberg et al., 2012) tandis que la mémoire sémantique est préservée jusqu'à un âge avancé, et ne décline que chez les personnes très âgées (Peters, 2006).

2.1.2.2. Profil caractéristique de la maladie d'Alzheimer

Les patients atteints de MA présentent des modifications cognitives caractéristiques, différentes de celles retrouvées au cours du vieillissement normal. Les premières définitions de la maladie, ainsi que ses critères diagnostiques (voir section 2.3), placent les troubles mnésiques au centre du tableau clinique de MA (Eustache et al., 2006). Ils sont d'ailleurs présents dès le stade MCI (Eustache et al., 2006; Nestor et al., 2004) et touchent principalement la mémoire épisodique dans les cas typiques de MA. L'atteinte de la mémoire épisodique concerne ses différentes composantes, c'est-à-dire à la fois l'encodage, le stockage et la récupération (Carlesimo & Oscar-Berman, 1992; Eustache et al., 2006; Salmon & Bondi, 2009). En opposition aux troubles dits « apparents » retrouvés dans le vieillissement normal, qui sont plutôt liés à des troubles de récupération de l'information, les troubles de la mémoire épisodique dans la MA sont dits « authentiques » puisque même dans les conditions de rappel indicé ou de reconnaissance, les performances de rappel ne sont que peu améliorées chez les patients MA (pour revue Isingrini & Taconnat, 2008). De plus, les intrusions sont fréquentes (Butters et al., 1987; Fuld et al., 1982; Jacobs et al., 1990), ce qui pourrait être dû à des déficits d'inhibition (Weintraub et al., 2012), ainsi qu'à de fausses reconnaissances (Hildebrandt et al., 2009).

En effet, des troubles de l'attention et des fonctions exécutives sont également mis en évidence de manière précoce dans la MA (pour revue Perry & Hodges, 1999), et touchent l'attention divisée (Perry & Hodges, 1999), la flexibilité mentale (Amieva et al., 1998; Baudic et al., 2006), l'inhibition de processus automatiques (Amieva et al., 2004; Binetti et al., 1996; Collette et al., 1999; Perry et al., 2000; Spieler et al., 1996) ainsi que la planification (Franceschi et al., 2007; Lange et al., 1995).

Ces troubles cognitifs s'étendent à la mémoire de travail (Belleville et al., 1996; Collette et al., 1999; Huntley & Howard, 2010) et à la mémoire sémantique (Adlam et al., 2006; Aronoff et al., 2006; Chertkow et al., 2008; Henry et al., 2004; Hodges & Patterson, 1995) avec l'avancée de la maladie, tandis que la mémoire procédurale et le système de représentations perceptives sont relativement préservés, jusqu'à des stades avancés de la maladie (Desgranges et al., 1996; Eustache et al., 2006; Hirono et al., 1997; Salmon & Bondi, 2009; van Halteren-van Tilborg et al., 2007).

2.1.3. Neuropathologie

Depuis 1907, la MA se caractérise par des processus neuropathologiques distincts maintenant bien connus. Les premiers, dits par lésions positives, sont liés à une accumulation et comprennent les dépôts extracellulaires de protéine β-amyloïde (Aβ) et les dégénérescences neurofibrillaires (DNF) intra-neuronales, qui forment les plaques séniles. Les lésions dites négatives sont quant à elles dues à des pertes neuronales et synaptiques. Les lésions positives constituent la base du diagnostic, tandis que les lésions négatives, moins spécifiques, ne sont associées à la MA qu'en présence de dépôts amyloïdes et de DNF (pour revue Duyckaerts et al., 2009).

2.1.3.1. Pathologie Amyloïde

2.1.3.1.1. Le peptide Aβ

Bien que le peptide amyloïde soit produit de façon naturelle dans le cerveau (Seubert et al., 1992; Shoji et al., 1992), on observe dans le cadre de la maladie d'Alzheimer une accumulation extracellulaire de dépôts de cette protéine (Figure 3). Ce peptide appelé β-Amyloïde est issu d'un double clivage de la protéine transmembranaire APP (*β-Amyloid Precurseur Protein*), tout d'abord par la β-sécrétase (dans son domaine extracellulaire), produisant un fragment C99, lui-même clivé par la γ-sécrétase, résultant en l'APP (Duyckaerts et al., 2009). Ce clivage n'est pas toujours identique et peut produire 2 isoformes de l'Aβ, le plus fréquent (80 à 90 %) étant l'Aβ40, composé de 40 acides aminés, tandis que l'Aβ42, composé de 42 acides aminés, n'est produit qu'à hauteur de 5 à 10% (Thinakaran & Koo, 2008).

Dans le processus pathologique, les peptides β-Amyloïde s'enrichissent en feuillets β-plissés, les rendant insolubles, résultant en une agrégation et une formation de dépôts amyloïdes. Or, l'isoforme l'Aβ42 est plus enclin à s'agréger en fibrilles du fait de sa nature hydrophobe (Burdick et al., 1992; Jarrett et al., 1993), qui prennent ensuite plus facilement une conformation en feuillets β-plissés constituant les dépôts amyloïdes cérébraux diffus (Ittner & Götz, 2011; Querfurth & LaFerla, 2010). Les oligomères préfibrillaires, alors solubles, peuvent quant à eux provoquer des dysfonctionnements cellulaires et synaptiques, les rendant plus toxiques que les dépôts eux-mêmes (Sakono & Zako, 2010; Walsh & Selkoe, 2007).

2.1.3.1.2. Topographie des dépôts de peptide Aβ

L'accumulation de ces formes insolubles de peptides Aβ n'est pas homogène dans le cerveau, et suit une progression hiérarchisée, d'abord décrite en 1991 par Braak et Braak (Braak & Braak, 1991). Ils décrivent 3 stades de progression (Figure 3), commençant dans les aires néocorticales orbito-frontales, temporales et occipitales au stade A, s'étendant ensuite au reste du lobe frontal et au lobe pariétal (et de façon moindre à l'hippocampe) au cours du stade B, pour finir par toucher l'ensemble du néocortex au stade C.

Une décennie plus tard, Thal et collaborateurs (2002) ont redéfini cette propagation de façon plus détaillée, distinguant 5 phases différentes (Figure 3). La première correspond à l'accumulation de dépôts amyloïdes dans le néocortex frontal, pariétal, temporal et occipital, tandis qu'au cours de la phase 2, ils touchent spécifiquement le cortex entorhinal, le champ CA1 de l'hippocampe et l'insula, voire chez certains individus (33 à 55 %), l'amygdale et le cortex cingulaire. Au cours de la phase 3, les dépôts se propagent aux noyaux sous-corticaux (noyaux caudés, le putamen, le thalamus, et l'hypothalamus) et la substance blanche, puis aux noyaux du tronc cérébral (*substantia nigra*, colliculus supérieur et inférieur) dans la phase 4. Pour finir, dans la phase 5, l'accumulation de peptides amyloïdes atteint le pont et le cervelet (Thal et al., 2002).

Il est à noter que ce processus débute bien avant la déclaration des premiers symptômes, puisqu'au cours de l'étude de Thal et collaborateurs, 9 sujets considérés sains révélaient une accumulation de dépôts de phase 1 à 3 (Thal et al., 2002). De plus, les études clinico-pathologiques ne montrent pas de corrélation entre dépôts amyloïdes et symptômes de MA (Ingelsson et al., 2004).

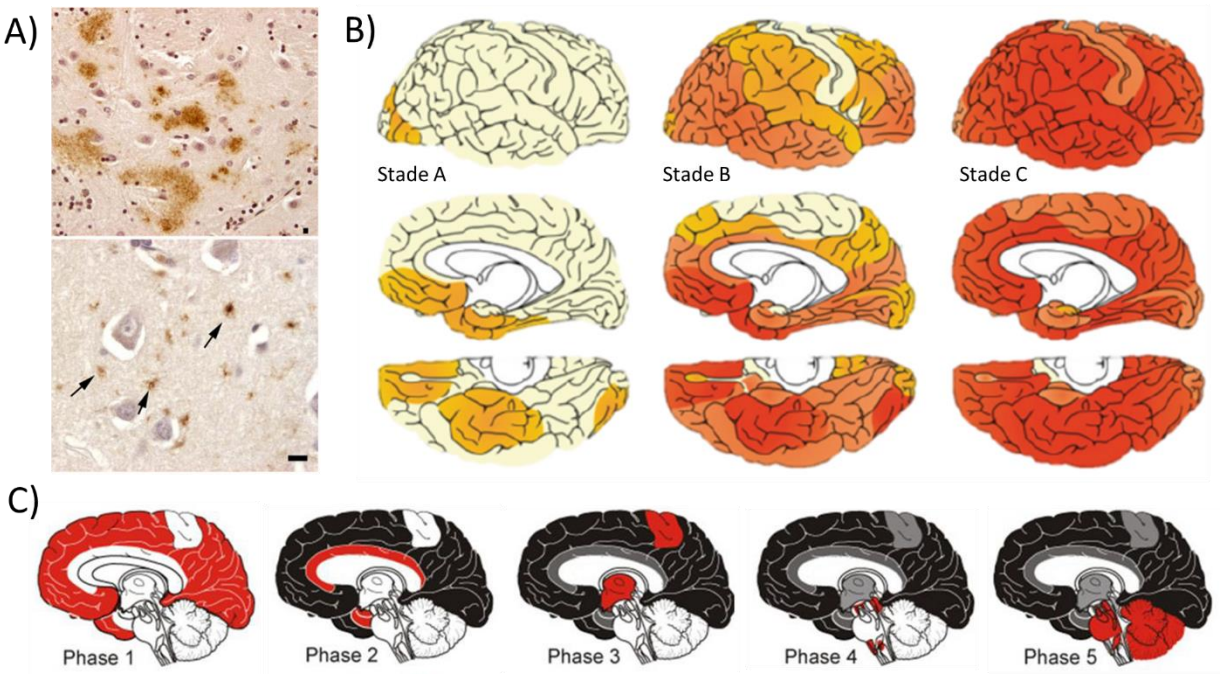

Figure 3 : Histologie et topographie de la pathologie amyloïde.
A) Histologie et microscopie des dépôts amyloïdes, *d'après Duyckaerts et al., 2009*; B) Topographie des stades de déposition des plaques amyloïdes en 3 stades, *d'après Braak et Braak, 1991* ; C) Topographie des stades de déposition des plaques amyloïdes en 5 phases, *d'après Thal et al., 2002.*

2.1.3.2. Pathologie Tau

2.1.3.2.1. Composition des dégénérescences neurofibrillaires (DNF)

La protéine tau (*Tubulin-Associated Unit*) fait partie des protéines associées aux microtubules (dites protéines MAP pour *Microtubule-Associated Proteins*). Dans des conditions physiologiques normales, le rôle principal de la protéine tau est de réguler l'assemblage et la stabilisation des microtubules, via des systèmes de phosphorylation, et influe donc sur la croissance dendritique et le trafic intracellulaire (Billingsley & Kincaid, 1997). Dans des conditions pathologiques comme la MA, la protéine tau est

hyperphosphorylée (Grundke-Iqbal et al., 1986; Ihara et al., 1986) dans le compartiment somato-dendritique, ce qui provoque le détachement des microtubules et leur agrégation en paires de filaments en intracellulaire (Figure 4). Cette désorganisation conduit à la perturbation du transport axonal puis à la mort cellulaire (Ballatore et al., 2007; Ittner & Götz, 2011; Querfurth & LaFerla, 2010). Cette accumulation de tau porte différents noms selon le compartiment cellulaire dans lequel il est observé. Dans le corps cellulaire du neurone elle compose les dégénérescences neurofibrillaires (DNF), dans les dendrites elle forme les fibres tortueuses (« *neuropil threads* ») et au niveau des extrémités axonales elle constitue la « couronne » des plaques dendritiques (Duyckaerts et al., 2009; Lace et al., 2009).

2.1.3.2.2. Topographie des DNF

Tout comme les dépôts de protéines Aβ, l'apparition des DNF suit une progression spatio-temporellement stéréotypée, décrite également en 1991 par Braak et Braak. Les auteurs ont défini 6 stades (Figure 4). Au cours du stade I, les lésions sont présentes au niveau du cortex transentorhinal, puis se propagent au stade II vers le cortex entorhinal et, bien que dans une moindre mesure, dans l'hippocampe. Lors du stade III, les lésions touchent entièrement l'hippocampe ainsi que le thalamus et l'amygdale, puis s'étendent progressivement au néocortex associatif au stade IV et V, pour finalement atteindre tout le cerveau au stade 6 (Braak & Braak, 1991). Ces stades peuvent être regroupés en 3 phases principales, les stades I et II formant le *transentorhinal stage*, les stades III et IV composant le *limbic stage*, et les stades V et VI formant l'*isocortical stage*.

Une dizaine d'années plus tard, ces stades ont été redétaillés en 10 stades (S1 à 10) par Delacourte et collaborateurs (Delacourte et al., 1999 ; Figure 4). Cette propagation, similaire aux stades de Braak et Braak, commence dans le cortex entorhinal (S1), continue dans le cortex entorhinal (S2), puis l'hippocampe (S3), avant d'atteindre le cortex temporal antérieur (S4), inférieur (S4) puis moyen (S6). Ensuite (S7), les DNF se propagent au cortex cingulaire et aux aires polymodales d'association (temporal supérieur, pariétal inférieur et frontal antérieur), pour finir par toucher l'aire de Broca (S8), le cortex moteur et les aires occipitales (S9) avant d'atteindre l'intégralité du néocortex (S10). D'un

point de vue clinique, les déficits cognitifs n'apparaitraient qu'à partir des stades S3 à S6 et la démence s'installerait pour la plupart à partir du stade S7, tandis que les premiers stades (S1 et S2) resteraient asymptomatiques (Delacourte et al., 1999).

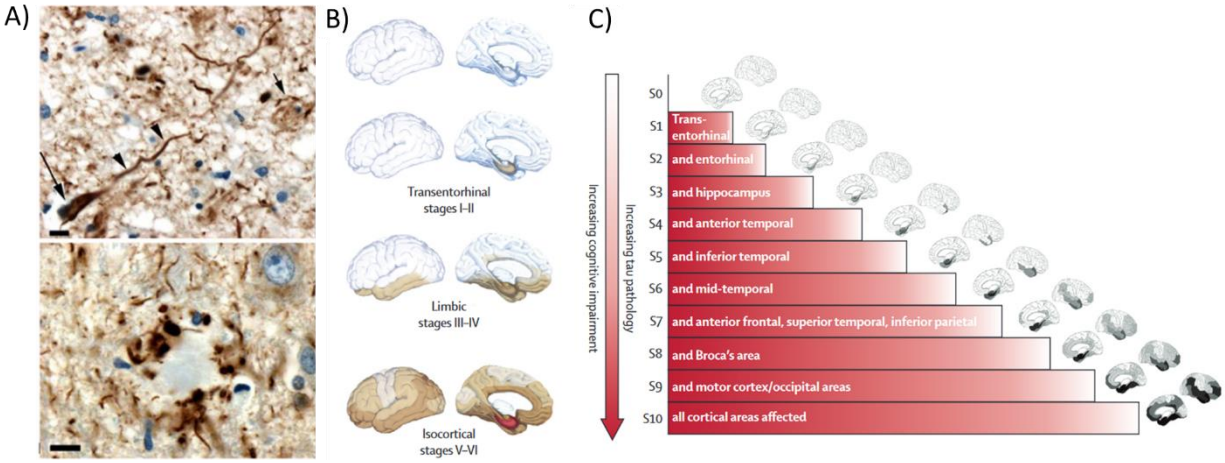

Figure 4 : Histologie et topographie de la pathologie tau.

A) Histologie et microscopie des DNF, *d'après Duyckaerts et al., 2009*; B) Topographie des DNF découpée en 3 stades par Braak et Braak en 1991, *d'après Villemagne et al., 2015* ; C) Topographie des DNF affinée en 10 stades en 2020 par Delacourte et collaborateurs*, d'après Villemagne et al., 2015.*

2.1.3.3. Pertes neuronales et synaptiques

L'atrophie cérébrale, longtemps considérée comme la modification principale de la maladie, est sous-tendue par une perte neuronale et synaptique. Ces pertes touchent principalement le lobe temporal interne, notamment le cortex entorhinal (jusqu'à 90% de perte) (Gómez-Isla et al., 1996) et l'hippocampe (principalement le sous-champ CA1) de façon précoce (Padurariu et al., 2012; Scheff & Price, 2006; West et al., 1994). Elles ont également été mises en évidence dans le lobe temporal externe au niveau temporal supérieur, dans les régions frontales et le gyrus supramarginal (DeKosky & Scheff, 1990; Gómez-Isla et al., 1997; Grignon et al., 1998; Scheff & Price, 2006).

La littérature n'est cependant pas encore unanime quant à leur origine, puisque certaines études font l'hypothèse qu'elles seraient une conséquence de la pathologie tau (Falke et al., 2003; Fukutani et al., 2000; Grignon et al., 1998; Jadhav et al., 2015; Rössler et al., 2002), tandis que d'autres pensent

qu'elles seraient dues à la pathologie amyloïde sous forme soluble (Pozueta et al., 2013; Tu et al., 2014).

De même, certaines études montrent l'implication des pertes neuronales et synaptiques dans l'apparition les symptômes cognitifs (Gómez-Isla et al., 1997), tandis que d'autres indiquent que l'atrophie n'apparaitrait qu'après leur manifestation (Grignon et al., 1998).

2.2. Neuroimagerie du vieillissement normal et de la MA

2.2.1. Volume de substance grise mesuré en Imagerie par Résonance Magnétique (IRM)

2.2.1.1. Le vieillissement normal

L'Imagerie par Résonance magnétique (IRM) structurale est une méthode d'imagerie non invasive, qui permet de mesurer les changements morphologiques *in vivo*. Elle permet notamment de mesurer le volume ou la densité de substance grise à l'échelle du cerveau entier ou dans des régions spécifiques, afin d'en visualiser l'atrophie due à une perte de neurones, de synapses et à une atteinte dendritique (Murray et al., 2014). Au cours du vieillissement normal ou « physiologique », on observe une diminution globale du volume cérébral de 0.2 à 0.5% par an en moyenne (Enzinger et al., 2005; Ezekiel et al., 2004; Fjell et al., 2014; Fotenos et al., 2005; Hedman et al., 2012; Scahill et al., 2003), dont l'amplitude diffère selon les régions (Driscoll et al., 2009; Fjell et al., 2009), mais aussi un élargissement des espaces ventriculaires contenant le liquide céphalo-rachidien (Raz et al., 2005). L'amplitude d'atrophie suit un gradient antéro-postérieur, touchant principalement les régions frontales (Fjell et al., 2009, 2014; Kalpouzos et al., 2009; Lockhart & DeCarli, 2014; Raz et al., 2005; Salat et al., 2004), ainsi que les régions temporales, telles que l'hippocampe et le cortex entorhinal (Driscoll et al., 2009; Ezekiel et al., 2004; Fjell et al., 2009, 2014; Giorgio et al., 2010; Pfefferbaum et al., 2013; Raz et al., 2005, 2010), et, bien que dans une moindre mesure, les lobes pariétaux et occipitaux (Fjell et al., 2014; Giorgio et al., 2010; Kalpouzos et al., 2009; Lockhart & DeCarli, 2014; Raz et al., 2005; Salat et al., 2004).

2.2.1.2. La maladie d'Alzheimer

Les patients atteints de MA présentent également une atrophie cérébrale, dont la séquence est caractéristique. En effet, contrairement aux sujets âgés sains, les patients MA présentent principalement une atrophie temporale interne, notamment de l'hippocampe (Chetelat & Baron, 2003; Colliot et al., 2008). Elle s'étend ensuite aux régions temporales et pariétales, pour finalement atteindre les aires multimodales aux stades les plus avancés de la pathologie (Apostolova et al., 2007; Apostolova & Thompson, 2008; Dickerson et al., 2009; Frisoni et al., 2009; La Joie et al., 2012; Lerch et al., 2005; Pini et al., 2016; Prestia et al., 2010; Schroeter et al., 2009; Singh et al., 2006) (voir figure 5). Parmi ces régions, l'hippocampe est particulièrement étudié dans le cadre de la MA du fait de son atteinte très précoce. En effet, on retrouve une atrophie hippocampique dès le stade MCI dans le sous-champ CA1 (Apostolova et al., 2010; Chételat et al., 2008; Frisoni et al., 2008; Kerchner et al., 2013; La Joie et al., 2013; Wang et al., 2006; West et al., 2004), qui s'étend ensuite aux autres sous-champs avec l'avancée de la maladie (de Flores et al., 2015).

En plus de l'hippocampe, les patients MCI présentent des modifications structurales dans le néocortex temporo-pariétal et le cortex cingulaire postérieur (Chételat et al., 2002; Risacher et al., 2009; Whitwell et al., 2007), qui seraient encore plus marquées chez les MCI convertissant vers une MA (Chételat et al., 2005; Karas et al., 2008; Risacher et al., 2009; Whitwell et al., 2008). Cependant, l'atrophie temporale interne reste la plus prédictive d'une conversion vers la MA (Ferreira et al., 2011). C'est donc un biomarqueur pertinent de MA puisqu'il est également très corrélé à la pathologie tau (Burton et al., 2009; Csernansky et al., 2004; Whitwell et al., 2008), bien que les liens avec l'amyloïde soient plus discutés (Bourgeat et al., 2010; Burton et al., 2009; Chételat et al., 2010; Csernansky et al., 2004; Mormino et al., 2009; Rowe et al., 2010), et qu'il soit peu spécifique car il est retrouvé dans d'autres pathologies (Geuze et al., 2005; Small et al., 2011).

2.2.2. Métabolisme du glucose mesuré en Tomographie par émission de positons (TEP)

2.2.2.1. Le vieillissement normal

De même que l'IRM, la Tomographie par Emission de Positons (TEP) est une méthode d'imagerie qui permet de visualiser des modifications cérébrales *in vivo*. C'est une technique cependant plus invasive, puisqu'elle nécessite l'injection de radiotraceurs émetteurs de positons dans la circulation sanguine, dont on mesure ensuite la répartition dans les tissus. Couplée au radiotraceur 18F-fluoro-2-deoxyglucose (TEP-FDG), la TEP permet de visualiser la consommation cérébrale du glucose au repos, qui reflète l'activité synaptique (Segobin et al., 2015).

Au cours du vieillissement normal, on observe une diminution globale du métabolisme du glucose cérébral (Bentourkia et al., 2000; Willis et al., 2002), avec un hypométabolisme dans l'insula, les régions temporales, pariétales, et particulièrement les régions frontales, notamment le cortex préfrontal et cingulaire antérieur (Chételat et al., 2013; Herholz et al., 2002; Hsieh et al., 2012; Kakimoto et al., 2016; Kalpouzos et al., 2009; Malpetti et al., 2017; Pardo et al., 2007; Willis et al., 2002; Yoshizawa et al., 2014 ; pour revue Berti et al., 2014). D'autres régions sont au contraire relativement préservées, telles que le cortex occipital et les régions médiales, le précunéus, l'hippocampe et parahipoccampe, l'amygdale, le thalamus et le cervelet (Herholz et al., 2002; Kalpouzos et al., 2009; Willis et al., 2002).

2.2.2.2. La maladie d'Alzheimer

Le profil de consommation de glucose chez les patients de MA est maintenant bien établi (Figure 5). Ils présentent en effet un hypométabolisme du glucose cérébral dans le cortex temporo-pariétal et cingulaire postérieur/précuneus (Chételat et al., 2008; La Joie et al., 2012; Minoshima et al., 1997; Nestor et al., 2003; Salmon et al., 2000), déjà détectable de façon précoce chez des patients MCI (Chetelat et al., 2003; Del Sole et al., 2008; Grothe et al., 2017; Langbaum et al., 2009; Schroeter et al., 2009; Wu et al., 2010). Cet hypométabolisme s'étend lentement jusqu'aux régions frontales, qui ne sont atteintes que plus tardivement (Chen et al., 2010; Stefanova et al., 2006), tandis que le cortex

sensori-moteur, le cortex visuel primaire et le cervelet sont relativement préservés (Herholz et al., 2002; Minoshima et al., 1997; Nestor et al., 2003). De façon intéressante, l'hypométabolisme du glucose dans les régions temporo-pariétales, cingulaire postérieur/précuneus et frontales serait prédictif de conversion d'un stade prédémentiel vers un stade démentiel (Chételat et al., 2003; Drzezga et al., 2003; Fouquet et al., 2009; Landau et al., 2011). Cependant, l'hypométabolisme du glucose dans les régions temporo-pariétales et cingulaire postérieur/précuneus a été mis en évidence précocement au stade MCI, et même au stade SCD (Scheef et al., 2012), tandis que celui des régions frontales n'est détectable que plus tardivement. C'est pourquoi, seul l'hypométabolisme temporo-pariétal et cingulaire postérieur/précuneus a été défini comme biomarqueur de la MA, et ce dès le stade préclinique (Albert et al., 2011; McKhann et al., 2011; Sperling et al., 2011).

2.2.3. Pathologie Amyloïde mesurée en TEP

La TEP, couplée à des radiotraceurs spécifiques, peut également être utilisée pour mesurer dans le cerveau *in vivo* les dépôts amyloïdes. Depuis quelques dizaines d'années, plusieurs marqueurs ont été développés. Le plus ancien, le FDDNP, n'est pas spécifique des dépôts amyloïdes, et marque également les DNF (Shoghi-Jadid et al., 2002; Small et al., 2006). Le PIB (Pittsburgh Compound-B) fut ensuite le premier marqueur sélectif de l'amyloïde et est l'un des plus largement utilisés dans la recherche (Counts et al., 2017; Klunk et al., 2004), bien que son marquage au ^{11}C d'une demi-vie de 20 min, nécessitant la présence d'un cyclotron sur le site d'examen, compromet son utilisation clinique. Trois radiotraceurs, ceux-ci marqués au ^{18}F, ont plus récemment été autorisés à la vente aux Etats-Unis par la Food and Drug Administration (FDA), le Florbetapir (Choi et al., 2009) sous le nom d'Amyvid™ (2012), le Flutemetamol (Koole et al., 2009) sous le nom Vizamyl™ (2013) et le Florbetaben (Rowe et al., 2008) sous le nom Neuraceq™ (2014).

La TEP amyloïde permet l'évaluation des dépôts amyloïdes à travers le temps, mais aussi, dans la pratique clinique, de distinguer visuellement les patients présentant un marquage important dans le cortex, les amyloïdes positifs (Aβ+), de ceux présentant un marquage faible, les amyloïdes négatifs

(Aβ-). Dans le cadre de la recherche, des méthodes quantitatives permettent de classifier de façon plus précise les individus, de manière globale ou dans des régions d'intérêt, à l'aide d'analyses voxel à voxel ou en extrayant l'intensité du signal.

De façon générale, les études ont mis en évidence une accumulation de protéines β-amyloïde en accord avec les études neuropathologiques, avec un marquage important dans le néocortex frontal, temporal, pariétal, cingulaire ainsi que dans le striatum, moindre dans le lobe occipital et le thalamus et similaire aux sujets sains dans le cortex sensorimoteur et le lobe temporal interne (hippocampe) (Chételat et al., 2011; Kemppainen et al., 2006; Klunk et al., 2004; La Joie et al., 2012; Rabinovici et al., 2007; 2010; Rowe et al., 2007; 2008; Shin et al., 2008; Villemagne, 2016) (Figure 5)

De façon intéressante, une méta-analyse récente indique que seul 88% des patients présentant un diagnostic clinique de MA sont positifs à l'amyloïde (Ossenkoppele et al., 2015), et ce pourcentage diminue avec l'âge, ce qui implique un mauvais diagnostic de certains patients et explique l'ajout des biomarqueurs dans les critères diagnostiques de MA (voir section 2.3.2).

La pathologie amyloïde retrouvée chez les patients est progressive et commence plusieurs décennies avant l'apparition de symptômes cognitifs, puisque 20% à 40% des sujets âgés cognitivement sains de plus de 60 ans, selon leur statut APOE, présentent un marquage positif (Jansen et al., 2015; Rodrigue et al., 2012), principalement dans les régions préfrontales et cingulaires postérieures (Mintun et al., 2006; Mormino et al., 2009; Rowe et al., 2007; 2008; Villemagne et al., 2008; 2016). Les MCI quant à eux, ont un marquage intermédiaire entre les patients déments et les sujets âgés cognitivement sains (Devanand et al., 2010; Lopresti et al., 2005; Price et al., 2005; Rowe et al., 2010), dont la topographie est similaire aux patients MA chez les MCI « converteurs » (Forsberg et al., 2008; Koivunen et al., 2011).

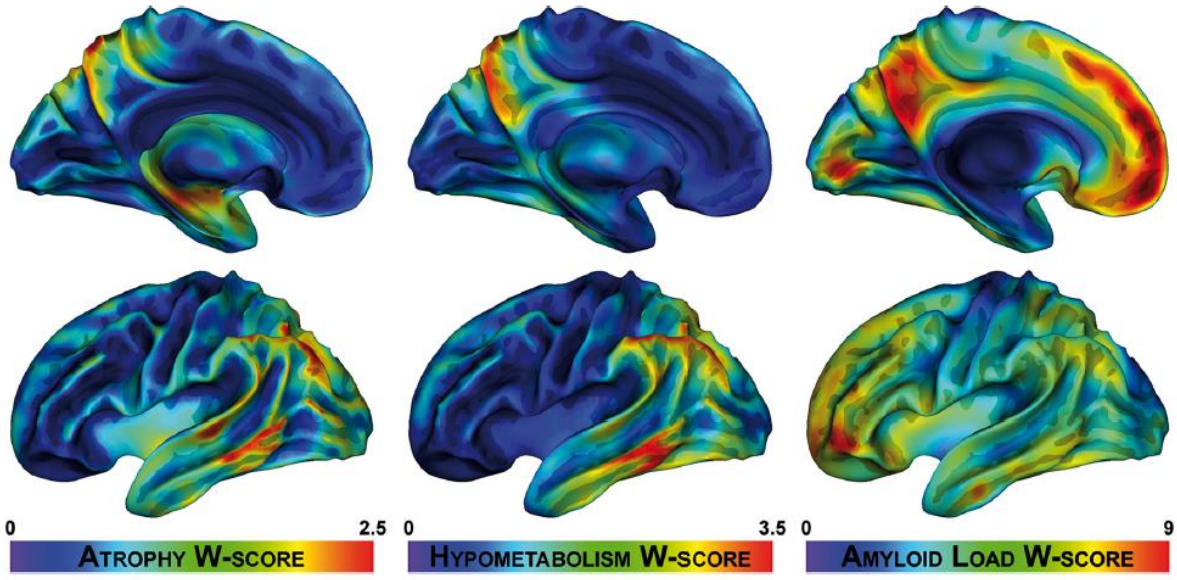

Figure 5 : Profils d'atrophie (gauche), d'hypométabolisme (centre), et de répartition des dépôts amyloïdes (droite) chez des patients MA, *d'après La Joie et al., 2012*.

2.2.4. Pathologie Tau mesurée en TEP

Contrairement à l'amyloïde, la pathologie tau est intracellulaire, et donc beaucoup plus complexe à mesurer. C'est pourquoi plusieurs radiotraceurs TEP n'ont été mis au point que très récemment pour mesurer la topologie et la propagation de la pathologie tau in vivo, jusqu'ici uniquement mesurable *post-mortem* ou dans le liquide céphalo-rachidien (LCR). Parmi ceux-ci, tous marqués au fluor 18, les plus utilisés sont le T807 (ou AV1451), le T808 et le THK 5351 (Chien et al., 2013; Harada et al., 2016; Leuzy et al., 2019; Lockhart et al., 2016).

La littérature croissante a permis de décrire *in vivo* les stades de Braak et Braak, avec un faible marquage chez les sujets cognitivement sains dans les régions temporales médiales (entorhinal, parahippocampe et l'hippocampe) (Hall et al., 2017; Lockhart et al., 2016; Ossenkoppele et al., 2016; Schöll et al., 2016), qui s'étend dans les régions pariétales et orbitofrontales chez des patients MCI et MA (Chiotis et al., 2016; Cho et al., 2016; Lockhart et al., 2016; Okamura et al., 2014; Villemagne et al., 2014)(Figure 6).

Bien que ces marqueurs corrèlent donc avec la neuropathologie et les mesures de tau du LCR (Chhatwal et al., 2016; Gordon et al., 2016; La Joie et al., 2018; Mattsson et al., 2018), ils présentent toujours des fixations non-spécifiques, notamment sur les monoamine-oxydases (Saint-Aubert et al., 2017; Vermeiren et al., 2018). Ils semblent donc prometteurs en tant que biomarqueurs, à la fois pour la recherche et la clinique, mais représentent toujours un challenge actuel de la recherche biomédicale.

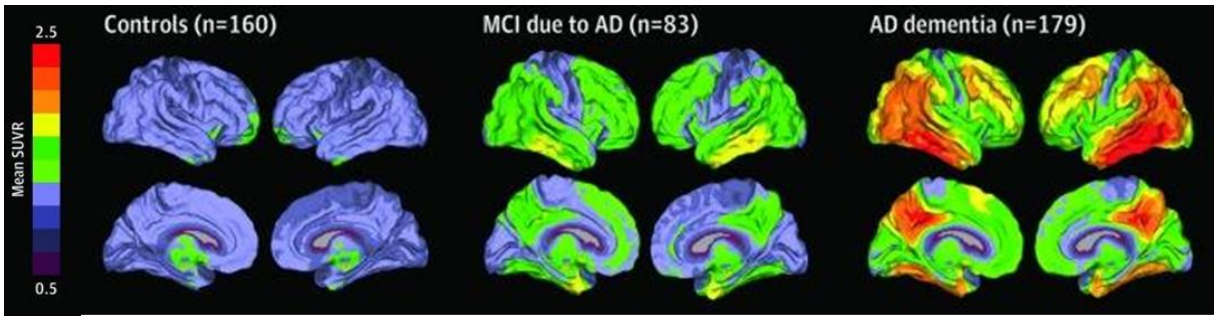

Figure 6 : Profil de répartition des DNF, mesuré en TEP ^{18}Flortaucipir chez des sujets sains (gauche) et des patients MCI (centre) et MA (droite), *d'après Ossenkoppele et al., 2018.*

2.3. Critères diagnostiques de MA

2.3.1. Critères cliniques : les différents stades

2.3.1.1. Stade démentiel : MA

Les critères diagnostiques cliniques de MA établis en 1984 par le groupe de travail NINCDS-ADRDA (*National Institute of Neurological and Communicative Disorders and Stroke – the Alzheimer's Disease and Related Disorders Association*) (McKhann et al., 1984) sont dits probabilistes, puisqu'ils proposent trois degrés de certitude du diagnostic : possible, probable et certain. Selon ces critères, le diagnostic de MA probable s'établit en présence d'un syndrome démentiel, c'est-à-dire une altération dans au moins deux fonctions cognitives et une détérioration progressive des performances mnésiques objectivées lors de tests neuropsychologiques, le tout entraînant une perte d'autonomie. Ce syndrome doit apparaître entre 40 et 90 ans (le plus souvent après 65 ans) et en l'absence d'affections

systémiques ou cérébrales qui pourraient expliquer ces troubles cognitifs. Ce diagnostic peut être renforcé par la détérioration de fonctions cognitives spécifiques telles que le langage (aphasie), les capacités motrices (apraxie) et les capacités perceptives (agnosie), ainsi qu'une histoire familiale de MA. Le diagnostic de MA possible se base plus simplement sur la présence d'un déclin sévère et progressif d'une seule fonction cognitive, en l'absence d'une autre cause identifiable.

Le diagnostic de certitude n'est quant à lui possible que *post-mortem*, en présence des lésions caractéristiques (DNF et plaques amyloïdes) lors de l'autopsie (voir section 2.1.3). Il est à noter que l'histopathologie seule ne permet pas non plus d'établir une MA certaine, car elle nécessite la présence d'un trouble démentiel *ante-mortem* (Hyman et al., 2012; Khachaturian, 1985; Mirra et al., 1991; Montine et al., 2012; The National Institute on Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease, 1997).

Ces critères diagnostiques sont très proches de ceux proposés dans le DSM IV (4e édition du *Diagnostic and Statistical Manual of Mental Disorders*), où les troubles cognitifs ne doivent pas être attribuables à d'autres causes qui peuvent être neurologiques, psychiatriques ou systémiques, et qui prennent notamment en compte l'âge de début d'apparition des symptômes, avec début tardif après 65 ans, ou précoce avant cet âge.

Ainsi ces critères ne permettent de diagnostiquer cette maladie qu'au stade de démence, puisqu'ils se basent essentiellement sur l'évaluation clinique et neuropsychologique du patient. Or les modifications cérébrales débutent plusieurs décennies avant le diagnostic clinique, et l'apparition des troubles cognitifs est également insidieuse et progressive. Les personnes dans cette phase de transition présentent donc des déficits cognitifs déjà détectables, qui ne sont pour autant pas suffisants pour constituer un diagnostic de démence (Figure 7). De nombreuses recherches se sont donc employées à étudier les stades pré-démentiels de la MA, dans le but d'identifier et détecter la maladie le plus précocement possible, avant que l'atteinte fonctionnelle ne soit trop avancée.

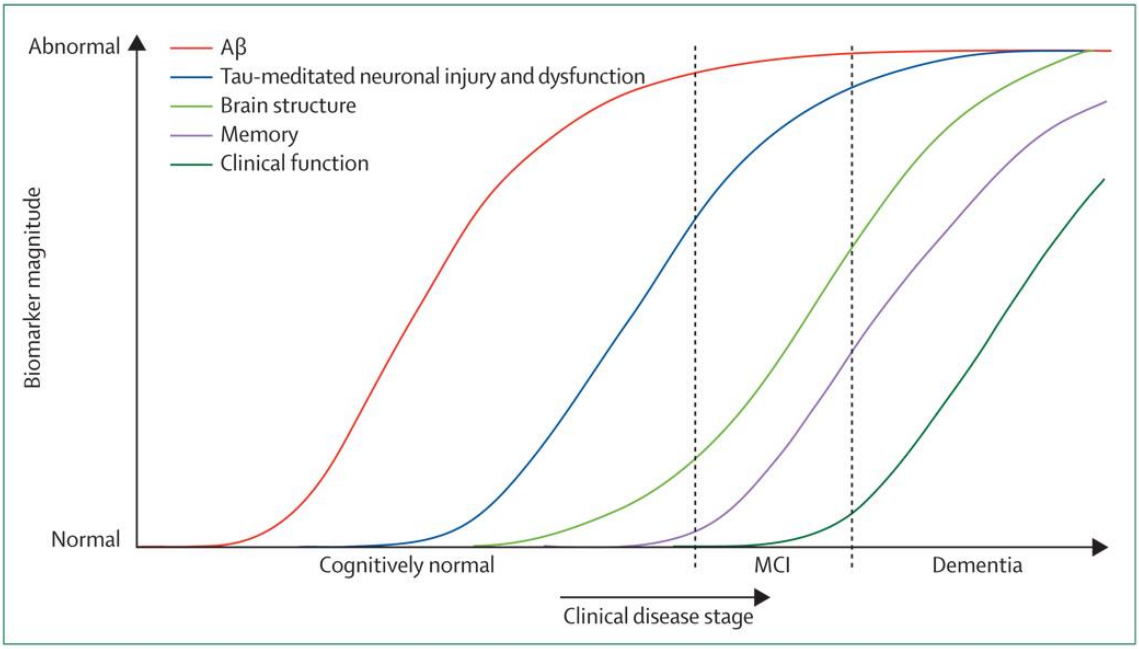

Figure 7 : Modèle hypothétique de la dynamique des biomarqueurs de la cascade pathologique de la maladie d'Alzheimer, *d'après Jack et al., 2010.*

2.3.1.2. Stade pré-démentiel : *le Mild Cognitive Impairment* (MCI)

Au vu de la nécessité de mieux comprendre cette phase pré-démentielle, le concept de *Mild Cognitive Impairment* (MCI, ou Trouble Cognitif Léger) a été introduit en 1988 (Reisberg et al., 1988). Précisés en 1999 par Petersen et al., les critères initiaux incluent une plainte mnésique émanant du patient (de préférence confirmée par un informant), avec des déficits mnésiques avérés à l'aide de tests neuropsychologiques et n'influençant pas les activités quotidiennes, bien que les autres fonctions cognitives soient préservées (Petersen et al., 2009).

Bien que les patients MCI ainsi diagnostiqués présentaient un taux de conversion vers une MA supérieur aux sujets sains d'âge comparable (Petersen et al., 2009), tous n'évoluaient pas vers une démence de type Alzheimer, rendant la population très hétérogène. Devant ce constat, de nouveaux critères ont été ajoutés en 2004, catégorisant les patients en sous-types dits amnésiques (présence de troubles mnésiques) ou non amnésiques (absence de troubles mnésiques), ou les classant selon le

nombre de fonctions cognitives impactées, *single domain* (déficit d'un seul domaine cognitif) ou *multi-domain* (déficit de plusieurs domaines cognitifs)(Figure 8 ; Petersen, 2004).

Cette classification a permis d'identifier des étiologies sous-jacentes préférentiellement associées aux troubles cognitifs pour chaque sous-type (Figure 8), avec un devenir clinique différent. En conséquence, bien que les patients MCI aient plus de risques de développer une MA, avec un taux annuel de conversion de 5 à 10% (Langa & Levine, 2014; Petersen et al., 2009), ces patients peuvent également convertir vers d'autres pathologies, rester stable ou même revenir à la normale au cours d'un suivi (jusqu'à 15 à 20%)(Ganguli et al., 2011; Koepsell & Monsell, 2012; Mitchell & Shiri-Feshki, 2009).

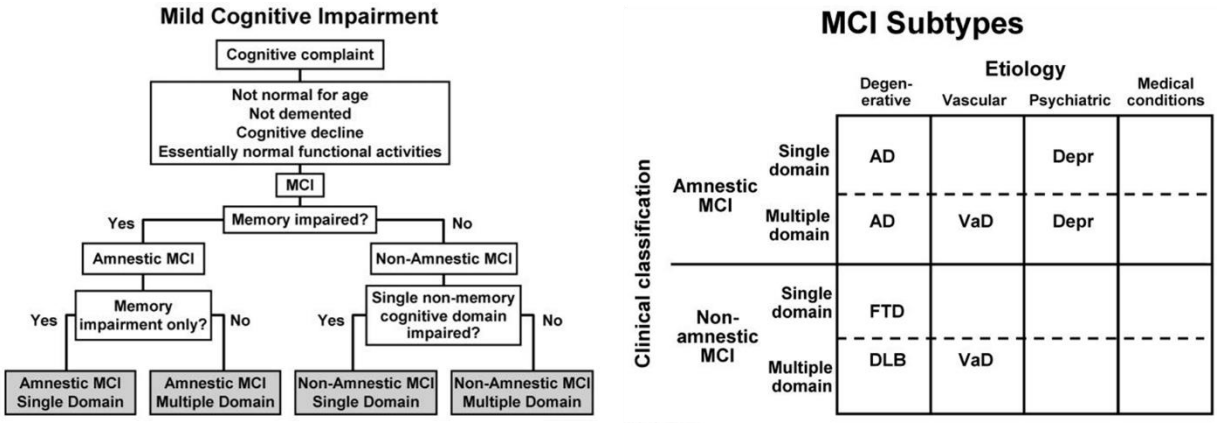

Figure 8 : Catégorisation (gauche) et étiologie (droite) des patients MCI selon les troubles cognitifs rapportés, *d'après Petersen et al., 2009*.

2.3.1.3. Stade préclinique : SCD

Au vu de l'absence de traitement curatif pour la MA, un des objectifs de la recherche est de mettre en place des stratégies interventionnelles permettant de prévenir ou de retarder l'entrée dans la démence. Bien que le MCI soit un premier pas dans la compréhension de la maladie avant la déclaration de la démence clinique, les modifications cérébrales et cognitives commencent avant ce stade (Figure 7). La définition d'une population encore plus précoce, le *Subjective Cognitive Decline* (SCD), a donc été proposée en 2014 par la *Subjective Cognitive Decline Initiative* (SCD-I) (Jessen et al., 2014) (Figure 9).

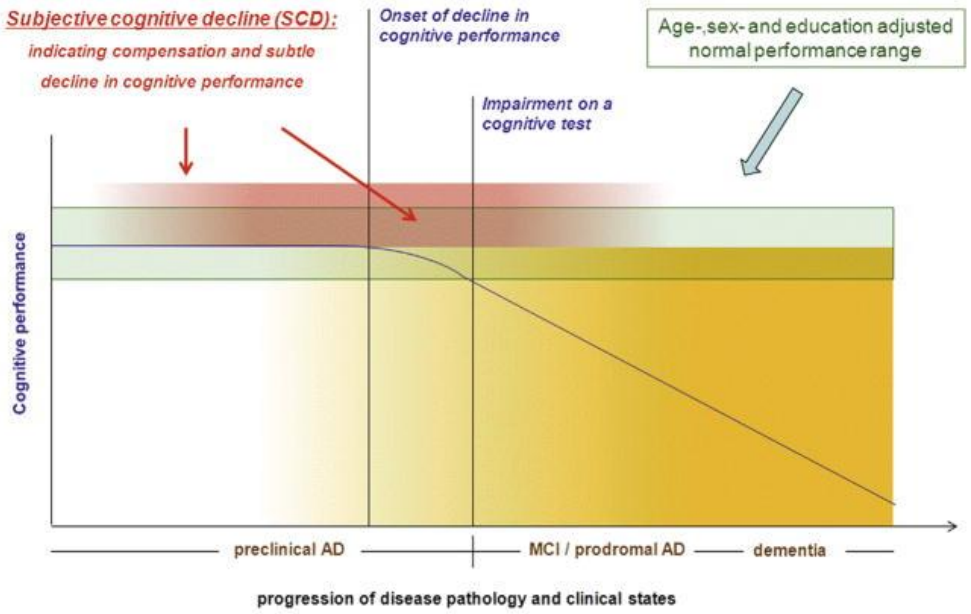

Figure 9 : Modèle d'évolution du déclin cognitif par rapport à l'avancée de la maladie d'Alzheimer, d'après *Jessen et al., 2014*. Le SCD est ici conceptualisé comme une population présentant un déclin cognitif subtil, non-détectable du fait de mécanismes compensatoires, évoluant vers un stade MCI.

Cette population est définie par la perception subjective d'un déclin persistant des capacités cognitives, comparée à une période antérieure, malgré des performances normales (selon l'âge, le genre et le niveau d'éducation) aux tests cognitifs servant au diagnostic de MCI. Cette plainte cognitive ne doit pas être expliquée par un évènement aigu spécifique, la prise de substances, un MCI, une MA prodromale, ou une démence, ni même par une autre pathologie psychiatrique ou neurologique.

Des études ont montré que la présence d'un SCD est un facteur de risques de déclin cognitif futur ainsi que de MCI et de démence de type Alzheimer (Dufouil et al., 2005; Glodzik-Sobanska et al., 2007; Jessen et al., 2010; Barry Reisberg et al., 2010), particulièrement en présence de biomarqueurs de MA (Peter et al., 2014; Prichep et al., 2006; van Harten et al., 2013). Cependant, le SCD regroupe des populations hétérogènes, c'est pourquoi des critères additionnels ont donc été précisés, définissant des SCD *plus*, qui sont plus à risque de présenter une MA préclinique par rapport aux autres SCD (Jessen et al., 2014). Les critères de SCD *plus* incluent le sentiment d'un déclin mnésique associé à de l'inquiétude, le sentiment de performances inférieures aux personnes de leur âge, et une apparition

de la plainte dans les 5 dernières années, après 60 ans. Ces données peuvent être renforcées par la confirmation d'un informant, un génotype APOE ε4, et la présence de biomarqueurs de MA (voir section 2.2.), si ces informations sont disponibles. Les critères actualisés publiés récemment par Jessen et collaborateurs sont similaires à ceux de 2014, mais ajoutent au groupe de SCD *plus* deux caractéristiques, la persistance du déclin cognitif subjectif avec le temps et le fait de consulter un professionnel de santé à ce propos (Jessen et al., 2020).

2.3.2. Evolutions biologiques des critères avec l'ajout des biomarqueurs

Comme discuté précédemment, les critères de MA établis par le NINCDS-ADRDA se basent uniquement sur la clinique du syndrome démentiel, et ne permettent donc qu'un diagnostic tardif et probabiliste. Les avancées et l'accessibilité grandissante des techniques de neuroimagerie et de biologie ont permis de mieux comprendre les mécanismes de la pathologie et d'identifier des biomarqueurs *in-vivo,* qui, pris ensemble, améliorent la sensibilité et la spécificité du diagnostic (de Jager et al., 2010). Ces biomarqueurs regroupent la pathologie amyloïde mesurée en TEP ou dans le LCR (niveaux d'Aβ42 ou ratio Aβ42/Aβ40), la pathologie tau mesurée en TEP ou dans le LCR également (niveau de t-Tau ou phospho-tau), et les marqueurs des pertes neuronales et synaptiques en neuroimagerie telles que l'atrophie de l'hippocampe et l'hypométabolisme temporopariétal (voir section 2.2.). Plusieurs groupes de travail se sont ainsi formés afin d'intégrer ces outils, voire s'affranchir dans certains cas des critères cliniques dans le but d'accéder à un diagnostic plus sûr et plus précoce.

Des critères révisés du NINCDS-ADRDA à des fins de recherche ont ainsi été proposés en 2007 par l'*International Working Group* (IWG) *for New Research Criteria for the Diagnosis of Alzheimer's Disease* (Dubois et al., 2007). En plus du déclin progressif de la mémoire épisodique, la présence d'au moins un biomarqueurs - atrophie temporale interne, dosage anormal de tau et/ou Aβ dans le LCR, profil d'imagerie caractéristique (hypométabolisme temporo-pariétal et/ou marquage cortical important) -

est nécessaire pour l'établissement d'un diagnostic de MA, ce qui permet de diagnostiquer la maladie avant l'apparition du syndrome démentiel. Ces critères ont ensuite été élargis pour prendre en compte les formes atypiques de la maladie, ainsi que différencier la « maladie d'Alzheimer » qui représente le trouble clinique, de la « pathologie Alzheimer » qui représente les changements biologiques (Dubois et al., 2010, 2014). De plus, l'IWG a redéfini le stade préclinique de la maladie, caractérisé par des marqueurs de pathologie à la fois Aβ et tau sans atteintes cognitives, et qui se distingue des individus asymptomatiques à risque, qui eux ne présentent que l'une de ces deux pathologies (Dubois et al., 2016).

Un autre groupe d'étude, le *National Institute of Aging-Alzheimer's Association* (NIA-AA), a quant à lui publié une série de nouveaux critères diagnostiques en 2011, redéfinissant à la fois la phase préclinique (Sperling et al., 2011), le stade de MCI (Albert et al., 2011) et la démence (McKhann et al., 2011), tout en prenant en compte les variantes non-mnésiques ou atypiques de la MA. Ils intègrent cette fois tous les biomarqueurs décrits ci-dessus, regroupés dans deux catégories principales : les marqueurs de la pathologie amyloïde (un marquage important de l'amyloïde corticale en TEP ou un dosage anormal dans le LCR), et les marqueurs de neurodégénérescence (regroupant le dosage de tau dans le LCR, l'atrophie hippocampique et l'hypométabolisme temporopariétal). C'est dans ces articles, prenant en compte à la fois les symptômes cliniques et la pathologie sous-jacente, qu'est introduite la notion de MCI dû à une MA (*MCI due to AD ;* Albert et al., 2011*)* et de démence due à une MA (*Dementia due to AD* ; McKhann et al., 2011).

Concernant la MA au stade préclinique, trois stades successifs ont été décrits en accord avec l'hypothèse principale de la cascade amyloïde, dans laquelle l'amyloïde apparaitrait en premier et induirait toutes les autres modifications cérébrales, comme illustré sur le modèle hypothétique de Jack (2010) présenté en figure 7 (Hardy & Selkoe, 2002; Jack et al., 2010). En effet, dans l'ordre, le stade 1 présente une amyloïdose asymptomatique ; le stade 2 présente une amyloïdose + neurodégénerescence ; et le stade 3 présente une amyloïdose + neurodégénerescence + déclin cognitif subtil, bien que restant dans les normes standardisées.

Les recommandations à visée de recherche les plus récentes ont été publiées en 2018 par Jack et collaborateurs (Figure 10). Elles placent les individus sur un continuum de MA, principalement en fonction de la présence d'amyloïde. En effet, même seule, celle-ci est associée à un changement pathologique de type Alzheimer, tandis que la présence de pathologie tau sans amyloïde est considérée comme un changement pathologique de type non MA (Jack et al., 2018). Dans cette configuration, les troubles cognitifs et la neurodégénérescence ne sont plus diagnostiques, mais nous informent sur la sévérité de la maladie. Il est à noter que cette cascade amyloïde ne fait pas l'unanimité et a été remise en cause (Chételat et al., 2013; Duyckaerts, 2004; Hardy, 2004; Terry, 2004). De plus, ces critères n'incluent plus la nécessité de symptômes cliniques, c'est pourquoi ils sont toujours aujourd'hui débattus dans la communauté scientifique (Jagust et al., 2019; Louie, 2019; McCleery et al., 2019).

<table>
<tr><th>AT(N) profiles</th><th colspan="2">Biomarker category</th></tr>
<tr><td>A-T-(N)-</td><td colspan="2">Normal AD biomarkers</td></tr>
<tr><td>A+T-(N)-</td><td>Alzheimer's pathologic change</td><td rowspan="4">Alzheimer's continuum</td></tr>
<tr><td>A+T+(N)-</td><td>Alzheimer's disease</td></tr>
<tr><td>A+T+(N)+</td><td>Alzheimer's disease</td></tr>
<tr><td>A+T-(N)+</td><td>Alzheimer's and concomitant suspected non Alzheimer's pathologic change</td></tr>
<tr><td>A-T+(N)-</td><td colspan="2">Non-AD pathologic change</td></tr>
<tr><td>A-T-(N)+</td><td colspan="2">Non-AD pathologic change</td></tr>
<tr><td>A-T+(N)+</td><td colspan="2">Non-AD pathologic change</td></tr>
</table>

Figure 10 : Catégorisation et profil des individus selon la présence ou l'absence des biomarqueurs A/T/N, *d'après Jack et al., 2018*.

Abréviations : A *Amyloïde* ; AD *Maladie d'Alzheimer* ; N *Neurodégénérescence* ; T *Tau*.

2.4. Les facteurs psychoaffectifs

2.4.1. Les symptômes neuropsychiatriques

Au cours de la démence, 90 % des patients présentent des perturbations comportementales et psychologiques aussi appelées symptômes neuropsychiatriques (SNP) (Finkel et al., 1996), en plus des symptômes caractéristiques nécessaires au diagnostic. En effet, même la patiente Auguste Deter, premier cas de MA décrit par Aloïs Alzheimer, présentait une détresse émotionnelle et des illusions d'infidélité couplées à de la jalousie excessive avant de développer des problèmes de mémoire et de langage (voir section 2.1.1). Ces symptômes n'ont cependant été inclus dans les critères diagnostiques de démence qu'en 2011 par McKhann et collaborateurs, qui indiquent que le diagnostic de démence Alzheimer probable peut être posé en présence de déclin cognitif ou comportemental, associé aux biomarqueurs. Ce déclin comportemental est décrit comme pouvant comprendre des changements en termes de personnalité, de comportement ou de conduite (i.e. agitation, comportements compulsifs ou obsessifs, perte de motivation, initiative, diminution de l'intérêt pour les activités précédentes, apathie, retrait social, perte d'empathie, comportements socialement inacceptables) (McKhann et al., 2011). Ils ne sont cependant toujours pas inclus dans les définitions les plus récentes de MA à la fois précliniques (Albert et al., 2011; Dubois et al., 2016), et cliniques (Dubois et al., 2014), bien qu'ils aient été présents dans les critères de démence du NIA-AA en 2011 (McKhann et al., 2011).

Dans une large cohorte de plus de 2000 sujets MA, quatre sous-domaines principaux des SNP ont été décrits dans la MA : psychose (délire, hallucination et trouble du sommeil), symptômes affectifs (dépression et anxiété), apathie (apathie et trouble de l'appétit) et hyperactivité (Aalten et al., 2007). Ces SNP et leurs fondements neurobiologiques intéressent de plus en plus la communauté scientifique, notamment à des stades précliniques en tant que potentielles cibles de prévention et de traitement de la MA (Mortby et al., 2018), et même en tant que symptômes précoces pouvant améliorer le diagnostic (Cerejeira et al., 2012). Bien que les pathologies psychiatriques associées à ces SNP aient reçu plus d'attention que les symptômes infra-cliniques, ces derniers ne sont pas négligeables au vu de leur prévalence plus élevée et leur impact à la fois social et financier. En effet, les SNP infra-cliniques

ont été associés à une diminution de la qualité de vie à la fois des patients et des aidants, à une institutionnalisation plus rapide, un moins bon pronostic ou même une plus grande mortalité. Pour finir, les SNP ont également été associés à un déclin cognitif et au risque de progression du stade MCI au stade démentiel (pour revue Cerejeira et al., 2012).

Pour le moment, les liens entre SNP et démence ne sont pas encore élucidés. Plusieurs hypothèses ont été avancées (Figure 11), parmi lesquelles : (1) La voie étiologique : les SNP reflètent une pathologie sous-jacente ou un état cérébral, cause de développement de la MA et des symptômes cognitifs associés ; (2) Un facteur de risque commun : les SNP sont associés de manière non causale à la MA, et c'est un troisième facteur (génétique et/ou environnemental) qui conduit au développement à la fois des SNP et de la MA ; (3) Les SNP causés par la MA : les SNP peuvent être une réaction psychologique à un déclin cognitif causé par la démence ou même une manifestation non cognitive directe de la neurodégénérescence due à la MA, affectant des zones clés du cerveau qui sous-tendent le comportement, les émotions ou la perception ; (4) Interaction : interaction synergique entre les SNP et un facteur biologique conduisant à la MA (Gallagher et al., 2017; Geda et al., 2013).

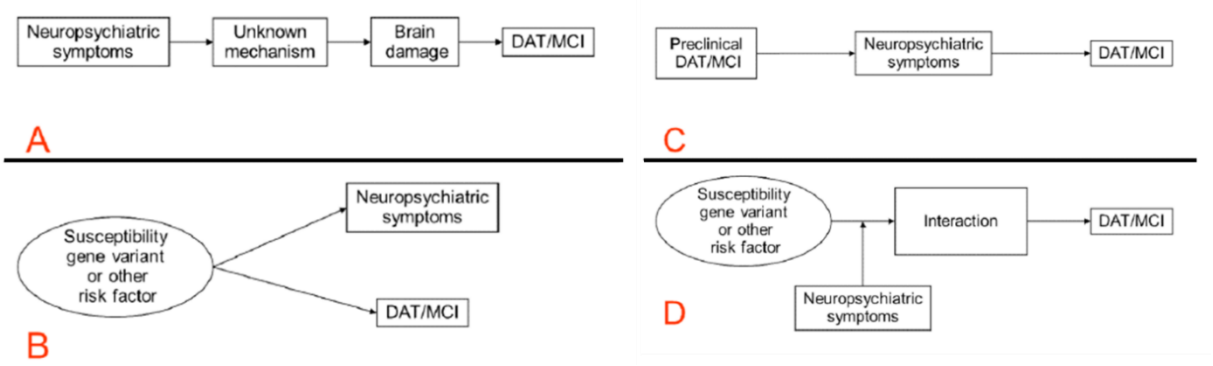

Figure 11 : Représentation schématique des différentes hypothèses mécanistiques liant les symptômes neuropsychiatriques à la démence, *d'après Geda et al., 2013*.

A) Voie étiologique ; B) Facteur de risque commun ; C) SNP causé par la MA ; D) Interaction. Abréviations : AD *Maladie d'Alzheimer* ; DAT *Démence de type Alzheimer* ; MCI M*ild Cognitive Impairment.*

Cependant, les bases cérébrales des SNP, en particulier dans les premiers stades de la MA, restent mal comprises, et chaque sous-syndrome peut avoir des corrélats neuroanatomiques et neurobiologiques sous-jacents distincts (Ballarini et al., 2016; Nowrangi et al., 2015). Pour cette raison, ces quatre mécanismes (et d'autres mécanismes possibles) ne s'excluent pas mutuellement et peuvent sous-tendre simultanément des SNP différents. Il est donc nécessaire d'étudier ces SNP indépendamment et non comme une seule entité uniquement. Dans la suite de ce travail, nous nous focaliserons de façon indépendante sur les symptômes dépressifs et anxieux infra-cliniques, formant le sous-syndrome affectif, qui font partie des SNP les plus fréquents au cours du vieillissement normal et chez les patients atteints de démence.

2.4.2. Les symptômes dépressifs

2.4.2.1. Définition et prévalence

La dépression constitue, selon l'OMS, la pathologie mentale la plus fréquente dans les pays développés, avec un impact majeur sur la société sur un plan économique et personnel. C'est un trouble mental qui se définit par une tristesse quasi-permanente, une perte d'intérêt ou de plaisir, des troubles du sommeil ou de l'appétit, une perte d'énergie, une agitation ou un ralentissement psychomoteur, un sentiment d'infériorité ou de culpabilité inapproprié, des troubles cognitifs et attentionnels, des idées noires et parfois même des idées morbides (OMS ; DSM IV). La dépression est alors gradée de légère, modérée à sévère en fonction du nombre et de la gravité des symptômes. Si ces derniers ne sont pas assez nombreux, intenses ou durables pour être qualifiés d'épisode dépressif (présence tous les jours d'au moins 5 de ces symptômes), on parle alors de symptômes dépressifs infra-cliniques (DSM IV).

Selon l'OMS, la dépression touche plus de 264 millions de personnes de tous âges dans le monde et fait partie des pathologies psychiatriques les plus communément diagnostiquées chez les personnes âgées. En effet, elle concerne jusqu'à 25% des plus de 65 ans résidant chez eux, jusqu'à 42% des seniors institutionnalisés et touche plus les femmes que les hommes (pour revue Djernes, 2006). Or il est estimé que 60 à 70 % des états dépressifs des personnes âgées sont négligés ou méconnus (Thomas &

Hazif-Thomas, 2008) et les symptômes dépressifs infra-cliniques sont considérés comme un stade prodromal de dépression majeure, car associés à un plus grand risque de développer cette pathologie (pour revue Cuijpers & Smit, 2004; Lyness et al., 2009). Bien que la dépression semble toucher plus les sujets jeunes que les sujets âgés (pour revue Fiske et al., 2009), une étude a montré une relation curvilinéaire des symptômes dépressifs avec l'âge, représentant une augmentation de ceux-ci jusqu'à environ 35 ans, puis une diminution, et une nouvelle augmentation vers 77 ans (Teachman, 2006).

Concernant les patients, les symptômes dépressifs infra-cliniques sont également courants. Cependant, leur prévalence est difficile à évaluer puisque les troubles dépressifs infra-cliniques (dépression subsyndromique et mineure) ont été définis de façon très variée, selon le nombre de symptômes et leurs durées, parfois selon des critères cliniques, parfois selon un seuil correspondant à l'échelle d'étude (Rodríguez et al., 2012). Bien que la prévalence des symptômes dépressifs infra-cliniques légers n'a pas été évaluée du fait de l'hétérogénéité de sa définition, deux méta-analyses se basant sur les critères du DSM IV rapportent une prévalence générale de 22% des troubles dépressifs mineurs chez les MA (pour revue Verdaguer et al., 2020) et de 20% chez des MCI (pour revue Polyakova et al., 2014). Dans ce sens, à l'exception d'une étude (Starkstein et al., 2005), la plupart ne montrent pas d'augmentation de la prévalence des symptômes dépressifs avec l'augmentation de la sévérité de la MA (Lyketsos et al., 1997; pour revue Verkaik et al., 2007).

2.4.2.2. Symptômes dépressifs en tant que facteurs de risque et liens avec la cognition

Les symptômes dépressifs sont associés à une diminution de la qualité de vie et une augmentation du risque de mortalité dans des populations âgées (Braam et al., 2014; pour revue Cuijpers et al., 2013). Ils sont également liés à une diminution de la qualité de vie des patients atteints de MA et de leurs aidants (Banerjee et al., 2006; Cheng, 2017; Teng et al., 2012).

Les symptômes dépressifs, chez les personnes âgées sans déficits cognitifs, sont associés à de moins bonnes performances cognitives à la fois globales (Booth et al., 2006; Ganguli et al., 2009; Köhler et al., 2010; Lyness et al., 1999; Wilson et al., 2011), mais aussi en termes de mémoire épisodique et sémantique (Beaudreau & O'Hara, 2009; Ganguli et al., 2009; Köhler et al., 2010; Wilson et al., 2011; Yochim et al., 2013; Zhang et al., 2020) et de fonctions exécutives (Ganguli et al., 2009; Vito et al., 2017; Zhang et al., 2020).

Bien que certains études ne retrouvent pas de liens entre les symptômes dépressifs et le déclin cognitif chez les personnes âgées cognitivement saines (Potvin et al., 2011), la plupart des études longitudinales mettent en évidence ce lien (Barnes et al., 2006; Donovan et al., 2014; Köhler et al., 2010; Sachs-Ericsson et al., 2005; Yang et al., 2020; Zhang et al., 2020). Notamment, une étude menée sur plus de 4000 participants de plus de 65 ans sans déficits cognitifs, montre que les symptômes dépressifs prédisent un déclin cognitif sur 5 ans (Wilson et al., 2004).

En plus de ce risque de déclin cognitif, des études ont montré un risque 2 fois plus élevé de développer un MCI chez des sujets âgés présentant des symptômes dépressifs (Barnes et al., 2006; Dean et al., 2014; Donovan et al., 2014; Geda et al., 2014), ainsi qu'un risque plus élevé d'incidence de la démence (Chan et al., 2011; Gatz et al., 2005; Palmer et al., 2007; Wilson et al., 2002), bien que certaines études ne retrouvent pas ce résultat (Wilson et al., 2011). Une étude portant sur 10 000 adultes sains de 35 à 55 ans à l'inclusion et suivis pendant 28 ans montre que ces symptômes dépressifs augmentent environ 10 ans avant le diagnostic de démence (Singh-Manoux et al., 2017) (Figure 12). Par ailleurs, une étude longitudinale sur 10 ans montrant que seuls les sujets âgés dont les facteurs dépressifs augmentent avec le temps ont un risque plus élevé de développer une MA (Mirza et al., 2016). Pour finir, les études chez les patients MCI sont conflictuelles, puisque certaines études montrent que les patients MCI présentant des symptômes dépressifs seraient plus à risque de convertir vers le stade clinique de démence (Brendel et al., 2015; Chan et al., 2011; Pink et al., 2015; Tan et al., 2019), tandis que d'autres ne retrouvent pas ce résultat (Cerbone et al., 2020; Palmer et al., 2007; Panza et al., 2008).

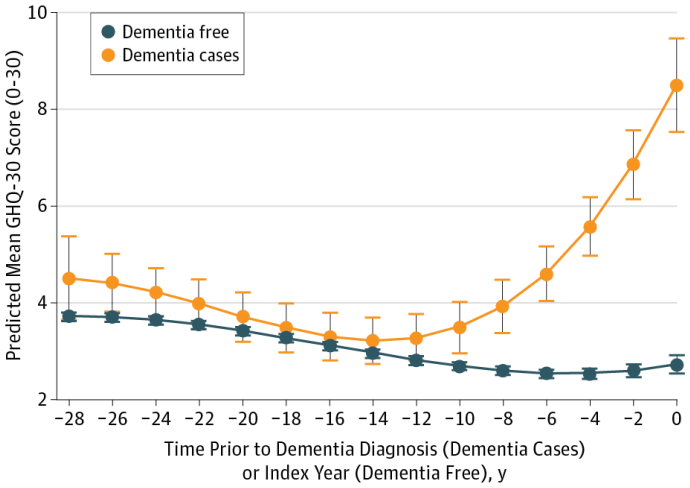

Figure 12 : Trajectoire des symptômes dépressifs 28 ans avant le diagnostic de démence, mesuré à l'aide du 30-Item General Health Questionnaire, *d'après Singh-Manoux et al., 2017*.

2.4.2.3. Neuroimagerie des symptômes dépressifs

2.4.2.3.1. Au cours du vieillissement normal

Les symptômes dépressifs font partie des facteurs psychoaffectifs les plus étudiés, à la fois dans le cadre du vieillissement normal et dans le cadre de la maladie d'Alzheimer, notamment au stade prédémentiel. Les études se focalisant uniquement sur les sujets âgés mettent en évidence une diminution de l'épaisseur corticale associée aux symptômes dépressifs dans les régions frontales et temporales (Pink et al., 2017), ainsi que du volume de substance grise dans le cortex orbitofrontal (Dotson et al., 2009), et temporal interne (hippocampe et parahippocampe) (Donovan et al., 2015; Zhang et al., 2020; Zhou et al., 2016). Sur une cohorte d'âges plus variés (21-62 ans), une étude ne montre cependant pas d'association entre le volume de substance grise et les symptômes dépressifs (Blackmon et al., 2011). Cela pourrait être dû à la variété des résultats mis en évidence chez les sujets plus jeunes. En effet, certaines études sur des participants jeunes ou d'âge moyen montrent une diminution du volume de substance grise dans le cortex préfrontal (Carlson et al., 2015), orbitofontal et cingulaire antérieur, le thalamus, le cortex frontal , et le cortex temporal supérieur (Webb et al., 2014) ; tandis que d'autres montrent une augmentation dans le gyrus fusiforme et parahippocampique (Cun et al., 2014), dans le cortex temporal supérieur, ainsi que le gyrus postcentral et occipital

(Besteher et al., 2017). Le lien entre substance grise et symptômes dépressifs pourrait donc n'être pas linéaire, et varier avec l'âge.

La notion de causalité dans ces relations n'est toujours pas élucidée puisque les études longitudinales ne montrent principalement pas de liens entre l'intensité symptômes dépressifs à baseline et l'évolution du volume de substance grise avec le temps, et réciproquement (Cotter et al., 2020; Dotson et al., 2009). Cependant une étude publiée en 2020 par Zhang et collaborateurs, portant sur 1188 sujets âgés sains et 733 MCI sur 5 ans, décrit une atrophie plus rapide de l'hippocampe et du cortex temporal moyen associée à des symptômes dépressifs infra-cliniques plus élevés à l'entrée dans l'étude (Zhang et al., 2020).

Certaines études rapportent des différences hommes-femmes dans les substrats cérébraux des symptômes dépressifs, avec cependant des discordances dans les résultats rapportés. Elles mettent en évidence une diminution du volume de substance grise dans le cortex préfrontal dorso-médian (Carlson et al., 2015), le gyrus frontal supérieur et le gyrus précentral (Taki et al., 2005), ainsi que dans l'hippocampe (Spalletta et al., 2014) uniquement chez les hommes. A l'inverse, une étude rapporte une association uniquement chez la femme (Hayakawa et al., 2013). Les femmes présentant des symptômes dépressifs infra-cliniques montrent un volume plus petit du cortex cingulaire antérieur et du gyrus rectal, comparé aux contrôles sans symptômes dépressifs.

Les corrélats métaboliques et moléculaires des symptômes dépressifs n'ont été évalués que chez des sujets âgés, et non sur l'ensemble de l'âge adulte. Ils mettent en évidence un hypométabolisme du glucose cérébral de façon globale (Krell-Roesch et al., 2016) et dans le cortex temporal, pariétal et cingulaire postérieur (Donovan et al., 2015) associé aux symptômes dépressifs. Des études ont montré que des symptômes dépressifs élevés étaient associés à une charge amyloïde globale élevée (Krell-Roesch et al., 2018), et de façon longitudinale, c'est la charge amyloïde élevée à l'inclusion qui prédirait une augmentation des symptômes dépressifs avec le temps (Babulal et al., 2016; Donovan et al., 2018). Les symptômes dépressifs infra-cliniques semblent donc associés à des modifications cérébrales

caractéristiques de la MA dans des populations âgées cognitivement saines, ce qui pourrait expliquer pourquoi ces symptômes sont considérés comme des facteurs de risque de développement de cette maladie (voir section 2.4.2.2).

2.4.2.3.2. Aux différents stades de MA

Les études évaluant les associations entre les symptômes dépressifs infra-cliniques et les modalités d'imagerie caractéristiques de la MA, s'intéressent principalement à la substance grise. La plupart de ces études ne montrent pas de liens avec le volume de substance grise chez des sujets MCI et MA (Serra et al., 2010) ou uniquement MA (Berlow et al., 2010; Bruen et al., 2008; Huey et al., 2017; Mori et al., 2014; Starkstein et al., 2009). Celles qui s'intéressent spécifiquement aux liens avec l'hippocampe, ne montrent également aucune association chez des patients MCI (Chung et al., 2016; Elcombe et al., 2015) ou MA (Berlow et al., 2010). Cependant, des études portant sur un nombre plus important de sujets montrent une épaisseur corticale plus petite dans les régions temporales et pariétales chez des patients MCI (n=186; Fujishima et al., 2014) et MA (n=189; Lebedeva et al., 2014). A ce jour, seule une étude chez des SCD/MCI montre de plus gros volumes de SG dans la ROI du lobe temporal médian associés à plus de symptômes dépressifs (Auning et al., 2015).

Très peu d'études se sont intéressées à l'évaluation des liens entre le métabolisme du glucose et les symptômes dépressifs infra-cliniques dans le cadre de la MA. Ces études récentes comparant des patients avec ou sans symptômes dépressifs ont montré un hypermétabolisme du glucose dans le groupe avec symptômes, dans les lobes frontaux et le gyrus fusiforme chez des patients MCI positifs pour l'amyloïde (Brendel et al., 2015) et chez des patients SCI/MCI (Auning et al., 2015).

Pour ce qui est de l'amyloïde mesurée en TEP, plusieurs études sur de larges cohortes ne montrent pas d'association entre les symptômes dépressifs et la charge amyloïde chez les patients MCI et MA, avec le radiotraceur 18F-Florbetapir (Bensamoun et al., 2016; Chung et al., 2015) et 11C-PIB (Mori et al., 2014). Cependant, cette association au stade prédémentiel pourrait être spécifique à une maladie d'Alzheimer sous-jacente, puisque dépendante du statut amyloïde du patient. En effet, les patients

MCI amyloïdes positifs auraient plus de chance de présenter des symptômes dépressifs que les patients amyloïdes négatifs (Krell-Roesch et al., 2019). De plus, une étude a mis en évidence chez 206 patients MCI amyloïdes positifs, que ceux présentant des symptômes dépressifs avaient un accumulation plus importante de dépôts amyloïdes dans le gyrus temporal supérieur, le gyrus parahippocampique, l'insula et le gyrus cingulaire que ceux n'en présentant pas (Brendel et al., 2015).

2.4.3. Les symptômes anxieux

2.4.3.1. Définition et prévalence

L'anxiété est un état psychologique complexe caractérisé par une peur généralisée et persistante, associée à des changements comportementaux. Contrairement à la peur, qui est une réponse à un danger réel imminent, l'anxiété correspond à l'anticipation plus ou moins consciente d'une menace future, associée à une tension musculaire et une vigilance constante ainsi qu'à des comportements d'évitement (5e édition du *Diagnostic and Statistical Manual of Mental Disorders*, 2013). Ce mécanisme, bien qu'universel et adaptatif, peut conduire à une surestimation du danger ou à des réactions excessives, prédisposant à l'apparition de troubles psychiatriques tels que la phobie, la dépression et le stress post-traumatique (Chambers et al., 2004; Karsten et al., 2011).

Les chercheurs ont identifié, dans sa forme non pathologique, deux types d'anxiété, la première dite « trait » et la deuxième dite « état » (Spielberger et al., 1970). L'anxiété « trait », correspond à un trait de personnalité anxieux considéré comme stable, défini comme une différence individuelle constante liée à une tendance à répondre par des inquiétudes, des craintes ou des préoccupations à des situations variées. L'anxiété « état » est définie comme un état émotionnel d'anxiété aigüe transitoire, associé à une augmentation temporaire de l'activité du système nerveux sympathique. Bien que certains considèrent ces deux aspects comme faisant partie d'un tout, d'autres suggèrent qu'ils seraient des constructions distinctes (Endler & Kocovski, 2001; Spielberger et al., 1970).

La prévalence mondiale des troubles anxieux est de 16,6% (pour revue Somers et al., 2006), et ils sont considérés comme l'une des pathologies psychiatriques les plus fréquentes chez les sujets âgés avec la dépression (Beaudreau & O'Hara, 2008). Les symptômes anxieux n'atteignant pas le seuil clinique sont encore plus fréquents que les pathologies (Beekman et al., 2000), allant de 15% à 52,3% chez les seniors recrutés dans la population générale, et sont deux fois plus élevés chez les femmes, notamment au moment de la ménopause (Siegel & Mathews, 2015). De plus, même si ces symptômes anxieux ne sont qu'infra-cliniques, ils ne doivent pas être sous-estimés, car ils sont associés à une augmentation du risque de développer un trouble anxieux au stade clinique (Karsten et al., 2011). Bien que des études montrent une prévalence plus élevée des symptômes anxieux chez des sujets jeunes comparés à des sujets âgés (Caspi et al., 2005; Charles et al., 2001; Flint et al., 2010), la plupart des études ne prennent pas en compte les personnes hospitalisées ou institutionnalisées, avec pour résultante une prévalence moins forte chez les seniors (pour revue Bryant et al., 2008). De façon intéressante, l'étude de Teachman (2006) relie de manière curvilinéaire les symptômes anxieux à l'âge, comme l'étude de Teachman l'a décrit pour les symptômes dépressifs (voir section 2.4.2.1). Les symptômes anxieux augmentent jusqu'à environ 35 ans, puis diminuent pour remonter à nouveau vers 77 ans (Teachman, 2006).

L'anxiété est également fréquente chez les patients MA allant de 5% à 21% pour les pathologies anxieuses, jusqu'à 71% pour les symptômes anxieux. Certaines études rapportent également une augmentation de l'anxiété chez le patient atteint de démence, suivie d'une diminution dans les stades tardifs (pour revue Seignourel et al., 2008; Bierman et al., 2007). Une méta analyse regroupant 25 études indique que l'anxiété fait partie des SNP les plus rapportés dans la MA, et montre une prévalence globale de 39% (12% à 72% selon les études) des symptômes anxieux chez un total de 8109 patients (Zhao et al., 2016). Bien que la différence de fréquence rapportée soit importante, les auteurs indiquent qu'elle est principalement expliquée par l'âge d'inclusion des participants et la méthode d'évaluation de l'anxiété. Pour ce qui est des stades pré-démentiels, une méta-analyse montre que 14,3% à 31,2% des sujets MCI, en fonction du mode de recrutement, rapportent de l'anxiété (Chen et

al., 2018). Chez les SCD, les études montrent qu'ils rapportent plus de symptômes anxieux que les sujets âgés sains, bien qu'aucune étude n'évalue spécifiquement leur fréquence (Jessen et al., 2014; Perrotin et al., 2017).

2.4.3.2. Symptômes anxieux en tant que facteurs de risque et liens avec la cognition

Au vu de la prévalence des symptômes anxieux et de leur impact sur les autres aspects de la santé, de la diminution de la qualité de vie qui leur est associée et de leur coût élevé pour la sécurité sociale (Haupt et al., 2000; Vasiliadis et al., 2013), ils représentent un enjeu de santé publique important. En effet la présence d'anxiété chez les personnes âgées contribue à leur fragilité, à une limitation de leurs activités et même à la morbidité (Siegel & Mathews, 2015). Dans la démence de type Alzheimer, ces symptômes sont également associés à une diminution de la qualité de vie, ainsi qu'à un plus gros fardeau de l'aidant, en augmentant notamment la dépendance des patients (Hoe et al., 2006; Orrell & Bebbington, 1996), menant à leur placement en institution (Gibbons et al., 2002).

Les symptômes anxieux « trait » et « état » sont également associés à une moins bonne cognition voire à un déclin cognitif. En effet, des études rapportent que les symptômes anxieux sont associés à une moins bonne cognition de façon générale (Beaudreau & O'Hara, 2009; Booth et al., 2006; Hogan, 2003; Petkus et al., 2016; Wetherell et al., 2002; Yochim et al., 2013), et à de moins bonnes performances dans des domaines spécifiques tels que la mémoire de travail, la mémoire épisodique et sémantique (Gallacher et al., 2009; Petkus et al., 2016; Wilson et al., 2011; Yochim et al., 2013) et les fonctions exécutives (Beaudreau & O'Hara, 2009; Yochim et al., 2013). Une étude nuance tout de même ces informations en précisant que l'anxiété état peut également avoir un effet positif sur le fonctionnement cognitif général et sur le traitement des informations visio-motrices lorsqu'elle est légère (Potvin et al., 2013).

Comme indiqué précédemment (voir section 2.4.3.1), les personnes âgées présentant des déficits cognitifs manifestent plus de symptômes anxieux que des seniors cognitivement sains, mais ces symptômes sont également associés au déclin cognitif de façon longitudinale (Gallacher et al., 2009; Potvin et al., 2011; Santabárbara et al., 2020; Wilson et al., 2011). Cependant, ces résultats sont controversés car des études ne retrouvent pas ce lien (de Bruijn et al., 2014; Yang et al., 2020), ce qui pourrait être dû à des différences de méthode d'évaluation de l'anxiété entre ces études. De façon intéressante, l'étude de Potvin et collaborateurs (2011) a montré que les symptômes anxieux prédisaient un déclin cognitif chez la femme, mais que chez l'homme, seule l'anxiété atteignant le seuil clinique influerait sur le déclin cognitif. A l'opposé, le déclin cognitif ne prédit l'anxiété dans aucune configuration (Potvin et al., 2011).

Une plus grande incidence de démence a également été mise en évidence chez des sujets âgés présentant des symptômes anxieux (Geda et al., 2014; Petkus et al., 2016; Santabárbara et al., 2020; Wilson et al., 2011). Une étude longitudinale de Petkus et collaborateurs (2016), incluant 172 participants, a mis en évidence qu'un score élevé d'anxiété augmente la probabilité d'incidence d'une démence dans la population globale (voir figure 13), mais également en comparant des paires de jumeaux, l'un avec et l'autre sans symptômes anxieux (Petkus et al., 2016). Pour finir, l'anxiété influe également sur l'évolution de la MA du stade prédémentiel au stade démentiel, puisque les patients MCI présentant des symptômes anxieux voient leur risque de progression vers le stade MA augmenter sur 3 ans, comparés à ceux n'en présentant pas (Palmer et al., 2007).

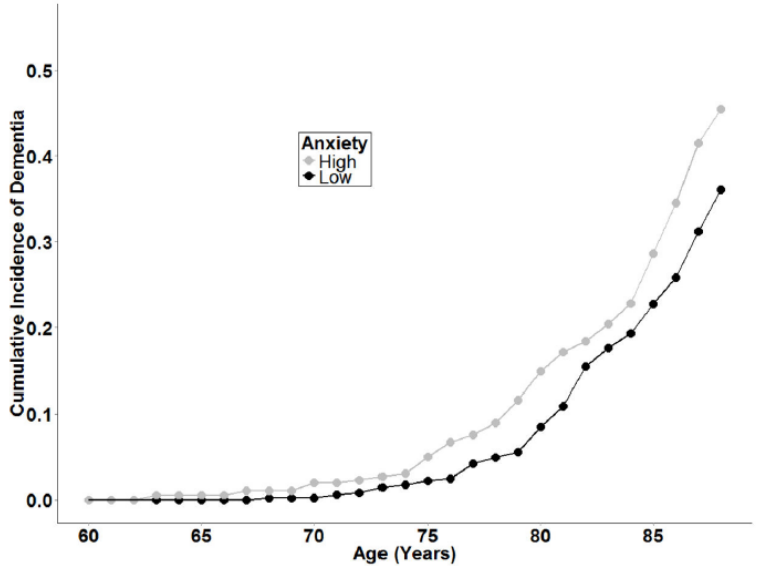

Figure 13 : Incidence cumulée de la démence par groupe d'anxiété, *d'après Petkus et al., 2016*.
Le groupe d'anxiété élevé correspond à un score supérieur à un écart-type au score de STPI (score d'anxiété état du *State-Trait Personality Inventory*), et le groupe d'anxiété faible correspond à un score inférieur à un écart-type.

2.4.3.3. Neuroimagerie des symptômes anxieux

2.4.3.3.1. Au cours du vieillissement normal

A ce jour, très peu d'études se sont intéressées aux substrats cérébraux des symptômes anxieux au cours du vieillissement, tandis qu'une plus large littérature est disponible concernant les différentes pathologies liées à l'anxiété. Chez les sujets âgés, une seule étude montre une diminution de l'épaisseur corticale dans le cortex frontal et temporal, l'insula, le parahippocampe, le cortex cingulaire antérieur et cortex préfrontal dorsolatéral (Pink et al., 2017). Deux études portant sur une population d'âge plus large, décrivent des résultats conflictuels. La première, de Blackmon et collaborateurs (2011), portant sur 25 sujets de 21 à 62 ans, indique une augmentation de l'épaisseur corticale dans le cortex orbitofrontal, et les régions temporopariétales, ainsi qu'une diminution du volume de l'amygdale gauche associées à des symptômes anxieux plus élevés (Blackmon et al., 2011). La seconde, de Donzuso et collaborateurs (2014), portant sur 121 sujets de 21 à 70 ans, montre uniquement une diminution de substance grise dans le cortex cingulaire antérieur et le cortex orbitofrontal médian

(Donzuso et al., 2014). La plupart des études sur les liens entre les symptômes anxieux et la substance grise portent sur des sujets adultes jeunes. Elles montrent que les symptômes anxieux infra-cliniques dans cette population seraient associés à une augmentation de volume de substance grise (Baur et al., 2012; Besteher et al., 2017), une diminution (Yamasue et al., 2008; Yin et al., 2016), ou même parfois les deux (Spampinato et al., 2009), dépendamment de la région cérébrale investiguée. Les augmentations de substance grise ont été décrites dans les régions préfrontales ventrolatérales, temporales supérieures et inférieures pariétales gauches, dans le gyrus pré- et post-central gauche, ainsi que le précunéus, le gyrus cingulaire moyen et l'hippocampe (Baur et al., 2012; Besteher et al., 2017; Spampinato et al., 2009), tandis que les diminutions concernent les régions préfrontales dorsolatérales, le gyrus cingulaire antérieur, et le gyrus parahippocampique. Cependant, le sens de l'association avec l'amygdale et le gyrus occipital est controversé (Baur et al., 2012; Spampinato et al., 2009; Yin et al., 2016). De façon générale, les régions les plus retrouvées sont le cortex préfrontal, l'amygdale et le cortex cingulaire, quel que soit le sens de l'association

Seules des études chez des seniors se sont intéressées aux liens des symptômes anxieux avec les modifications fonctionnelles vues en TEP-FDG, ou avec les modifications moléculaires de protéines amyloïdes vues avec différents marqueurs TEP. Ces études indiquent que les symptômes anxieux sont associés à une diminution du métabolisme du glucose cérébral global (Krell-Roesch et al., 2016), à une augmentation de la pathologie tau/amyloïde dans le cortex frontal et temporal médian (Lavretsky et al., 2009), et à une augmentation de la pathologie amyloïde uniquement dans l'amygdale, le thalamus, et le striatum (Hanseeuw et al., 2018).

2.4.3.3.2. Aux différents stades de MA

En termes anatomiques, les études n'ont pas montré de liens entre les symptômes anxieux et le volume de substance grise, notamment dans des ROI temporales médianes (i.e. hippocampes) chez des sujets SCD (Banning et al., 2019), MCI (Banning et al., 2019; Serra et al., 2010) et MA (Banning et al., 2019; Bruen et al., 2008; Huey et al., 2017; Mori et al., 2014; Serra et al., 2010), à l'aide du sous-

score d'anxiété du NPI-Q. Une étude sur cerveau entier a cependant montré une diminution du volume de substance grise dans le précunéus et le lobule pariétal inférieur dans un groupe de 26 patients MA (Tagai et al., 2014) à l'aide de l'échelle BEHAVE-AD (Behavioral Pathology in Alzheimer's Disease Rating Scale). Il serait donc intéressant de refaire les études avec l'échelle de NPI-Q dans chacun de ces groupes avec la méthode de cerveau entier, puisque les liens entre les symptômes d'anxiété et le volume de substance grise ne semblent pas spécifique à l'hippocampe.

Une seule étude s'est intéressée aux liens entre le métabolisme du glucose et les symptômes anxieux dans le cadre de la MA, mais aucune au stade prédémentiel(Hashimoto et al., 2006). Elle a montré que les patients MA anxieux présentaient, en comparaison des patients MA non anxieux, une diminution du métabolisme du glucose cérébral dans le cortex entorhinal, le parahippocampe antérieur, le gyrus temporal supérieur et l'insula associée à une augmentation de l'anxiété, ainsi qu'un métabolisme plus bas dans le pôle temporal antérieur et le temporal inférieur (avec une tendance pour le temporal supérieur et le parahippocampe).

En termes moléculaires, aucun lien n'a été montré entre les symptômes anxieux et la charge amyloïde chez des patients MA. Chez des patients MCI, les symptômes anxieux se sont révélés être associés à une augmentation des dépôts amyloïdes de façon globale ainsi que dans les régions frontales (Bensamoun et al., 2016). Plus indirectement, une étude a également montré que les patients MCI présentant une haute charge amyloïde avaient plus grande probabilité de présenter des symptômes anxieux (Krell-Roesch et al., 2019).

3. Etudes réalisées

3.1. Problématique et objectifs de la thèse

Depuis la découverte de la MA de nombreuses avancées ont été faites, notamment concernant les symptômes cognitifs et neurobiologiques qui y sont associés. Cependant, les modifications comportementales et neuropsychiatriques n'ont reçu que peu d'attention de la part de la communauté scientifique, bien que de plus en plus de chercheurs s'y intéressent. En effet, les défis actuels de la recherche sont de mieux comprendre les stades précliniques et les facteurs de risque de la maladie d'Alzheimer. Cela permettrait d'identifier une potentielle cible thérapeutique et de mettre en place des méthodes de prévention, mais aussi, au vu de l'absence actuelle de traitement efficace, de promouvoir le bien-être des patients et des aidants. Comme décrit précédemment, les symptômes anxieux et dépressifs sont courants chez les personnes âgées et représentent des facteurs de risque de déclin cognitif et de démence. Dans le cadre de la MA, ces symptômes sont exprimés chez presque tous les patients et sont associés à une aggravation de la maladie et à une diminution de la qualité de vie, à la fois des patients et des aidants. Cependant les études sont hétérogènes quant à leurs substrats cérébraux à la fois dans le vieillissement et dans la MA. Les bases neurobiologiques des sous-domaines des symptômes neuropsychiatriques, en particulier dans les premiers stades de la MA, restent donc mal comprises. De plus, aucune étude n'a combiné plusieurs modalités d'imagerie mesurant les modifications cérébrales classiquement associées à la MA dans un même échantillon, bien que l'approche multimodale en neuroimagerie soit une méthode complète qui permet de mieux comprendre et intégrer les associations observées.

Dans ce contexte, cette thèse vise à mieux comprendre, à l'aide de 3 études originales, les liens entre les facteurs psychoaffectifs (symptômes dépressifs et anxieux) et les atteintes structurales, fonctionnelles et moléculaires associées à la maladie d'Alzheimer. Chaque étude décrite ci-dessous utilise une approche *in vivo* de neuroimagerie multimodale, mais se concentre sur une étape différente de la maladie, commençant par le vieillissement normal (Etude 1), puis le stade à risque (étude 2 et 3) et enfin le stade clinique (Etude 2).

Dans une première étude, nous avons étudié les liens des symptômes dépressifs et anxieux avec l'âge, la cognition globale et la neuroimagerie dans une population de sujets cognitivement sains, allant de 19 à 86 ans. Au vu de la plus grande prévalence de l'anxiété et de la dépression chez les femmes, nous nous sommes également intéressés à l'interaction de ces associations avec le sexe, dans des populations d'hommes et de femmes séparées. Nous avons également effectué des analyses longitudinales sur un suivi de 2 ans en moyenne, afin d'établir si les scores baseline de symptômes anxieux et dépressifs prédisent une évolution de la cognition globale et des mesures de neuroimagerie, ou inversement (si la cognition et la neuroimagerie en baseline prédisent l'évolution des valeurs psychoaffectives).

Dans une deuxième étude nous nous sommes intéressés aux substrats cérébraux des symptômes anxieux et dépressifs dans une population à risque composée de SCD, et dans une population clinique présentant des atteintes cognitives et une pathologie amyloïde cérébrale avérée (MCI et MA amyloïde positifs).

La troisième étude concerne plus spécifiquement le groupe de SCD. En effet, c'est un groupe dit « à risque » de MA car il présente plus de risque de déclin cognitif (Kaup et al., 2015; Koppara et al., 2015), ou même de MCI ou de démence de type MA (Jessen et al., 2014; Mitchell et al., 2014; Barry Reisberg et al., 2010). Cependant, cette plainte ne serait pas toujours une conséquence de pathologie Alzheimer, mais pourrait aussi être due au vieillissement (Ponds et al., 1997), à des troubles du sommeil, ou à la présence de symptômes anxieux ou dépressifs (Clarnette et al., 2001; Comijs et al., 2002; Gamaldo et al., 2019; Kang et al., 2017; Lauriola et al., 2017; Paradise et al., 2011). De ce fait, des associations avec les biomarqueurs de MA n'ont pas toujours été rapportées dans cette population, ce qui pourrait être une conséquence de l'hétérogénéité du mode de recrutement, qui peut avoir lieu dans la population générale (SCD-communauté), ou dans des centres mémoire après consultation (SCD-clinique) (Perrotin et al., 2017).

L'objectif de cette étude a donc été de mieux caractériser les SCD en fonction de leur mode de recrutement, concernant leurs différences et similarités en termes de facteurs psychoaffectifs, de performance cognitive, et de plainte cognitive subjective. Nous avons également évalué les substrats de cette plainte en termes de symptômes anxieux et dépressifs, de cognition, et de neuroimagerie afin de mieux comprendre les raisons de cette plainte cognitive. Pour finir, nous nous sommes intéressés à l'évolution longitudinale (moyenne 2,4 ans), de ces différentes mesures, les différences de cartes d'atrophie entre les SCD, ainsi que la prédiction du déclin cognitif par les variables de facteurs psychoaffectifs et de plainte cognitive de baseline.

3.2. Contexte général de la thèse – Le Protocole IMAP+

Cette thèse a été réalisée dans le cadre du protocole de recherche clinique IMAP+ « Etude longitudinale en imagerie multimodale de la maladie d'Alzheimer à un stade précoce : biomarqueurs de détection et de progression et mécanismes physiopathologiques », piloté par la Dr Gaëlle Chételat, coordinatrice scientifique, et le Pr Vincent de la Sayette, médecin investigateur. Ce programme longitudinal a été mis en place en 2012 en lien avec le CHU de Caen, et fait suite au protocole IMAP démarré en 2008. L'objectif général de ce projet est d'identifier des marqueurs précoces de la maladie d'Alzheimer au stade pré-démentiel, voire présymptomatique, en termes de neuroimagerie, de neuropsychologie ou de biologie, permettant de mieux comprendre les mécanismes physiologiques de la maladie. Ce protocole, dont les inclusions ont commencé en 2008 et se sont terminées en 2016, a inclus des sujets cognitivement sains (à partir de 18 ans) de la population générale, ainsi que des patients à différents stades de MA recrutés dans des centres mémoire. Ces patients sont inclus selon leur diagnostic clinique, comprenant des participants avec une MA probable à un stade de démence légère (McKhann et al., 1984), des patients MCI (Petersen & Morris, 2005), et des patients SCD (ou SCI pour *Subjective Cognitive Impairment*) présentant des déficits cognitifs subjectifs sans déficits avérés. Chaque participant a réalisé une batterie de tests neuropsychologiques évaluant notamment des fonctions cognitives sensibles à la MA, un ensemble d'examens de neuroimagerie, ainsi qu'un

prélèvement sanguin, et ce en baseline ainsi qu'à différents temps de suivi allant jusqu'à 36 mois, en fonction du groupe d'inclusion, comme décrit sur la figure 14.

L'ensemble des données acquises et disponibles pour ce projet de thèse a donc été prétraité, contrôlé et analysé en parallèle du recrutement et des suivis des participants et des patients, avant mon arrivée dans l'équipe.

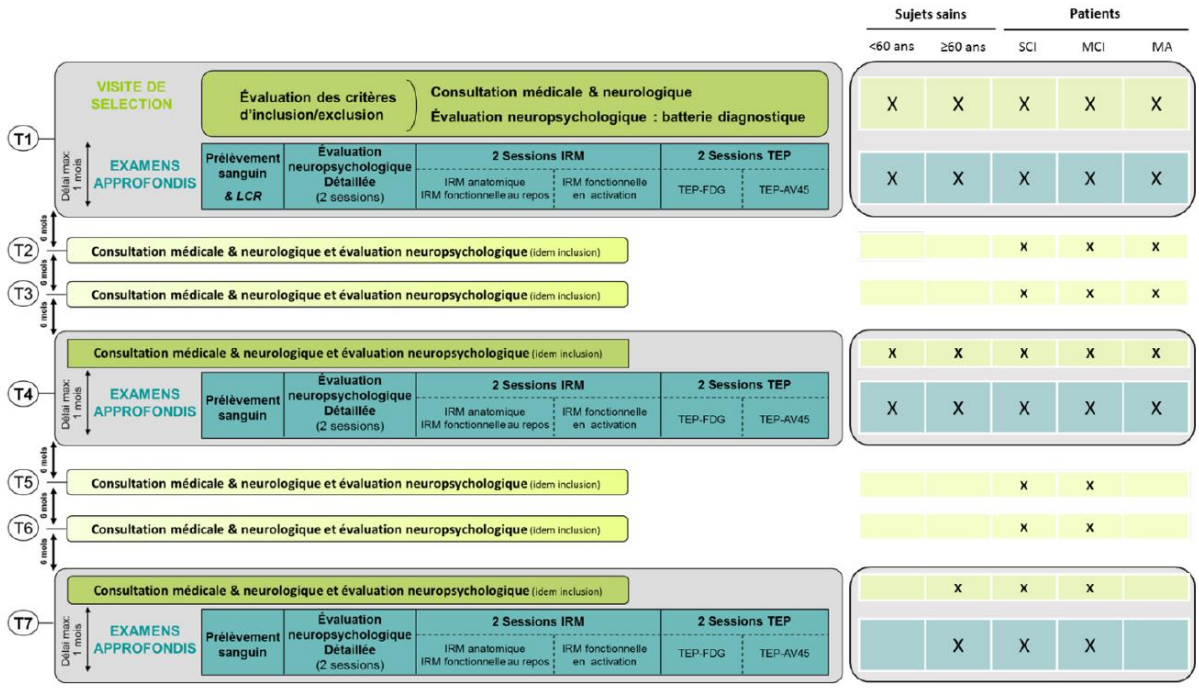

Figure 14 : Design général de l'étude IMAP+

Les évaluations cliniques et neuropsychologiques nécessaires au diagnostic des participants sont notées en vert, tandis que la partie expérimentale (i.e. examens neuropsychologiques complémentaires et examens biologiques et de neuro-imagerie) est notée en bleu. A droite, les croix indiquent quels groupes ont participé aux suivis longitudinaux cliniques et /ou en imagerie à 18 et 36 mois.

3.3. Etude 1 : Facteurs psychoaffectifs dans le vieillissement normal

Comme nous l'avons vu précédemment, les symptômes anxieux et dépressifs infra-cliniques, sont très fréquents (Bryant et al., 2008; Forlani et al., 2014), particulièrement chez la femme (Altemus et al., 2014), et sont associés à une diminution de la qualité de vie (Braam et al., 2014; Haupt et al., 2000; Vasiliadis et al., 2013) et à une augmentation du risque de développer une pathologie anxieuse ou dépressive (Chambers et al., 2004; Karsten et al., 2011). Chez les personnes âgées, ils sont également associés à un déclin cognitif, ainsi qu'à une augmentation du risque de développer une démence de type Alzheimer (Barnes et al., 2006; Donovan et al., 2014; Gallacher et al., 2009; Petkus et al., 2016; Santabárbara et al., 2020; Wilson et al., 2002). Or, l'étude et la compréhension de la maladie d'Alzheimer présymptomatique est actuellement un sujet d'intérêt dans le domaine du vieillissement.

Les études concernant les liens entre les symptômes anxieux et les modifications typiques de la MA sont peu nombreuses et conflictuelles ; celles évaluant l'interaction du sexe dans ce contexte sont plus rares encore. L'objectif de cette première étude était donc de mieux comprendre les liens entre les symptômes anxieux et dépressifs avec la neuroimagerie multimodale, ainsi que des potentielles différences en fonction du sexe, tout au long de la vie adulte. Les symptômes d'anxiété et de dépression étant des facteurs de risque modifiables par prévention et/ou traitement (Serfaty et al., 2009; van Zoonen et al., 2014; van't Veer-Tazelaar et al., 2009), l'amélioration de notre compréhension de leur impact relatif à ce niveau préclinique est particulièrement pertinente pour la gestion clinique et la réduction du risque, tant des troubles psychoaffectifs que de la MA.

Pour ce faire, 210 sujets cognitivement sains âgés de 19 à 86 ans (dont 101 hommes et 109 femmes) issus du protocole IMAP+ ont été inclus dans cette étude. Ces participants ont complété une batterie diagnostique mesurant notamment la cognition globale (*Mattis Dementia Rating Scale*), ainsi que des mesures de neuroimagerie comprenant une IRM structurale mesurant le volume de substance grise, une TEP mesurant le métabolisme du glucose cérébral à l'aide du radiotraceur ^{18}F-fluorodeoxyglucose et une TEP mesurant la charge amyloïde cérébrale à l'aide du radiotraceur ^{18}F-florbetapir. Les

symptômes d'anxiété état ont été mesurés au cours de l'examen d'IRM avec le questionnaire *Spielberger State-Trait Anxiety Inventory form Y-A* (STAI-A), et les symptômes dépressifs ont été mesurés par un clinicien durant la batterie diagnostique à l'aide du *Montgomery-Åsberg Depression Rating Scale* (MADRS). Des données de suivi sur une moyenne de 2 ans ont été utilisées pour des analyses longitudinaules, et étaient disponibles pour 167 participants. Dans un premier temps, nous avons mesuré les liens et l'interaction du sexe entre les symptômes psychoaffectifs et l'âge, puis avec la cognition globale et la neuroimagerie de façon transversale. Lorsque l'interaction du sexe était significative, nous avons répété les corrélations dans le groupe d'hommes et le groupe de femmes de façon individuelle, afin d'évaluer leurs spécificités. De façon longitudinale, nous avons également mesuré les liens de prédiction entre les facteurs psychoaffectifs en baseline et la pente d'évolution de la cognition globale et des mesures de neuroimagerie, et inversement.

Les résultats principaux de cette étude montrent qu'avec l'âge, les symptômes dépressifs diminuent dans la population générale, tandis que les symptômes anxieux augmentent uniquement chez les femmes. Une augmentation des symptômes anxieux est également associée à une diminution du volume de substance grise ainsi que du métabolisme du glucose cérébral, et ce uniquement chez les femmes. Les analyses longitudinales montrent qu'un bas volume de substance grise cérébrale est associé à une augmentation des symptômes anxieux, avec une interaction du sexe montrant cette relation uniquement chez les femmes et non chez les hommes. Aucune autre corrélation longitudinale n'a été mise en évidence.

Cette étude montre que les symptômes anxieux sont liés à la neurodégénérescence et donc à une plus grande vulnérabilité cérébrale au cours du vieillissement, et montrent également un effet important du sexe, puisque cette relation a été retrouvée uniquement chez la femme. Les résultats longitudinaux suggèrent que les symptômes anxieux pourraient être une conséquence de ces modifications cérébrales. Cependant d'autres interprétations sont possibles, par exemple, les symptômes anxieux et la neurodégénérescence pourraient être causés par un autre facteur extérieur non étudié ici. De plus,

ces interprétations restent basées sur les résultats de corrélations, certes à partir de données longitudinales, mais néanmoins insuffisantes pour établir avec certitude un lien causal. Enfin, cette étude ne permet en aucun cas d'écarter l'hypothèse selon laquelle les symptômes dépressifs représenteraient un facteur de risque de la maladie, simplement nous n'avons pas apporté d'évidences en faveur de cette hypothèse dans cette étude. En conclusion, cette étude souligne la nécessité de prévenir, de surveiller et de traiter les symptômes d'anxiété au cours du vieillissement, en particulier chez les femmes, afin d'améliorer la santé mentale et de réduire potentiellement le risque de MA.

Ces résultats ont fait l'objet d'une communication orale en 2019 (*Medit-ageing Consortium meeting*) et l'article correspondant à cette étude est actuellement soumis à la revue *Translational Psychiatry*.

Sex-specificities in anxiety and depressive symptoms across the lifespan and their links with multimodal neuroimaging

Running title: Anxiety is related to neurodegeneration in women

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Abstract

Improving mental health and well-being in older adults is a priority in our aging societies. Anxiety and depressive symptoms are associated with impaired well-being, higher risk of developing psychoaffective disorders and are risk factors for Alzheimer's disease (AD). We aimed to assess the relationships between anxiety and depressive symptoms with age and to AD neuroimaging biomarkers across the adult lifespan, to further our understanding of their impact in the elderly, with a focus on assessing sex specificities. 210 cognitively normal participants aged 19 to 86 years (101 men and 109 women) completed assessments of anxiety and depressive symptoms with Spielberger State-Trait Anxiety Inventory form Y-A and Montgomery-Åsberg Depression Rating Scale respectively, and neuroimaging measurements including structural MRI, FDG-PET and amyloid-PET. 167 of those were followed-up over a mean period of 2 years. We assessed the changes in anxiety and depressive symptoms with age, and their links with neuroimaging measures, both cross-sectionally and longitudinally, testing for the moderating effect of sex. Depressive symptoms decreased with age, while anxiety symptoms increased only among women. Higher anxiety symptoms were associated with lower grey matter (GM) volume and glucose metabolism, with a significant interaction of sex, indicating that this relationship was significant in women but not in men. Longitudinally, only low GM volume at baseline predicted an increase in anxiety symptoms with time. This study emphasizes the need to consider anxiety symptoms in assessments for dementia risk, particularly in women.

1. Background

Subclinical symptoms of anxiety and depression are frequently observed in older adults[1,2], and are associated with a high risk of developing anxiety and depressive disorders[3–5]. Elevated levels of anxiety and depression are associated with a worsening of the quality of life of seniors, fragility, sleep problems and cognitive disorders, or even with increased rates of mortality, morbidity and disability[1,4,6].

Moreover, subthreshold anxiety and depressive symptoms were found to increase the risk of developing dementia[7–9]. Compared to individuals without symptoms of anxiety and depression, they were twice as likely to develop amnestic Mild Cognitive Impairment (MCI), a prodromal phase of Alzheimer's dementia, over 3–6 years[10]. Anxiety and depressive symptoms could also be a reaction to a perceived cognitive decline[11] and/or a prodromal manifestation of an underlying AD pathology[12]. Assessing the links between these factors and the neuroimaging markers of neurodegeneration, namely, grey matter (GM) volume using structural magnetic resonance imaging (MRI) or brain glucose metabolism using fluorodeoxyglucose 18F (FDG) uptake on positron emission tomography (PET), but also more specific biomarker of AD e.g. brain amyloidosis with amyloid tracer retention on PET imaging[13–15], both cross-sectionally and longitudinally, would help further understanding their relevance across the adult lifespan.

Previous studies showed that anxiety and depressive symptoms were associated with poorer cognition or cognitive outcome[8,16–22]. Only few studies investigated the neural correlates of subclinical anxiety and depression in cognitively normal older adults. They showed that anxiety and depressive symptoms were associated with reduced global cortical thickness[23–25] and GM volume[26] notably in the frontal cortex. Moreover, both subclinical anxiety and depressive symptoms were associated with lower global cortical glucose metabolism[27]. Mixed results were found for amyloid load, with studies reporting a positive association between anxiety/depressive symptoms and amyloid deposition as measured with PET[28–30], while others did not find any relationship[31]. Finally, higher amyloid load was found to predict an increase in depressive symptoms[10,30].

Women have twice the lifetime rates of depression and most anxiety disorders, show more subclinical anxiety and depression symptoms[32], and also have higher risk of developing dementia[9] compared to men. Only few studies however investigated the sex specificities in the neural substrates of anxiety and depression symptoms. They reported conflicting results, showing that depressive symptoms were associated with decreased GM volume in the hippocampus and frontal regions only in males[33–35], or with decreased GM volume in frontal areas only in women[36]. Only one study assessed the relationship of anxiety symptoms with GM volume considering possible sex-differences, and found that harm avoidance - a core feature of anxiety - was associated with reduced GM in left anterior prefrontal cortex only in women[37]. No study assessed sex-specificities in the links of depressive and anxiety symptoms with brain glucose metabolism or amyloid load to date.

The aim of this study was to further our understanding of the relationships of anxiety and depressive symptoms to neuroimaging measures, and sex specificities, throughout the adult lifespan. Given that anxiety and depressive symptoms are modifiable risk factors through prevention and treatment[38–40], improving our understanding of their relative impact at this preclinical stage and level is particularly relevant for clinical management and risk reduction of both psychoaffective disorders and AD.

To do so, we first assessed the relationship of anxiety and depressive symptoms with age and the possible interactive effect of sex. Secondly, we investigated the links between these psychoaffective factors and global cognition and memory, as well as neuroimaging biomarkers including GM volume, glucose metabolism and amyloid deposition. We then assessed the longitudinal changes of anxiety and depressive symptoms over a 2-year- follow-up period. Lastly, we assessed the predictive value of baseline psychoaffective symptoms on neuroimaging changes over time, and reversely the predictive value of baseline cognitive and neuroimaging measures on changes over time in anxiety and depressive symptoms.

2. Methods

2.1. Participants

Two hundred and ten (101 men and 109 women) cognitively normal participants aged 19 to 86 years from the 'Imagerie Multimodale de la Maladie d'Alzheimer à un stade Précoce' (IMAP+) cohort in Caen, France, were included in the present study. Participants were recruited from the general population through advertisement or word of mouth. They had no history or clinical evidence of neurologic or psychiatric disorder, no psychotropic drug intake, and performed in the normal range in all neuropsychological tests (including tests of episodic memory, working memory, language skills, executive functions, and visuospatial abilities). Notably, none of the participants met diagnostic criteria for major depression or anxiety disorder, as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition[41–43]. The IMAP+ study was approved by the local ethics committee, and written informed consent was obtained from all participants after complete description of the study. Longitudinal data was available for 167 of the participants.

2.2. Psychoaffective assessment

Depressive symptoms were assessed using the clinician-administered Montgomery-Åsberg Depression Rating Scale (MADRS), a 10-item questionnaire[44] used to rate the severity of depressive symptoms (from 0 to 60) at the time of the evaluation. State anxiety symptoms were assessed with the Spielberger State-Trait Anxiety Inventory form Y-A (STAI-A), a 20-item self-report questionnaire[45] rating the severity of anxiety symptoms (from 20 to 80) at the time of the evaluation. For both scales, higher scores indicated higher levels of symptoms of anxiety and depression; yet scores remained low, as participants were screened so as not to meet diagnostic criteria for major depression or anxiety disorder. Our goal was to assess anxiety and depressive symptoms on a continuum[46,47] so these scores were used as continuous variables.

2.3. Global cognition assessment

Global cognition was measured using the 30-point scale Mini Mental State Examination (MMSE; scores from 0 to 30)[48] and the 144-point global score of the Mattis Dementia Rating Scale (DRS)[49].

2.4. Neuroimaging data

Grey Matter (GM) volume was assessed with Magnetic Resonance Imaging (MRI), brain glucose metabolism with 18F-fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) and amyloid deposition with florbetapir-PET. Global values of GM volumes, FDG and florbetapir standardized uptake value ratios (SUVr) were obtained as described below and used as continuous variables in the following analyses. All participants underwent neuroimaging scans on the same MRI and PET scanners at the Cyceron Centre (Caen, France) within 3-month interval from the psychoaffective and cognitive assessments.

2.4.1. Neuroimaging acquisition

MRI data, high-resolution T1-weighted anatomical images, were acquired on a Philips Achieva 3.0 T scanner using a 3D fast-field echo sequence (3D-T1-FFE sagittal; repetition time = 20 ms; echo time = 4.6 ms; flip angle = 10°; 180 slices with no gap; slice thickness = 1 mm; field of view = 256 x 256mm^2; in-plane resolution = 1 x 1mm^2).

PET scans, both FDG and florbetapir, were acquired with a Discovery RX VCT 64 PET-CT device (General Electric Healthcare) with a resolution of 3.76 x 3.76 x 4.9mm^3 (field of view = 157 mm). Forty-seven planes were obtained with a voxel size of 1.95 x 1.95 x 3.27 mm^3. A transmission scan was performed for attenuation correction before the PET acquisition.

FDG-PET acquisitions were performed after at least 6 hours of fasting, and after 30 minutes at rest in a dark and quiet room. Participants were injected intravenously with ~180 MBq of FDG and after 50 minutes, the participants underwent a 10 minutes' scan. Florbetapir-PET scan was acquired for each participant during 20 minutes, 50 minutes after the intravenous injection of ~4 MBq/kg of florbetapir, except for 14 participants (8 men and 6 women) who had a 10-minute (50 to 60) acquisition.

2.4.2. Neuroimaging processing

The Statistical Parametric Mapping version 12 (SPM12) software (Wellcome Trust Centre for Neuroimaging, London, UK) was used for all neuroimaging processing steps.

T1-weighted MRI images were first segmented and spatially normalized to the Montreal Neurological Institute (MNI) space. The normalized GM segments were then modulated to correct for non-linear warping effects[50–52].

PET images were corrected for partial volume effects using the Müller-Gärtner method, then coregistered onto their corresponding MRI, and normalized with the deformation parameters used for the MRI procedure. The cerebellar GM was then used as the reference region to quantitatively normalize the resultant images[50–53].

Total GM volume and FDG-PET global value were obtained for each participant using a binary mask of GM (including voxels with a GM probability > 30% excluding the cerebellum) on the corresponding preprocessed images. The global neocortical SUVr value was calculated from the florbetapir-PET images using a neocortex mask (including all regions but the cerebellum, hippocampus, amygdala and subcortical grey nuclei), as described in details elsewhere[51].

2.5. Longitudinal assessment

All psychoaffective, cognitive and imaging measures described above were also obtained at follow up, i.e. after a mean duration of 2 years (± 0.12 years). Participants with follow-up measures of anxiety and depressive symptoms, and at least one of the other measures of interest, were included in the longitudinal analyses (total n=167, men n=81, women n=86). A slope of change for each variable and each participant was calculated with simple linear regression[54] 'y = ax + b' (with y: score of interest; a: slope of the regression; x: number of months from the initial evaluation; b: intercept) and used in the longitudinal analyses as measures of rate of change.

2.6. Statistical analysis

2.6.1. Cross sectional data

To assess the relationship between psychoaffective factors and age, we performed multiple regressions between depressive and anxiety symptoms with age, correcting for education and anxiety symptoms or depressive symptoms respectively. Indeed, because anxiety and depression scores are expected to be related, all analyses with one of these measures was corrected for the other and inversely. To evaluate the effect of sex, we performed General Linear Models (GLMs) and tested the interactive effect of sex on the association between anxiety or depression and age (e.g. MADRS × Age × Sex). If a significant interaction was found, we repeated the multiple regressions within the subgroups of men and of women separately.

The substrates of psychoaffective factors were assessed using multiple regressions, between psychoaffective measures (i.e. depressive symptoms and anxiety symptoms) on the one hand, and global cognition and imaging data (i.e. GM volume, glucose metabolism and amyloid load) on the other hand. Results are presented with correction for level of education and anxiety symptoms for correlations with depressive symptoms, and for level of education and depressive symptoms for correlations with anxiety symptoms, to independently evaluate the links of those psychoaffective symptoms with cognition and brain parameters along the ageing process. We then performed GLMs to evaluate the possible interactive effects of sex on these associations (e.g. MADRS × Global DRS × Sex) and repeated the multiple regressions within the subgroups of men and of women separately if the interaction was significant. Age was not included as a covariate in our main analyses because we were specifically interested in assessing the age-related relation between anxiety and depressive symptoms with global cognition and neuroimaging markers. However, all analyses were repeated, and results were also reported, with age as a covariate to check whether possible relationships where

entirely driven by age. Pairwise deletion was used in case of missing data and all statistical analyses were performed using the STATISTICA software (v13.0, StatSoft Inc., Tulsa, OK).

2.6.2. Longitudinal data

The slopes of change of psychoaffective factors were compared to zero with one sample t-tests to assess whether they changed over time. We then compared the slopes of change of psychoaffective factors between men and women with ANCOVA, correcting for education, to assess sex-specificities. We then performed multiple regressions between baseline psychoaffective measures and slopes of change in global cognition and imaging data, and then between baseline cognition and imaging data and slopes of change in psychoaffective measures, correcting for baseline education and baseline anxiety symptoms or depressive symptoms depending of the analysis. When specified, baseline age was also included in the model as a covariate to assess the links independently from age effects. Lastly, we performed GLMs to evaluate the interactive effect of sex in the predictions (e.g. Baseline MADRS × slope of Global DRS × Sex), and repeated the multiple regressions in subgroups of men and of women separately when the interactive effect of sex was significant. Pairwise deletion was used in case of missing data and all statistical analyses were performed using the STATISTICA software (v13.0, StatSoft Inc., Tulsa, OK).

2.6.3. Supplementary analyses

Since neither the anxiety nor the depressive score showed a normal distribution, correlation analyses were repeated with non-parametric Spearman's correlation tests. Also, as an important floor effect was observed on MADRS data with a large number of participants having a score of zero, we repeated all analyses with depressive symptoms excluding these participants, i.e. within a subgroup of participants with at least one depressive symptom (n=89). The cross-sectional and longitudinal multiple regressions between depressive symptoms and age, cognition and brain parameters were assessed in this subgroup, correcting for level of education and anxiety symptoms, and when specified,

for age. The interactive effect of sex was also tested in this subsample in order to check that the results were consistent and not driven by the floor effect.

3. Results

3.1. Description of the population

The demographics of the study participants are listed in Table 1 (see age distribution in supplementary figure 1) and in supplementary table 5 for the participants included in the longitudinal analyses. Amongst the 210 cognitively unimpaired adults, 48% were women. There was no difference between men and women in age, education, or anxiety symptoms and depressive symptoms. However, we found lower GM volume and higher glucose metabolism in women. Additionally, as expected, anxiety and depression scores were correlated (non-parametric p=0.001).

3.2. Psychoaffective associations with age

We found a decrease in depressive symptoms with age, while anxiety symptoms did not significantly change with age (Table 2 and Figure 1). This result did not hold in non-parametric analyses (p=0.191; supplementary table 1 and 2).

Regarding sex differences in age-related associations with psychoaffective factors, we found no moderating effect of sex on depressive symptoms, and a trend on anxiety symptoms (Table 2 and Figure 1). Analyses within each sex subgroup revealed that anxiety symptoms significantly increased with age in women but not in men (Table 2 and Figure 1). Non parametric analyses showed similar results (supplementary table 1).

Findings for depressive symptoms in the subgroup with at least one depressive symptom were similar but less significant (supplementary table 3).

3.3. Psychoaffective associations with cognition

Neither depressive symptoms nor anxiety symptoms were associated with global cognition (Table 2). We found the same results, in the subgroup with at least one depressive symptom, and/or when also

correcting for age (supplementary table 1, 2, 3 and 4). There was no moderating effect of sex in any of these analyses (Table 2; supplementary table 1, 3 and 4).

3.4. Psychoaffective associations with brain parameters

Depressive symptoms showed no association with either GM volume, or amyloid deposition, and only a trend for brain glucose metabolism which tended to increase as depressive symptoms increased (Table 2). No moderating effect of sex was observed (Table 2). Results were similar with non-parametric analyses, in the subgroup with at least one depressive symptom, and/or when also correcting for age (supplementary table 1, 2, 3 and 4).

Anxiety symptoms were associated with lower brain glucose metabolism, weakly associated with lower GM volume, and not associated with amyloid (Table 2 and Figure 2). Sex moderated relationships with glucose metabolism and GM volume such that higher anxiety symptoms were associated with lower GM volume and brain glucose metabolism only in women (Table 2 and Figure 2).

Non parametric analyses showed the same moderating effects of sex and the same findings within each sex group (supplementary table 1). Effects were attenuated when correcting for age but findings remained similar (supplementary table 4).

3.5. Longitudinal changes and links of psychoaffective factors with cognition and brain parameters

There was no significant change over time in psychoaffective factors, cognitive measures and glucose metabolism. GM volume decreased over time and amyloid deposition increased over time (additional files 5). When comparing the slopes of change of the different measures over time between men and women, we only found a trend for amyloid load, and one-sample t-test in each sub-group showed an increase in amyloid load only in women (supplementary table 5).

Baseline psychoaffective factors did not predict slopes of change in cognition or brain measures in the main analyses (Table 3), with non-parametric analyses (supplementary table 6), in the subgroup with

at least one depressive symptom (supplementary table 3) and/or after correcting for age (supplementary table 7).

As for the relationships between baseline cognition or brain measures and slope of change in psychoaffective factors, low GM volume at baseline predicted increase in anxiety symptoms over time (Table 3) with a trend for an interaction with sex indicating that this relationship was found in women, but not in men (Table 3). Non parametric analyses and those correcting for age showed similar results (supplementary table 6 and 7).

4. Discussion

To our knowledge this is the first study to assess the links of anxiety and depressive symptoms with cognition and multiple neuroimaging biomarkers (i.e. GM volume, glucose metabolism and amyloid deposition), together with sex-specificities, across the adult lifespan. We showed that depressive symptoms decreased with age, but were not associated with cognitive or neuroimaging measures. We showed sex-specific effects with anxiety symptoms, in that they increased with age, and were associated with lower GM volume and brain glucose metabolism, only in women.

Psychoaffective factors associations with age

When assessing the link with age in the whole sample, we found no change in anxiety symptoms, but an age-related decrease in depressive symptoms. This trend remained after removing participants who scored 0 in the cross-sectional analysis. Consistently, we also found a trend for a decrease in depressive symptoms in our longitudinal analysis. Our results are supported by those from previous studies who reported a decrease in the prevalence of mood disorders[55] or negative affect[56] with age. This decrease is thought to reflect better coping skills in older adults, with avoidance of negative interactions, and/or lower physiological arousal in response to emotional events[56]. The lack of association between age and anxiety symptoms might reflect the lower sensitivity of anxiety to age effects and/or methodological choices such as the anxiety scale or the population.

Cognitive correlates of psychoaffective symptoms

In this study we found no links between anxiety or depressive symptoms and global cognitive performance. This is at odds with previous studies that reported a relationship between increased anxiety and depressive symptoms and decreased global cognition and memory performance in elders[16–18,21,22]. This might be due to the fact that previous studies focused on elderly population while we cover the entire adult age range, and that we assessed cognition as a whole without focusing on specific cognitive domains. Also, previous studies focused on trait anxiety (i.e. a personality trait), while we assessed state anxiety, suggesting that only the former would influence cognitive performance. This is in line with a previous study also showing that state anxiety in older adults was not deleterious for cognitive performance and can even be beneficial, depending on the cognitive domains[57].

Neuroimaging correlates of psychoaffective symptoms

Depressive symptoms were not associated with neuroimaging markers (i.e. GM volume, glucose metabolism, and amyloid load) in this study, either cross-sectionally or longitudinally. Previous studies regarding this matter showed mixed results, some reporting an association of depressive studies with brain parameters[25,27,28,30,35,41,58], while others didn't[36,59]. This might be related to the age range considered, as all studies assessing the same large age range than in the present study, covering the full adult life span, did not find an association (range 21-62 years[59]; range 37-71[36]); while all the studies that found a link assessed only elderly[25,27,28,30,35,41,41,58]. It is thus possible that this link is specific to the elderly, or that those associations are different depending on age.

In contrast, we found anxiety symptoms to be associated with lower GM volume and glucose metabolism, which is consistent with previous studies in young and elderly adults[23,24,26,27]. This link was found specifically with neurodegeneration, while no relationship was found with amyloid load, suggesting that it is not directly related to this AD pathological change. Only one study found an association but only in subcortical studies that were not assessed here[29]. Decrease in GM volume, cortical thickness, brain activity, and glucose consumption is observed in ageing and still more in

AD[60,61]. The fact that anxiety symptoms were associated with neurodegeneration biomarkers suggest that individuals with anxiety undergo more severe brain aging and/or are more vulnerable to age-related neurodegenerative changes which might in turn reduce brain reserve and increased risk of developing dementia.

Longitudinal relationships

However, our longitudinal analyses showed that low baseline GM volume predicted an increase in anxiety symptoms, while baseline anxiety did not predict any change in cognitive or neuroimaging variables. This finding suggest that neurodegeneration/structural changes precede and possibly lead to anxiety symptoms, rather than the reverse[62]. However, an additional risk factor may synergistically interact with neurodegeneration, or may lead to neuropsychiatric symptoms with a cofounder such as age[24]. This might not exclude other possible mechanisms, such as anxiety/depression being responsible for neurodegenerative processes and/or amyloid deposition – even if we failed to find evidence in support of these alternative hypotheses. Importantly, the different neuropsychiatric symptoms might have distinct causal relationships with brain integrity and dementia/Alzheimer's disease, which would stress the relevance to assess them each separately instead of as a global measure of neuropsychiatric symptoms.

Sex differences

Studies have shown that women tend to show more anxiety and depressive symptoms than men[32], and that their risk to develop AD is also higher[9]. We thus aimed to assess the effect of sex on age-related changes in psychoaffective factors and on their links with cognition and neuroimaging measures. Interestingly, we showed sex-specificities in anxiety symptoms with age across the adult lifespan, and in their links with neuroimaging biomarkers. More specifically, we found anxiety symptoms to increase with age only among women, and to be associated with neurodegeneration (being GM volume loss or glucose hypometabolism) also in women only. These findings are in line with previous studies reporting higher anxiety levels in elderly women compared to elderly men[63], and

decreased frontal GM volume associated with higher anxiety-related personality traits only in women[37]. Here we extend the finding of specific anxiety-related brain changes in women to brain function (glucose metabolism) as well. It is possible that women are more vulnerable to anxiety symptoms than men, which could be at least partly related to hormonal differences. Indeed, the difference in prevalence of anxiety symptoms between men and women arise at puberty and the menstrual cycle, pregnancy and menopause are triggers for onset, recurrence and exacerbation of affective disorders [32]. The higher level of anxiety symptoms in women, which is associated with neurodegeneration, could partly explains their higher risk of developing AD.

Methodological considerations and perspectives

In line with previous studies[64,65], anxiety symptoms and depressive symptoms are interrelated. Yet we were able to evidence specific relationships with brain measures as the relationships between e.g. anxiety and neurodegeneration biomarkers remained significant when correcting for depression. This emphasizes the differences between these two measures as actually reflecting distinct psychoaffective factors, that show different sensitivity to age and independent relationships with neuroimaging data, highlighting the relevance to assess, and account for them both[19].

One of the limitations of our study refers to the small number of participants reporting depressive symptoms (43%). This was expected as all our participants were cognitively healthy community-dwelling participants selected for the lack of clinically significant anxiety or depression. However, this limited the variability of the measure and thus both the validity but also the sensitivity (power) of our statistical tests when assessing the effect of age or links with cognition/neuroimaging. To limit this bias and verify the validity of our findings, we repeated all analyses with non-parametric tests, as well as in a subgroup only including individuals with at least one depressive symptom, and findings were considered as relevant only if they remained significant in this subgroup. However, we cannot exclude the fact that this floor effect and related low variability in the measure prevented us from detecting subtle changes with age and/or links with cognition/neuroimaging. Additionally, the mean duration of

the follow-up period in our longitudinal analyses was 2.4 years, which might not be enough to capture protracted age-related (and/or preclinical-AD related) processes associated with very subtle changes. Moreover, our study focused on a sample of highly educated cognitively normal participants with subclinical anxiety and depression, so our results could not be generalized to the global population. Future work could investigate anxiety and depressive symptoms in a larger spectrum of adults in terms of cognition and psychoaffective state, with a longer follow-up. Ideally, interventional studies would allow researchers to assess the impact of reducing anxiety and depressive symptoms on cognition, brain integrity, and risk of AD.

Conclusions

Our results showed, using multimodal neuroimaging, a link between anxiety symptoms and lower GM volume and glucose metabolism. They also suggest that the rate of change in anxiety symptoms depends on GM volume, but it is also possible that neurodegeneration results from greater anxiety. Importantly, we highlighted sex-specificities as these relationships were only found in women. Thus, women showed age-related increase in anxiety and anxiety was specifically related to neurodegeneration in women. This study highlights the relevance of assessing anxiety symptoms early as part of dementia screening measures, especially in women.

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6. Conflicts of interest

The authors declare that they have no conflict of interest.

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8. Figure:

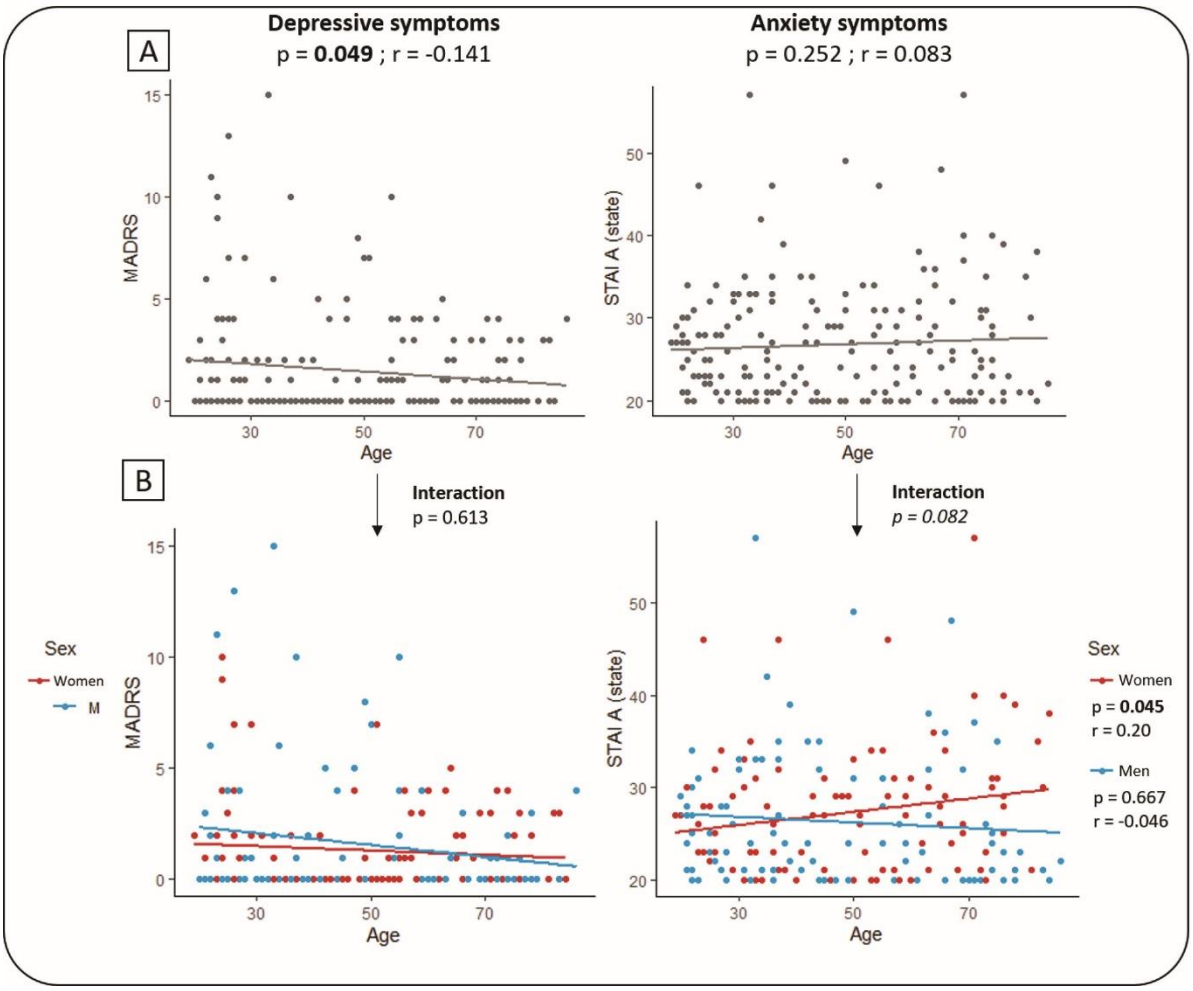


Figure 1: Multiple regressions of psychoaffective factors with age and interactions with sex. Graphs indicate p and r values of multiple regressions. **A:** Multiple regression of depressive symptoms or anxiety symptoms with age, corrected for the level of education and anxiety symptoms or depressive symptoms respectively. **B:** Interactive effects of sex on the multiple regression of depressive symptoms or anxiety symptoms with age, corrected for the level of education and anxiety symptoms or depressive symptoms respectively, in the group of Men and Women separately. Values in bold correspond to significant p values ($p<0.05$) and values in italic correspond to trends ($0.01<p<0.05$). *MADRS* Montgomery-Asberg dementia rating scale, *p* p value, *r* r value, *STAI A* Spielberger state-anxiety inventory state form.

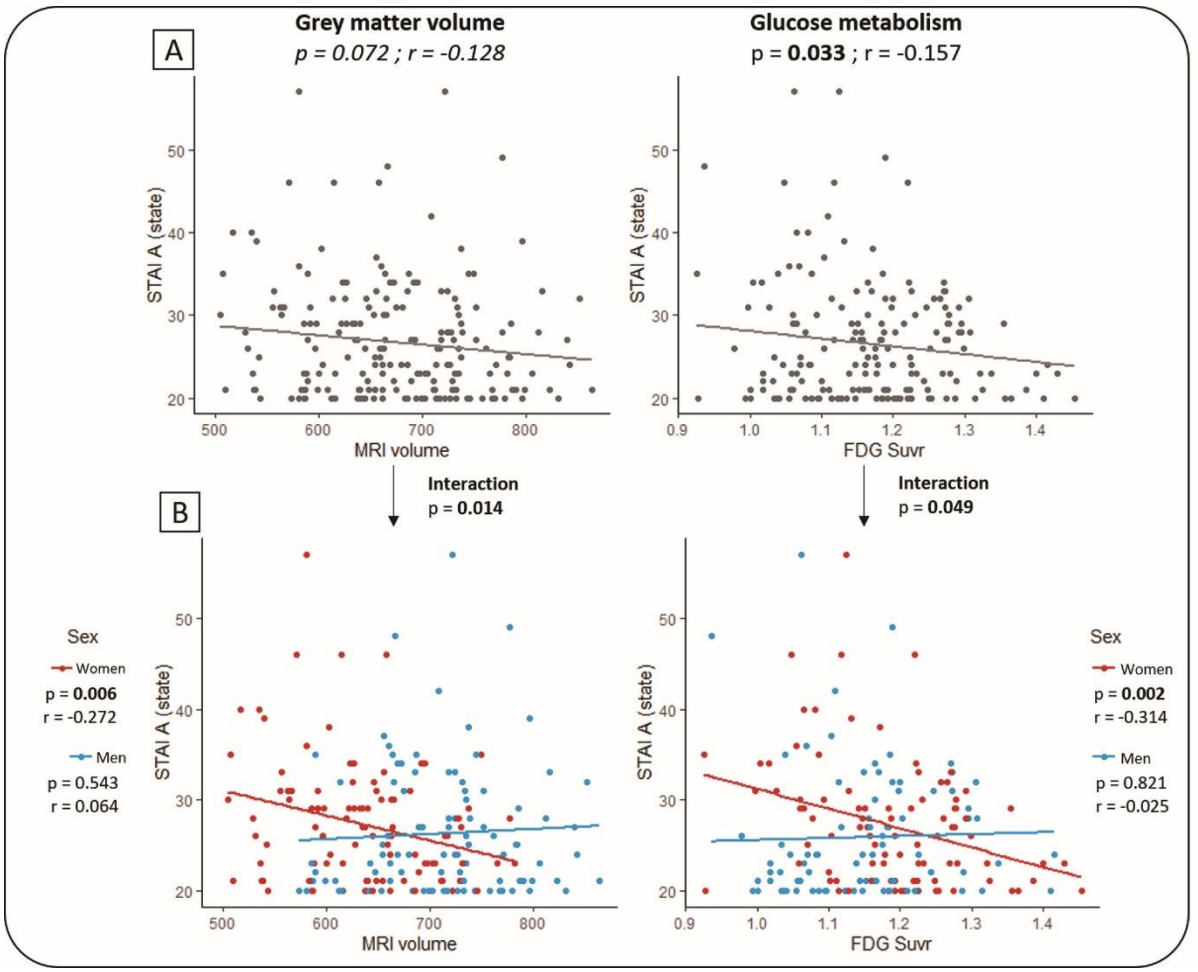


Figure 2: Sex-specific relationships between psychoaffective factors and neuroimaging measures. Graphs indicate p value and r value of multiple regressions. **A:** Multiple regression of grey matter volume and glucose metabolism with depressive symptoms or anxiety symptoms, corrected for level of education and anxiety symptoms or depressive symptoms respectively. **B:** Interactive effects of sex on the links between anxiety symptoms, and grey matter volume or glucose metabolism, corrected for level of education and depressive symptoms, showing a negative relationship in women only. Values in bold correspond to significant p values ($p<0.05$) and values in italic correspond to trends ($0.01<p<0.05$). *FDG* Fluorodeoxyglucose, *MADRS* Montgomery-Asberg dementia rating scale, *MRI* Magnetic resonance imaging, *p* p value, *r* r value, *STAI A* Spielberger state-anxiety inventory state form.

9. Tables

Table 1: Cross-sectional study sample characteristics.

	Total population	n	Men	n	Women	n	ANOVA
Age	48.41 ± 18.99	210	47.51 ± 19.32	101	49.25 ± 18.73	109	0.508
Level of education	13.18 ± 3.16	210	13.33 ± 3.43	101	13.05 ± 2.89	109	0.521
Depressive symptoms (MADRS)	1.44 ± 2.52	210	1.61 ± 2.98	101	1.29 ± 2.02	109	0.367
Anxiety symptoms (STAI A)	26.73 ± 7.04	198	26.24 ± 7.23	96	27.20 ± 6.85	102	0.341
Cognition (MMSE)	29.26 ± 0.90	210	29.28 ± 0.81	101	29.24 ± 0.98	109	0.782
Global cognition (DRS)	141.81 ± 2.56	209	141.65 ± 2.84	100	141.96 ± 2.27	109	0.378
GM volume	671.49 ± 79.06	207	712.98 ± 69.39	98	634.18 ± 68.04	109	**0.000**
Glucose metabolism	1.16 ± 0.10	189	1.15 ± 0.10	91	1.18 ± 0.11	98	**0.048**
Amyloid load	0.91 ± 0.11	138	0.90 ± 0.11	70	0.91 ± 0.11	68	0.321

Values indicate mean ± standardized deviation. Values in bold correspond to significant ANOVA comparing men and women, p values ($p<0.05$). *DRS* Dementia Rating Scale, *MADRS* Montgomery-Åsberg Depression Rating Scale, *MMSE* Mini Mental State Examination, *STAI A* Spielberger state-anxiety inventory state form.

Table 2: Cross-sectional relationships of psychoaffective factors to global cognition and neuroimaging measures and interaction with sex.

Depressive symptoms (MADRS)	Total group	Interactions with sex	Men	Women
Age	**0.049 (-0.141)**	0.613	-	-
Global cognition (DRS)	0.423 (-0.060)	0.895	-	-
GM volume	0.388 (0.062)	0.233	-	-
Glucose metabolism	*0.069 (0.135)*	0.307	-	-
Amyloid load	0.940 (0.006)	0.865	-	-
Anxiety symptoms (STAI A)	Total group	Interactions with sex	Men	Women
Age	0.252 (0.083)	*0.082*	0.667 (-0.046)	**0.045 (0.200)**
Global cognition (DRS)	0.712 (-0.027)	0.854		
GM volume	*0.072 (-0.128)*	**0.014**	0.543 (0.064)	**0.006 (-0.272)**
Glucose metabolism	**0.033 (-0.157)**	**0.049**	0.821 (-0.025)	**0.002 (-0.314)**
Amyloid load	0.182 (0.116)	0.238	-	-

Values indicate p (r) values of the multiple linear regressions between depressive or anxiety symptoms on the one hand, and the corresponding cognitive or neuroimaging variables on the other hand. All analyses with depressive symptoms were corrected for level of education and anxiety symptoms, while all analyses with anxiety symptoms were corrected for level of education and depressive symptoms. Values in bold correspond to significant p values ($p<0.05$) and values in italic correspond to trends ($0.01<p<0.05$). *DRS* Dementia Rating Scale, *MADRS* Montgomery-Åsberg Depression Rating Scale, *STAI A* Spielberger state-anxiety inventory state form.

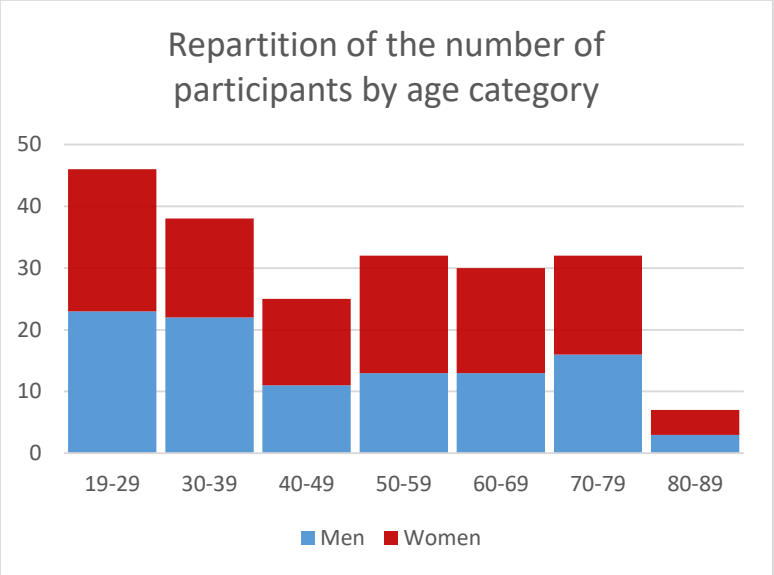
Table 3: Relationships between baseline psychoaffective measures and slopes of change in cognition and neuroimaging measures and reversely.

		Global cognition (DRS) slope of change	GM volume slope of change	Glucose metabolism slope of change	Amyloid load slope of change
Baseline depressive symptoms (MADRS)	Total group	0.323 (0.081)	0.169 (-0.111)	0.699 (0.037)	0.176 (-0.174)
	Interaction of sex	0.396	0.824	0.588	0.670
Baseline anxiety symptoms (STAI A)	Total group	0.206 (-0.103)	0.293 (0.085)	0.721 (-0.034)	0.345 (0.121)
	Interaction of sex	0.650	0.882	0.955	0.107
		Depressive symptoms (MADRS) slope of change			
Baseline predictor		Total group	Interaction of sex	Men	Women
Global cognition (DRS)		0.356 (0.07)	*0.068*	0.547 (-0.072)	*0.082 (0.193)*
GM volume		0.142 (-0.117)	0.114	-	-
Glucose metabolism		0.108 (-0.150)	0.256	-	-
Amyloid load		0.936 (0.009)	0.838	-	-
		Anxiety symptoms (STAI A) slopes of change			
Baseline predictor		Total group	Interaction of sex	Men	Women
Global cognition (DRS)		0.700 (-0.032)	0.713	-	-
GM volume		**0.040 (-0.170)**	*0.097*	0.939 (-0.009)	**0.044 (-0.234)**
Glucose metabolism		0.440 (0.079)	0.777	-	-
Amyloid load		0.542 (-0.075)	0.674	-	-

Values indicate p (r) values of the multiple linear regressions between baseline or slopes of changes in depressive symptoms or baseline or slopes of changes in anxiety symptoms on the one hand, and the corresponding baseline or slopes of changes in cognitive or neuroimaging variables on the other hand. All analyses with baseline or slopes of changes in depressive symptoms were corrected for the level of education and baseline anxiety symptoms while all the analyses with baseline or slopes of anxiety symptoms were corrected for the level of education and baseline depressive symptoms. Values in bold correspond to significant p values ($p<0.05$) and values in italic correspond to trends ($0.01<p<0.05$). *DRS* Dementia Rating Scale, *MADRS* Montgomery-Åsberg Depression Rating Scale, *STAI A* Spielberger state-anxiety inventory state form.

Supplementary material

Supplementary figure 1: Age distribution of the total population.



Supplementary table 1: Non-parametric cross-sectional relationships of psychoaffective factors to global cognition and neuroimaging measures, and interaction with sex.

Depressive symptoms (MADRS)	Total group	Interactions with sex	Men	Women
Age	0.191 (-0.091)	0.565	-	-
Global cognition (DRS)	0.279 (-0.075)	0.550	-	-
GM volume	0.892 (0.010)	0.705	-	-
Glucose metabolism	0.290 (0.078)	0.340	-	-
Amyloid load	0.332 (0.083)	0.268	-	-
Anxiety symptoms (STAI A)	Total group	Interactions with sex	Men	Women
Age	0.792 (0.019)	**0.033**	0.205 (-0.130)	*0.080 (0.174)*
Global cognition (DRS)	**0.0249 (-0.161)**	0.923	-	-
GM volume	0.125 (-0.109)	**0.018**	0.482 (0.073)	**0.008 (-0.262)**
Glucose metabolism	0.595 (-0.040)	**0.001**	*0.070 (0.193)*	**0.003 (-0.309)**
Amyloid load	0.152 (0.125)	**0.032**	0.623 (-0.060)	**0.013 (0.310)**

Values indicate the results of Spearman's correlations p (r) values between depressive symptoms or anxiety symptoms on the one hand, and the corresponding cognitive or neuroimaging variables on the other hand. Values in bold correspond to significant p values ($p<0.05$) and values in italic correspond to trends ($0.01<p<0.05$). *DRS* Dementia Rating Scale, *MADRS* Montgomery-Åsberg Depression Rating Scale, *STAI A* Spielberger state-anxiety inventory state form.

Supplementary table 2: Non-parametric cross-sectional and longitudinal relationships of psychoaffective measures to global cognition and neuroimaging measures, and interaction with sex, in the subgroup with at least one depressive symptom.

Cross-sectional	Depressive symptoms (MADRS)		**Longitudinal**	Depressive symptoms (MADRS) slope of change			
	Total group	Interaction with sex	Baseline predictor	Total group	Interaction with sex	Men	Women
Age	0.682 (-0.044)	0.163					
Global cognition (DRS)	0.132 (-0.160)	0.825	Global cognition	0.820 (0.030)	*0.075*	0.307 (-0.193)	0.132 (0.281)
GM volume	0.283 (0.116)	0.596	GM volume	0.145 (-0.192)	*0.051*	**0.009 (-0.476)**	0.928 (0.017)
Glucose metabolism	0.304 (0.116)	0.135	Glucose metabolism	*0.061 (-0.270)*	0.416	-	-
Amyloid load	0.321 (0.123)	0.665	Amyloid load	0.509 (0.120)	0.960	-	-
Longitudinal				Global cognition (DRS) slope of change	GM volume slope of change	Glucose metabolism slope of change	Amyloid load slope of change
Baseline depressive symptoms (MADRS)			Total group	0.386 (0.114)	0.112 (-0.209)	0.913 (-0.016)	0.196 (-0.257)
			Interaction with sex	0.638	0.204	0.927	**0.003**
			Men	-	-	-	0.245 (0.347)
			Women	-	-	-	**0.003 (-0.738)**

Values indicate p (r) values of Spearman's correlations between cross-sectional depressive symptoms and cognitive and neuroimaging measures; between baseline or slopes of depressive symptoms and baseline or slopes of anxiety symptoms; and the corresponding baseline or slopes of cognitive or neuroimaging variables on the other hand. Values in bold correspond to significant p values ($p<0.05$) and values in italic correspond to trends ($0.01<p<0.05$). *DRS* Dementia Rating Scale, *MADRS* Montgomery-Åsberg Depression Rating Scale.

Supplementary table 3: Cross-sectional and longitudinal relationships of depressive symptoms to global cognition and neuroimaging measures, and interaction with sex, in the subgroup with at least one depressive symptom.

Cross-sectional - Depressive symptoms (MADRS)	corrected for the level of education and anxiety symptoms		corrected for the level of education, age and anxiety symptoms	
	Total group	Interactions with sex	Total group	Interactions with sex
Age	*0.083 (-0.192)*	0.507	-	-
Global cognition (DRS)	0.551 (-0.069)	0.950	0.519 (-0.073)	0.714
GM volume	0.251 (0.127)	0.116	0.960 (-0.007)	0.216
Glucose metabolism	0.100 (0.189)	0.487	0.634 (0.066)	0.458
Amyloid load	0.809 (-0.031)	0.539	0.638 (0.063)	0.527
Longitudinal - Depressive symptoms slope of change (MADRS)	corrected for the level of education and anxiety symptoms		corrected for the level of education, age and anxiety symptoms	
Baseline predictor	Total group	Interactions with sex	Total group	Interactions with sex
Global cognition (DRS)	0.479 (0.096)	*0.094*	0.418 (0.111)	0.112
GM volume	*0.098 (-0.213)*	0.164	*0.070 (-0.358)*	0.185
Glucose metabolism	0.620 (-0.070)	0.504	0.470 (0.143)	0.437
Amyloid load	0.889 (-0.025)	0.713	0.433 (-0.149)	0.815
Longitudinal - Baseline depressive symptoms (MADRS)	Global cognition (DRS) slope of change	GM volume slope of change	Glucose metabolism slope of change	Amyloid load slope of change
corrected for the level of education and anxiety symptoms — Total group	0.810 (0.032)	0.383 (-0.120)	0.901 (0.018)	0.218 (-0.262)
corrected for the level of education and anxiety symptoms — Interaction with sex	0.966	0.727	0.940	0.279
corrected for the level of education, age and anxiety symptoms — Total group	0.895 (0.018)	0.399 (-0.117)	0.965 (0.007)	0.151 (-0.293)
corrected for the level of education, age and anxiety symptoms — Interaction with sex	0.976	0.742	0.995	0.537

Values indicate p (r) values of multiple linear regressions between cross-sectional depressive symptoms and cognitive and neuroimaging measures; between baseline or slopes of depressive symptoms and baseline or slopes of anxiety symptoms; and the corresponding baseline or slopes of cognitive or neuroimaging variables on the other hand. Values in bold correspond to significant p values ($p<0.05$) and values in italic correspond to trends ($0.01<p<0.05$). *DRS* Dementia Rating Scale, *MADRS* Montgomery-Åsberg Depression Rating Scale.

Supplementary table 4: Cross-sectional relationships of psychoaffective factors to global cognition and neuroimaging measures and interaction with sex, corrected for the level of education, age, and anxiety or depressive symptoms.

Depressive symptoms (MADRS)	Total group	Interaction with sex	Men	Women
Global cognition (DRS)	0.319 (-0.074)	0.782	-	-
GM volume	0.592 (-0.050)	0.204	-	-
Glucose metabolism	0.439 (0.070)	0.323	-	-
Amyloid load	0.479 (0.064)	0.892	-	-
Anxiety symptoms (STAI A)	Total group	Interaction with sex	Men	Women
Global cognition (DRS)	0.801 (-0.018)	0.976	-	-
GM volume	0.167 (-0.130)	**0.014**	0.666 (0.071)	*0.057 (-0.258)*
Glucose metabolism	*0.072 (-0.120)*	*0.051*	0.531 (-0.087)	**0.015 (-0.304)**
Amyloid load	0.351 (0.085)	0.237	-	-

Values indicate the results of multiple linear regressions p (r) values between depressive symptoms or anxiety symptoms on the one hand, and the corresponding cognitive or neuroimaging variables on the other hand. All the analyses with depressive symptoms were corrected for level of education, age and anxiety symptoms, while all the analyses with anxiety symptoms were corrected for the level of education, age and depressive symptoms. Values in bold correspond to significant p values ($p<0.05$) and values in italic correspond to trends ($0.01<p<0.05$). *DRS* Dementia Rating Scale, *MADRS* Montgomery-Åsberg Depression Rating Scale, *STAI A* Spielberger state-anxiety inventory state form.

Supplementary table 5: Longitudinal study sample characteristics of the changes over time in psychoaffective factors, global cognition and neuroimaging measures.

	Total population	n	Men	n	Women	n	ANOVA
Depressive symptoms (MADRS)	-0.021 ± 0.086	167	0.010 ± 0.084	81	0.031 ± 0.087	86	0.390
Anxiety symptoms (STAI A)	0.019 ± 0.235	159	-0.010 ± 0.188	76	0.046 ± 0.280	83	0.310
Global cognition (DRS)	-0.003 ± 0.081	166	-0.011 ± 0.096	80	0.005 ± 0.069	86	0.322
GM volume	-0.164 ± 0.423	165	-0.199 ± 0.395	79	-0.132 ± 0.446	86	0.492
Glucose metabolism	-0.0002 ± 0.002	122	-0.0002 ± 0.002	65	-0.0002 ± 0.002	57	0.961
Amyloid load	0.001 ± 0.003	69	0.0002 ± 0.002	35	0.002 ± 0.003	34	*0.080*
One sample t-test	Total population		Men		Women		
Depressive symptoms (MADRS)	*0.082*		0.571		*0.064*		
Anxiety symptoms (STAI A)	0.459		0.759		0.271		
Global cognition (DRS)	0.758		0.465		0.662		
GM volume	**0.0003**		**0.001**		**0.049**		
Glucose metabolism	0.352		0.625		0.352		
Amyloid load	**0.043**		0.809		**0.020**		

Values indicate mean ± standardized deviation (number of available data) or p value. Values in bold correspond to significant one-sample t-test, or ANOVA comparing men and women, p values ($p<0.05$) and values in italic correspond to trends ($0.01<p<0.05$). *DRS* Dementia Rating Scale, *MADRS* Montgomery-Åsberg Depression Rating Scale, *STAI A* Spielberger state-anxiety inventory state form.

Supplementary table 6: Non-parametric longitudinal relationships of baseline psychoaffective measures to slopes of change in global cognition and neuroimaging measures and reversely, and interaction with sex.

		Global cognition (DRS) slope of change	GM volume slope of change	Glucose metabolism slope of change	Amyloid load slope of change
Baseline depressive symptoms (MADRS)	Total group	0.124 (0.120)	0.138 (-0.116)	0.885 (0.013)	0.609 (-0.063)
	Interaction with sex	*0.070*	0.425	0.725	0.713
	Men	0.923 (-0.011)	-	-	-
	Women	**0.019 (0.270)**	-	-	-
Baseline anxiety symptoms (STAI A)	Total group	0.419 (0.065)	0.318 (0.080)	0.207 (-0.118)	0.184 (0.167)
	Interaction with sex	0.660	0.908	0.636	0.129
		Depressive symptoms (MADRS) slope of change			
Baseline predictor		Total group	Interactions with sex	Men	Women
Global cognition (DRS)		0.578 (0.044)	*0.058*	0.342 (-0.108)	*0.079 (0.190)*
GM volume		0.629 (-0.038)	*0.081*	*0.063 (-0.213)*	0.567 (0.063)
Glucose metabolism		*0.070 (-0.172)*	0.375	-	-
Amyloid load		*0.055 (0.224)*	0.695	-	-
		Anxiety symptoms (STAI A) slope of change			
Baseline predictor		Total group	Interactions with sex	Men	Women
Global cognition (DRS)		0.677 (-0.033)	0.874	-	-
GM volume		*0.064 (-0.147)*	**0.008**	0.493 (0.080)	**0.002 (-0.338)**
Glucose metabolism		0.315 (0.098)	0.290	-	-
Amyloid load		0.750 (-0.038)	0.863	-	-

Values indicate p (r) values of Spearman's correlations between baseline or slopes of depressive symptoms or baseline or slopes of anxiety symptoms on the one hand, and the corresponding baseline or slopes of cognitive or neuroimaging variables on the other hand. Values in bold correspond to significant p values ($p<0.05$) and values in italic correspond to trends ($0.01<p<0.05$). *DRS* Dementia Rating Scale, *MADRS* Montgomery-Åsberg Depression Rating Scale, *STAI A* Spielberger state-anxiety inventory state form.

Supplementary table 7: Longitudinal relationships of baseline psychoaffective measures to slopes of change in global cognition and neuroimaging measures and reversely, corrected for level of education, age, and anxiety or depressive symptoms levels.

		Global cognition (DRS) slope of change	GM volume slope of change	Glucose metabolism slope of change	Amyloid load slope of change
Baseline depressive symptoms (MADRS)	Total group	0.402 (0.069)	0.178 (-0.109)	0.756 (0.030)	0.216 (-0.155)
	Interaction with sex	0.396	0.888	0.613	0.547
Baseline anxiety symptoms (STAI A)	Total group	0.237 (-0.100)	0.299 (0.084)	0.713 (-0.036)	0.341 (0.123)
	Interaction with sex	0.652	0.856	0.961	0.124

	Depressive symptoms (MADRS) slope of change				Anxiety symptoms (STAI A) slope of change	
Baseline predictor	Total group	Interactions with sex	Men	Women	Total group	Interaction with sex
Global cognition (DRS)	0.299 (0.084)	*0.089*	0.806 (-0.030)	*0.084 (0.193)*	0.699 (-0.033)	0.722
GM volume	0.240 (-0.127)	0.109	-	-	**0.005 (-0.312)**	0.129
Glucose metabolism	0.664 (-0.052)	0.228	-	-	0.205 (0.167)	0.793
Amyloid load	0.596 (-0.067)	0.901	-	-	0.607 (-0.067)	0.666

Values indicate p (r) values of multiple linear regressions between baseline or slopes of depressive symptoms or baseline or slopes of anxiety symptoms on the one hand, and the corresponding baseline or slopes of cognitive or neuroimaging variables on the other hand. All analyses with baseline or slopes of depressive symptoms were corrected for the level of education, age at baseline and baseline anxiety symptoms while all the analyses with baseline or slopes of anxiety symptoms were corrected for level of education, age at baseline and baseline depressive symptoms. Values in bold correspond to significant p values ($p<0.05$) and values in italic correspond to trends ($0.01<p<0.05$). *DRS* Dementia Rating Scale, *MADRS* Montgomery-Åsberg Depression Rating Scale, *STAI A* Spielberger state-anxiety inventory state form.

3.4. Etude 2 : Facteurs psychoaffectifs dans la démence de type Alzheimer

Dans le prolongement de l'étude précédente, qui s'intéressait au vieillissement normal, nous nous sommes intéressés aux associations des symptômes anxieux et dépressifs avec les modifications cognitives et cérébrales typiques de la MA. En effet, des études montrent que ces symptômes sont fréquents au cours de la maladie (Banning et al., 2019; Monastero et al., 2009; Verdaguer et al., 2020), et sont associés à une diminution de la qualité de vie du patient et de son entourage, à une augmentation de la charge des aidants et à une institutionnalisation précoce (Gilley et al., 2004; Hoe et al., 2006; Hoe et al., 2007; Karttunen et al., 2011; Orrell & Bebbington, 1996). De plus, les personnes âgées présentant des symptômes anxieux et dépressifs sont plus à risque de développer un déclin cognitif (Geda et al., 2008, 2014; Santabárbara et al., 2020; Wilson et al., 2011; Yang et al., 2020; Zhang et al., 2020), ou même une démence (Dean et al., 2014; Donovan et al., 2014; Harrington et al., 2015; Petkus et al., 2016; Santabárbara et al., 2020; Wilson et al., 2011). L'objectif de cette étude a donc été d'évaluer les associations des symptômes anxieux et dépressifs avec la cognition globale, la mémoire, le volume de substance grise, le métabolisme du glucose et la charge amyloïde, à la fois au stade de SCD et dans le continuum Alzheimer, i.e. chez des patients MCI ou MA présentant des dépôts amyloïdes.

Dans ce but, nous avons inclus 91 patients ainsi que 56 contrôles tous âgés de plus de 50 ans. Ces derniers ont été sélectionnés pour leur absence de troubles cognitifs et une charge amyliode négative en examen TEP. Les patients ont été regroupés en 2 groupes, 35 patients présentant des déficits cognitifs subjectifs en l'absence de déficit cognitif objectifs formant le groupe de SCD, et 56 patients présentant des troubles cognitifs MCI (n=28) ou MA (n=28) avec une charge amyloïde positive, formant le groupe de continuum Alzheimer. Tous ces participants étaient issus du protocole IMAP et ont complété une batterie diagnostique et des examens neuropsychologiques variés comprenant notamment une mesure de cognition globale, le *Mini Mental State Examination* (MMSE), et une mesure de mémoire, le sous-score de rappel libre de la tâche d'« Encodage, Stockage et Récupération » (ESR). Ils ont également effectué des examens de neuroimagerie tels qu'une IRM

structurale, une TEP couplée au ^{18}F-fluorodeoxyglucose et une TEP couplée au ^{18}F-florbetapir. Les symptômes anxieux état et dépressifs ont été mesurés respectivement à l'aide du questionnaire *Spielberger State-Trait Anxiety Inventory form Y-A* (STAI-A) et du *Montgomery-Åsberg Depression Rating Scale* (MADRS). Ces derniers ont été comparés entre les 3 groupes et des corrélations ont été effectuées dans chaque groupe entre ces symptômes psychoaffectifs (i.e. les symptômes anxieux et dépressifs) d'une part, et les mesures de cognition (i.e. cognition globale et mémoire) et de neuroimagerie (i.e. volume de substance grise, métabolisme du glucose cérébral, charge amyloïde) d'autre part.

Nos résultats montrent que les symptômes dépressifs sont plus élevés chez les SCD et les patients du continuum Alzheimer, mais ne diffèrent pas entre ces deux groupes. Chez les SCD, une augmentation de ces symptômes est associée à une augmentation de la charge amyloïde, tandis que chez les patients du continuum Alzheimer, elle est associée à une meilleure cognition et une meilleure mémoire, ainsi qu'à un métabolisme du glucose plus élevé. Des analyses complémentaires nous ont permis de mieux comprendre ces résultats non attendus chez les patients du continuum Alzheimer, en montrant que les symptômes dépressifs élevés sont associés à une meilleure conscience de ses troubles cognitifs dans ce groupe, et donc à un meilleur fonctionnement cognitif et fonctionnel.

Cette étude montre que les symptômes dépressifs ont une signification évolutive au cours des différents stades, puisque chez les SCD, ils sont associés à plus de pathologie amyloïde, tandis qu'inversement, ils refléteraient une plus grande prise de conscience des déficits cognitifs et sont associés à un stade cognitif et fonctionnel moins sévère de la maladie dans le continuum Alzheimer. Pour conclure, cette étude montre la pertinence de surveiller les symptômes dépressifs chez les SCD, et de les traiter chez les patients présentant des troubles cognitifs, afin d'améliorer la prévention et la santé mentale des patients ainsi que des aidants.

Cette étude a fait l'objet d'une communication orale en 2019 (*Medit-ageing Consortium meeting*) et l'article correspondant est actuellement en préparation.

Relationships of depressive symptoms to brain markers of neurodegeneration and amyloid deposition across the Alzheimer's continuum

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En préparation

Abstract

Introduction: Anxiety and depressive symptoms are very frequent in Alzheimer's Disease (AD), and in the preclinical stages they are associated with increased risk of developing AD. To further our understanding of clinical relevance and underlying mechanisms of anxiety and depressive symptoms, we assessed their relationships with neuroimaging biomarkers of AD at the preclinical and clinical stages of the disease.

Methods: We assessed anxiety symptoms with State-Trait Anxiety Inventory form Y-A and depressive symptom with Montgomery-Åsberg Depression Rating Scale among 56 cognitively healthy controls (HC) over 60 years, 35 subjective cognitive decline (SCD) and 56 amyloid-positive cognitively impaired patients on the Alzheimer's continuum (ADC patients). They also underwent cognitive and episodic memory assessment, as well as neuroimaging measurements including structural MRI, FDG-PET and amyloid-PET.

Results: Depressive symptoms, but not anxiety, were higher in SCD and ADC patients compared with HC. They were associated with higher amyloid load in SCD and higher global cognition, episodic memory performance and glucose metabolism in the group of ADC patients. Additional analyses in this same group showed that higher depressive symptoms were in fact associated with better self-awareness and thus better cognition and episodic memory performance. State anxiety was not associated with any neuroimaging measure.

Discussion: This study shows that depressive symptoms have opposite relationships to neuroimaging markers of brain integrity across the cognitive continuum from cognitively normal to dementia. Thus, at the SCD stage, depressive symptoms are associated with more amyloid pathology. In contrast, in later stages when cognitive deficits are present, depressive symptoms are associated with less neurodegeneration, which likely reflect the progressive loss of awareness of cognitive and/or psychoaffective deficits as the disease progresses. This study highlights the relevance of assessing and treating depressive symptoms in preclinical AD.

1. Introduction

Neuropsychiatric symptoms (NPS) are present in 90% of patients with Alzheimer's disease (AD) dementia (Finkel et al., 1996), with depressive and anxiety symptoms being two of the most common NPS (Banning et al., 2019). They are associated with decrease in quality of life, caregiver's burden, and increased institutionalization (Gilley et al., 2004; Hoe et al., 2006; Hoe et al., 2007; Karttunen et al., 2011; Orrell & Bebbington, 1996). In cognitively unimpaired individuals, it has been shown that anxiety and depressive symptoms, even at a subclinical level, increased the risk of cognitive decline (Geda et al., 2008, 2014), of developing AD (Harrington et al., 2015; Petkus et al., 2016), and of progressing from the pre-dementia stage to the dementia stage (Palmer et al., 2007; Seignourel et al., 2008).

With regards to the cognitive and brain substrates of anxiety and depressive symptoms, studies are sparse and findings are mixed. In patients with AD dementia, one previous study found that patients with persistent neuropsychiatric symptoms had worse cognitive and functional outcomes (Poulin et al., 2017). Regarding neuroimaging biomarkers, some studies found that anxiety and depressive symptoms were associated with more AD neuroimaging hallmarks in either Mild Cognitive Impairment (MCI) or AD, such as lower grey matter volume (GM) (Auning et al., 2015; Fujishima et al., 2014; Lebedeva et al., 2014; Tagai et al., 2014; Wu et al., 2020), lower glucose metabolism (Hashimoto et al., 2006), and higher amyloid deposition (Bensamoun et al., 2016; Brendel et al., 2015; Krell-Roesch et al., 2019); but conflicting results have been reported in other studies showing a link between depressive symptoms and higher glucose metabolism (Auning et al., 2015; Brendel et al., 2015) or no association between psycho-affective factors and neuroimaging markers (Banning et al., 2019; Bensamoun et al., 2016; Chung et al., 2015; Huey et al., 2017; Mori et al., 2014; Serra et al., 2010; Starkstein et al., 2009). Moreover, there is no study to date that assessed these relationships in patients with subjective cognitive decline (SCD) but without any objective cognitive deficits, even though anxiety and depressive symptoms are higher in SCD patients compared to healthy elders (Jessen et al., 2014; Perrotin, et al., 2017).

We therefore aimed at examining the associations between anxiety and depressive symptoms with neuroimaging measures to further our understanding of relevance and mechanisms of psychoaffective factors in preclinical and clinical AD. Given the impact of anxiety and depressive symptoms on quality of life and even prognosis, improving our knowledge of their brain substrates across Alzheimer's continuum is particularly relevant for clinical management and AD risk reduction.

In a cross-sectional study, we first compared the level of anxiety and depressive symptoms between a group of healthy controls, a group of SCD and a group of patients on the Alzheimer's continuum, including both mild cognitive impairment (MCI) and AD dementia patients with amyloid deposition in their brain (amyloid positive on PET scan). Secondly, we investigated, in each group, the links between these psychoaffective symptoms and relevant cognitive and neuroimaging biomarkers of AD (i.e. global cognition, episodic memory, GM volume, glucose metabolism, amyloid deposition). We hypothesised that anxiety and depressive symptoms would be associated with more severe AD cognitive and neuroimaging deficits such as lower global cognition and episodic memory performance, lower grey matter volume and glucose metabolism and higher amyloid load in all groups.

2. Methods

2.1. Participants

All participants were recruited as part of the *Imagerie Multimodale de la Maladie d'Alzheimer à un Stade Précoce* (IMAP+) Study in Caen, France, which required written informed consent from all participants and was approved by the local ethics committee. Participants were over 50 years old, living at home, had no history nor clinical evidence of neurologic or psychiatric disorder, alcohol use disorder or drug abuse. Notably, none of the participants met diagnostic criteria for major depression or anxiety disorder, as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Donovan et al., 2015; Lavretsky & Kumar, 2002; Lyness et al., 2009). The inclusion and group classification of the participants were based on a clinical interview and a standardized neuropsychological assessment (including tests of episodic memory, working memory, language skills,

executive functions, and visuospatial abilities), according to internationally agreed criteria (see inclusion and exclusion criteria in previous studies ; La Joie et al., 2012, 2016; Mutlu et al., 2017; Perrotin et al., 2017).

In the present study, 91 patients and 56 controls above 50 years old were included. Patients were either patients with SCD (n=35) or patients on the Alzheimer's continuum (n=56). Patients were recruited from local memory clinics and selected according to corresponding internationally agreed criteria. SCD patients reported memory complaints and underwent standardized neuropsychological testing which did not identify any objective cognitive impairment (scores were in the normal range for each neuropsychological test). During the interview, the clinician ensured that the complaint was not related to current medication nor medical condition, and did not fulfil NINCDS-ADRDA criteria for probable AD (McKhann et al., 1984). Patients on the Alzheimer's continuum (ADC patients) included patients with MCI selected based on Petersen's criteria for (n=28) (Petersen & Morris, 2005) and patients with dementia (n=28) fulfilling NINCDS-ADRDA clinical criteria for probable AD (McKhann et al., 1984). Clinical diagnosis was assigned by consensus under the supervision of a senior neurologist and neuropsychologists. Finally, 56 controls Healthy elderly subjects were recruited from the community and performed in the normal range on all neuropsychological tests from a cognitive battery assessing multiple domains of cognition. Only ADC patients with a positive florbetapir-PET scan (see Neuroimaging processing for the positivity selection), and controls with a negative florbetapir-PET scan were included in this study selected to be all amyloid negative.

2.2. Psychoaffective assessment

The Montgomery-Åsberg Depression Rating Scale (MADRS), a clinician-administered 10-item questionnaire (Montgomery & Asberg, 1979), was used to assess depressive symptoms at the time of the evaluation (from 0 to 60). The Spielberger State-Trait Anxiety Inventory form Y-A (STAI-A), a 20-item self-rated questionnaire (Spielberger et al., 1970), assessed state anxiety symptoms at the time of the evaluation (from 20 to 80). For both scales, higher scores indicated higher levels of symptoms

of anxiety and depression, even if scores were not very high given that participants were screened so as not to meet diagnostic criteria for major depression or anxiety disorders. Our goal was to assess anxiety and depressive symptoms on a continuum (Altman & Royston, 2006; Laborde-Lahoz et al., 2015) so that these scores were used as continuous variables in all analyses (see below).

2.3. Cognitive assessment

Global cognition was measured using the 30-point scale Mini Mental State Examination (MMSE; scores from 0 to 30) (Folstein et al., 1975), while episodic memory was assessed using the Encoding, Storage and Recuperation (ESR) word list free recall sub-score (Eustache et al., 2015), consisting on the recall of two 16-word lists (maximum score for each list = 16).

2.4. Neuroimaging data

All participants underwent neuroimaging scans on the same MRI and PET scanners at the Cyceron Centre (Caen, France), as described below, within a 3-month interval from the psychoaffective and cognitive assessments. We measured grey matter (GM) volume with Magnetic Resonance Imaging (MRI), brain glucose metabolism with 18F-fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) and amyloid deposition with 18F-florbetapir-PET. Global GM volumes and neocortical standardized uptake value ratio (SUVr) were extracted as decribed below and used in the following analyses as continuous variables.

2.4.1. Neuroimaging acquisition

High-resolution T1-weighted MRI anatomical images were acquired on a Philips Achieva 3.0 T scanner using a 3D fast-field echo sequence (3D-T1-FFE sagittal; repetition time = 20 ms; echo time = 4.6 ms; flip angle = 10°; 180 slices with no gap; slice thickness = 1 mm; field of view = 256 x 256mm^2; in-plane resolution = 1 x 1mm^2).

Both FDG and florbetapir PET images were acquired with a Discovery RX VCT 64 PET-CT device (General Electric Healthcare) with a resolution of 3.76 x 3.76 x 4.9mm^3 (field of view = 157 mm). Forty-seven planes with a voxel size of 1.95 x 1.95 x 3.27 mm^3 were obtained and an attenuation correction was

performed before the PET acquisition with a transmission scan.

FDG-PET acquisitions were performed after at least 6 hours of fasting, and after 30 minutes of rest in a quiet and dark room. Fifty minutes after intravenous injection of ~180 MBq of FDG, the participants underwent a 10-minute scan. Florbetapir-PET scan was acquired for each participant 50 minutes after the intravenous injection of ~4 MBq/kg of florbetapir, for a duration of 20 minutes, except for two SCD, and three ADC patients, who had a 10-minute acquisition.

2.4.2. Neuroimaging processing

All neuroimaging pre-processing steps were performed with The Statistical Parametric Mapping version 12 (SPM12) software (Wellcome Trust Centre for Neuroimaging, London, UK).

T1-weighted MRI images were segmented and spatially normalized to the Montreal Neurological Institute (MNI) space and non-linear warping effects on volumes were corrected for by modulating the resulting normalized GM segments (Chételat et al., 2008; La Joie et al., 2012; Villain et al., 2008). PET images were corrected for partial volume effects using the Muller-Gartner method. Resulting images were coregistered onto their corresponding MRI, normalized with the deformation parameters used for the MRI procedure, and then quantitatively normalized using the cerebellar GM as the reference region (Bejanin et al., 2019; Chételat et al., 2008; La Joie et al., 2012; Villain et al., 2008).

For each participant, a total GM volume and global FDG-PET value was calculated by applying a binary mask of GM (including voxels with a GM probability > 30% excluding the cerebellum) on the corresponding preprocessed images. The global neocortical SUVr value was obtained from the florbetapir-PET images using a neocortex mask (including all regions but the cerebellum, hippocampus, amygdala and subcortical grey nuclei), as described in details elsewhere (La Joie et al., 2012). This global neocortical SUVr value was used as a continuous variable for further analyses (see below) but also to classify subjects as positive or negative for amyloid to select amyloid-negative HC and amyloid-positive AD patients. The threshold was calculated from a group of 45 young participants from the IMAP project (between 20 and 40 years old) using the mean + 2SD, corresponding to a SUVr of 1.02

under which participants were considered amyloid negative and above which patients were considered amyloid-positive (Besson et al., 2015; Perrotin et al., 2017).

2.5. Statistical analysis

2.5.1. Main analyses

To assess of the differences in psychoaffective factors across clinical groups, we performed analyses of covariance (ANCOVA) with education, age and sex as covariates. We also performed multiple regressions to assess within group associations between psychoaffective measures (i.e. depressive symptoms and anxiety symptoms) on the one hand, and cognition (global cognition and episodic memory) and neuroimaging data (GM volume, glucose metabolism and amyloid load) on the other hand. Results are presented with correction for level of education, age and sex. When specified, as anxiety and depression scores were correlated in the ADC patient group (non-parametric p=0.01), all analyses with one of this score was additionally corrected for the other and inversely, to independently evaluate their substrates across Alzheimer's continuum. Pairwise deletion was used in case of missing data and all statistical analyses were performed using the STATISTICA software (v13.0, StatSoft Inc., Tulsa, OK).

2.5.2. Supplementary analyses

Scores of depressive and anxiety symptoms were not normally distributed; thus correlation analyses were repeated with non-parametric Spearman's correlation tests. The score for depressive symptoms also showed an important floor effect with a large number of participants having a score of zero. To check that the results were consistent and not driven by the floor effect, we repeated all analyses with depressive symptoms excluding these participants, i.e. within subgroups of participants with at least one depressive symptom (n=21 HC, 23 SCD, 42 ADC patients). Finally, analyses within the group of ADC patients were repeated in a group of MCI and AD not selected for being Aβ+ (i.e. including both Aβ+ and Aβ- patients with MCI or AD).

3. Results

3.1. Group characteristics

Group characteristics are listed in Table 1. While there was no difference in sex, the level of education differed across group with ADC patients being less educated than HC and SCD and there was a trend for a group effect on age. Age and education were corrected for in all analyses. As expected, there was a difference in global cognition, episodic memory, GM volume, glucose metabolism and amyloid load, with ADC patients showing lower global cognition, episodic memory, GM volume and glucose metabolism and a higher amyloid load than HC and SCD. Additionally, HC had lower glucose metabolism than SCD.

Table 1: Study sample characteristics.

	HC	n	SCD	n	ADC patients	n	ANCOVA p value
N (H/F)	56 (25/31)		35 (18/17)		56 (31/25)		NS
level of education	12.64 ± 3.82	56	13.43 ± 3.11	35	11.3 ± 3.71	56	**0.013**
Age	69.75 ± 5.61	56	67.51 ± 6.85	35	71.18 ± 8.65	56	*0.075*
Psychoaffective measures							
Depressive symptoms	0.85 ± 1.34	55	3.8 ± 4.44	35	3.62 ± 3.68	55	**0.000**
State anxiety symptoms	27.85 ± 8.09	48	27.17 ± 8.90	29	31.08 ± 11.01	53	*0.080*
Cognitive measures							
Global cognition	29 ± 1.08	54	28.88 ± 1.05	33	23.71 ± 4.80	56	**0.000**
Episodic memory	14.39 ± 3.37	56	14.34 ± 3.73	35	5.84 ± 2.52	50	**0.000**
Neuroimaging measures							
GM volume	611.25 ± 62.86	53	632.57 ± 50.12	28	577.96 ± 60.97	56	**0.000**
Glucose metabolism	1.08 ± 0.07	49	1.13 ± 0.07	27	0.99 ± 0.08	55	**0.000**
Amyloid load	0.88 ± 0.06	43	0.96 ± 0.18	27	1.49 ± 0.30	56	**0.000**

Values indicate mean ± standardized deviation. Values in bold correspond to significant ANOVA corrected for the level of education, age and sex, comparing HC SCD and ADC patients, p values ($p<0.05$) and values in italic correspond to trends ($0.01<p<0.05$). Abbreviations *ADC* Alzheimer's continuum *ANOVA* Analysis of variance *ANCOVA* Analysis of covariance *HC* Healthy controls *NS* not significant *SCD* subjective cognitive decline.

3.2. Psychoaffective factors and their link with cognition and neuroimaging biomarkers

As regard to psychoaffective factors, depressive symptoms significantly differed across groups (Table 1 and Figure 1) even after correction for anxiety symptoms ($p=0.00004$). Post-hoc analyses showed

that patients, either SCD or ADC patients, had more depressive symptoms than HC, but did not differ from each other (HC-SCD p= 0.0002; HC-ADC patients p= 0.0001; SCD-ADC patients p=0.9). Regarding anxiety symptoms, we found a trend (Table 1 and Figure 1) that did not hold when also correcting for depressive symptoms (p=0.1), and post-hoc analyses revealed trend for higher anxiety symptoms in ADC patients (HC-SCD p= 0.9; HC-ADC patients p= 0.1; SCD-ADC patients p=0.1).

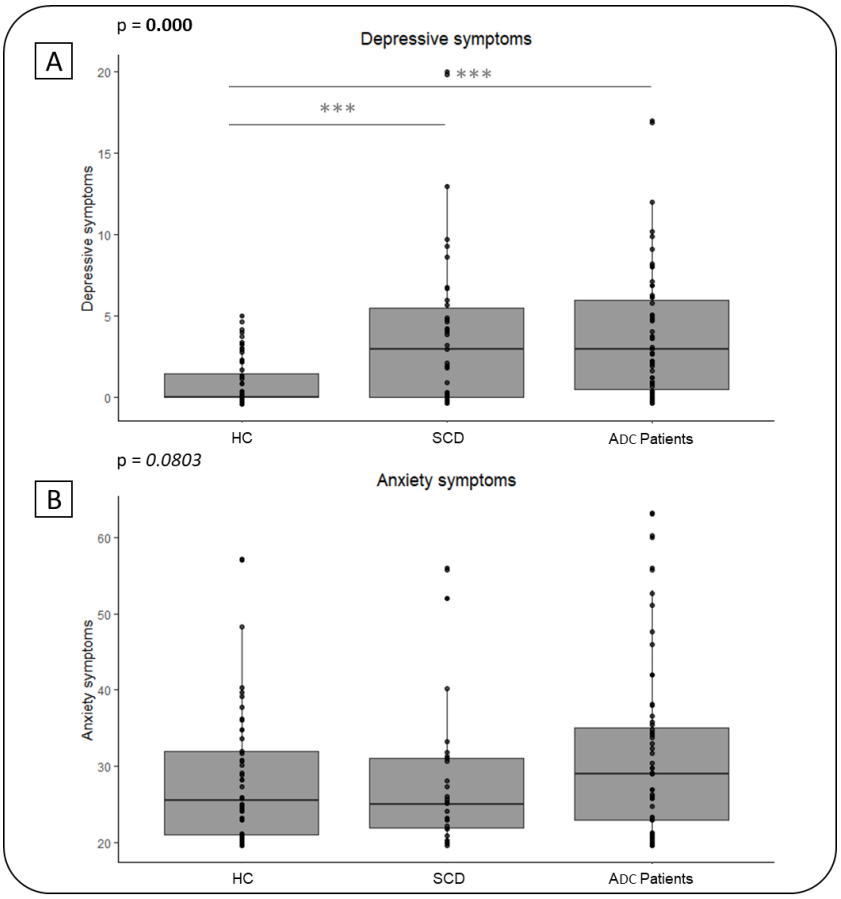

Figure 1: Difference in psychoaffective factors between groups of healthy controls, SCD and ADC patients**.** Graphs indicate boxplots of anxiety and depressive symptoms in each group. The p value of the main effect of group, measured with ANOVAs corrected for the level of education, age and sex, is indicated on the graph. Values in bold correspond to significant p values (p<0.05), values in italic correspond to trends (0.01<p<0.05). Significant post-hoc results between each group are indicated with stars, *** corresponding to p values (p<0.005). **A:** ANCOVA on depressive symptoms. **B:** ANCOVA on anxiety symptoms. Abbreviations *ADC* Alzheimer's continuum *ANOVA* Analysis of variance *ANCOVA* Analysis of covariance *HC* Healthy controls *p* p value *SCD* subjective cognitive decline.

The results of the analyses assessing the links between depressive or anxiety symptoms on the one hand, and cognitive or neuroimaging measures on the other hand, are reported in Table 2. An increase in depressive symptoms was associated with an increase in amyloid load in the group of SCD, while it was associated with increase in episodic memory performance and glucose metabolism in ADC patients, and tended to be related to an increase in global cognition as well. We found the same results when also correcting for anxiety symptoms, however the association with global cognition was not significant anymore (p= 0.1; see additional files 1). Non parametric analyses showed similar yet less significant results with a trend for the association between amyloid and depressive symptoms in SCD (p=0.071; see additional files 2) and between episodic memory performance and glucose metabolism with depressive symptoms (p=0.074 and p=0.073 respectively; see additional files 2) in ADC patients. We found the same results as in our main analyses in the subgroup with at least one depressive symptom, except for the association between depressive symptoms and episodic memory performance in ADC Patients group, that was not significant anymore (See additional files 3). Finally, to test whether the link between depressive symptoms and amyloid load was specific to the SCD stage, or reflected the increased variability of the amyloid measure in the SCD group as it includes both Aβ+ and Aβ- patients, we repeated this analysis in a group of MCI+AD not selected for being Aβ+ (i.e. including both Aβ+ and Aβ- patients with MCI or AD). Results of our main analysis were recovered as we found no correlation (p=0.9) between depressive symptoms and amyloid load in the group of Aβ+ and Aβ- MCI and AD patients.

As for anxiety symptoms a positive association was found with global cognition within ADC patients, and, as a trend, within the SCD (Table 1). However, with non-parametric analyses, only the association in the SCD group was significant (p= 0.03; see additional file 3), while when also correcting for depressive symptoms only the association in the ADC Patients group showed a trend (p= 0.08; see additional file 1).

No association was found in the group of healthy controls with either depressive of anxiety symptoms (Table 2 and additional files 1, 2 and 3).

Table 2: Relationships of psychoaffective factors to cognition and neuroimaging measures.

Depressive symptoms	HC	SCD	ADC patients
Cognitive measures			
Global cognition	0.358 (-0.139)	0.404 (0.165)	*0.065 (0.272)*
Episodic memory	0.914 (-0.015)	0.845 (0.042)	**0.015 (0.360)**
Neuroimaging measures			
GM volume	0.765 (-0.064)	0.881 (-0.038)	0.430 (-0.0135)
Glucose metabolism	0.428 (0.128)	0.372 (0.209)	**0.024 (0.319)**
Amyloid load	0.528 (0.107)	**0.015 (0.496)**	0.359 (-0.142)
Anxiety symptoms	**HC**	**SCD**	**ADC patients**
Cognitive measures			
Global cognition	0.484 (0.118)	*0.081 (0.369)*	**0.012 (0.079)**
Episodic memory	0.655 (-0.070)	0.230 (-0.287)	0.221 (0.178)
Neuroimaging measures			
GM volume	0.961 (-0.011)	0.318 (-0.269)	0.818 (-0.038)
Glucose metabolism	0.272 (-0.192)	0.928 (-0.022)	0.619 (0.068)
Amyloid load	0.778 (-0.051)	0.440 (-0.184)	0.902 (-0.019)

Values indicate p (r) values of the multiple linear regressions between depressive or anxiety symptoms on the one hand, and the corresponding cognitive or neuroimaging variables on the other hand for each group. All analyses with depressive symptoms were corrected for level of education, age, sex and anxiety symptoms while all analyses with anxiety symptoms were corrected for level of education, age, sex and depressive symptoms. Values in bold correspond to significant p values ($p<0.05$) and values in italic correspond to trends ($0.01<p<0.05$). Abbreviations *ADC* Alzheimer's continuum *GM* grey matter *HC* Healthy controls *SCD* subjective cognitive decline.

3.3. Additional analyses

The positive relationship between episodic memory performance and depressive symptoms in ADC patients was not expected. Interestingly, a study showed similar results and suggested that awareness of one's cognitive deficits could be associated with worsened mood (Cerbone et al., 2020).

Along this line, we hypothesized that our finding with episodic memory might reflect anosognosia, such that ADC patients at a more advanced cognitive stage (i.e. with lower episodic memory

performance) would be more anosognosic, either about their depression (so that they have lower depression score because they are less aware of their depressive symptoms); or about their cognitive deficits (so that they are less depressed about those). We thus ran additional analyses to test this hypothesis. We computed two composite delta score of anosognosia, one for global cognition and one for episodic memory performance, corresponding to the difference between the z-score of objective performance and the reversed z-score of subjective assessment for either global cognition (MMSE) or episodic memory (ESR). The subjective measure of global cognitive difficulties was the Cognitive Difficulties Scale (McNair & Kahn, 1983), a 39-item self-rated questionnaire assessing the frequency of particular cognitive difficulties in everyday life, from which we removed gender-specific items (e.g. related to cooking or sewing) as they depend on age-specific cultural norms, resulting in 34 items (Kuhn et al., 2019; McNair & Kahn, 1983). The subjective measure of memory difficulties consisted of 12 selected items from the CDS corresponding to memory items based on a previous study from our team (La Joie et al., 2016). Raw scores were converted to z-scores using the mean and standard deviation from the HC group as a reference. The subjective scores were reversed so that a high score reflected a high estimated level of performance, and the two z-scores were then subtracted from one another (z-score objective – reversed z-score subjective). This way, a higher (more positive) delta-score indicated greater awareness of cognitive/memory deficits, while a lower (more negative) delta score indicated more severe anosognosia (Perrotin et al., 2015; Vannini et al., 2017). To test our hypothesis, we then assessed the link between this delta score and depressive symptoms with multiple regressions corrected for level of education, age and sex. We found a positive association between the delta scores (awareness of cognitive and memory difficulties) and depressive symptoms ($p=0.01$ and $p=0.0001$ respectively), as well as objective performances in global cognition ($p<0.0001$) and episodic memory ($p=0.0001$). This suggests that individuals with better cognitive and/or memory performance, are more aware of their cognitive difficulties and show more depressive symptoms; or reversely, than those with greater cognitive/memory deficits who are more agnosognosic and report less depressive symptoms.

4. Discussion

This study is, to our knowledge, the first to assess the links of anxiety and depressive symptoms with multiple AD-relevant indices, including cognitive and neuroimaging measures (i.e. global cognition, episodic memory, GM atrophy, glucose metabolism and amyloid deposition), in SCD and Alzheimer's continuum. Altogether, we showed that SCD and ADC patient groups had higher depressive symptoms compared to healthy elders, which were associated with higher amyloid pathology in SCD, and with higher episodic memory performance and glucose metabolism in ADC patients.

In this study, we found no difference between groups regarding anxiety symptoms, but higher depressive symptoms in SCD and ADC patients compared to controls. This is in line with a previous study showing a higher frequency of depressive symptoms in clinical MCI and AD patients compared to controls, while anxiety symptoms were only different between mild and severe AD (Fernández-Martínez et al., 2010). Additionally, we found no association of anxiety symptoms with cognition and neuroimaging data, which is at odds with previous studies showing significant relationships with GM atrophy (Tagai et al., 2014; Hayata et al., 2015) and glucose hypometabolism (Hashimoto et al., 2006) in AD. This might be due to the fact that in the present study we focused on state measures of either anxiety or depressive symptoms, while these previous studies assessed trait anxiety. In addition, in these studies, the patients' anxiety symptoms level was measured through an interview with their caregiver, while in our study it was self-rated by the patient. Thus, the differences in results could reflect discrepancies between self-rated and informant-rated anxiety.

SCD group

In the SCD group, we found that depressive symptoms were not related to objective cognitive/memory performance but were associated with higher amyloid load. While some previous studies found higher depressive symptoms (Balash et al., 2013; Buckley et al., 2013), and higher amyloid load (Amariglio et al., 2012, 2015; Perrotin et al., 2012; Perrotin et al., 2017; Snitz et al., 2015) associated with subjective cognitive decline, no study to date formally assessed the links between depressive symptoms and

amyloid deposition, or even neuroimaging measures in general, in this specific population. Our finding of an association between depressive symptoms with amyloid load in SCD could indicate that depressive symptoms represent a manifestation of the ongoing pathology and/or are a risk factor promoting amyloid accumulation, or that both depressive symptoms and amyloid plaques are caused by a common, yet unknown, factor.

Furthermore, we found that this association between depressive symptoms and amyloid was specific to this SCD stage, where there is subjective but no objective cognitive deficits, as it was neither found in the HC group nor in the MCI/AD patients, even when not selected for being Aβ+. Previous findings were conflicting. In cognitively unimpaired elders (corresponding to our HC), some (Krell-Roesch et al., 2018), but not all (Donovan et al., 2015) studies found a relationship between depressive symptoms and amyloid load. Similarly, other studies reported a link between depressive symptoms and amyloid load in MCI (Brendel et al., 2015; Krell-Roesch et al., 2019). A recent review showed that most studies in fact did not find any association, and that discrepancies could reflect the inclusion of younger individuals compared to studies that did not find any association (Banning et al., 2019).

Recent criteria for SCD and updates about this concept have highlighted that SCD with biomarker evidence for AD have increased risk for future cognitive decline (Jessen et al., 2014, 2020). As we found depressive symptoms to be associated with amyloid deposition in SCD patients in our study, this suggests that SCD patients with depressive symptoms might also be at increased risk for cognitive decline. Altogether, this suggests that depressive symptoms in SCD is not a mere psychological consequence of their memory concern, but might be considered as an additional risk factor, and thus treated, in this population.

Alzheimer's continuum

In the ADC patient group, we found depressive symptoms to be associated with better episodic memory performance and higher glucose metabolism, i.e. with a less advanced clinical and neurodegenerative stage of the disease. Our findings are in line with recent studies showing higher

glucose metabolism in frontal regions and the fusiform gyrus in MCI patients with depressive symptoms (Auning et al., 2015; Brendel et al., 2015). Previous findings were conflicting. One study found worse cognitive performance associated with depressive symptoms, but they assessed a mixed group of cognitively healthy elders and MCI patients (Zhang et al., 2020). Another study found no association between depressive symptoms and global cognition in either MCI or AD patients (Fernández-Martínez et al., 2010). However, our findings are in line with a recent study showing that MCI patients with lower depression scores showed steeper decline in dementia severity measures compared to those with higher depression scores (Cerbone et al., 2020). The authors suggested that being aware of one's cognitive deficits could be associated with worsened mood, while MCI patients without depressive symptoms may not appreciate the extent of their cognitive impairment. Other studies confirmed this statement on a group of AD patients showing depressive symptoms to be associated with less anosognosia (Kashiwa et al., 2005) and a study showing that greater anosognosia in MCI was associated with reduced glucose metabolism in the posterior cingulate cortex, hippocampus (Perrotin et al., 2015; Vannini et al., 2017) and superior temporal gyrus (Nobili et al., 2010). Here, we specifically showed that, in a group of MCI and AD patients with Alzheimer's pathologic changes, higher depressive symptoms were associated with better awareness of cognitive difficulties and better episodic memory performance.

In contrast to cognition and glucose metabolism, we found no link between depressive symptoms and GM volume nor amyloid deposition in ADC patients. Previous findings are conflicting, with studies also reporting no links (Berlow et al., 2010; Bruen et al., 2008; Huey et al., 2017; Mori et al., 2014; Starkstein et al., 2009) while others found a positive (Auning et al., 2015; Enache et al., 2015), or a negative (Lebedeva et al., 2014; Wu et al., 2020) association with depressive symptoms in MCI or AD populations. Our findings suggest that glucose metabolism appears to be more strongly associated to depressive symptoms in Aβ+ MCI-AD patients than GM volume or amyloid deposition.

Methodological considerations and perspectives

Even though the MADRS has been shown to be a good measure of depression relatively independent from dementia severity (Müller-Thomsen et al., 2005), as our participants were selected for the lack of clinically significant anxiety or depression, one of the limitations of our study refers to the skewed distribution of MADRS, with 42 % of the total participants reporting depressive symptoms. To limit the bias associated with the low variability and thus low power of analyses, we repeated all analyses with non-parametric tests, as well as in subgroups including only individuals with at least one depressive symptom.

Our study assessing multiple hallmarks of AD (i.e. global cognition, episodic memory, grey matter volume, glucose metabolism and amyloid load), was cross-sectional in design and thus couldn't assess the directionality of the relationships, which could be measured in future longitudinal analyses. Similarly, as discussed above, we investigated state measures of anxiety and depressive symptoms as they represent states at a given time that we expect to easily change over time and be modifiable through treatment/interventions. Future studies could explore these symptoms as traits rather reflecting the personality of the individuals.

Conclusions

Our multimodal study showed a link between depressive symptoms and higher amyloid load in SCD, and a link with better cognition and episodic memory performance and higher glucose metabolism in the group of patients on the Alzheimer's continuum. Overall, our findings suggest that depressive symptoms reflect distinct process along the course of AD, with higher symptoms reflecting increasing amyloid pathology at the SCD stage, while, conversely, they would reflect greater awareness of cognitive deficits associated with less severe cognitive stage of the disease in the Alzheimer's continuum. Thus, this study shows the relevance of assessing and following depressive symptoms in SCD, and to manage them in cognitively impaired patients, to improve the prevention as well as the prognosis and quality of life of both patients and caregivers.

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6. Conflicts of interest

The authors declare that they have no conflict of interest.

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8. Additional tables

Additional Table 1: Psychoaffective factors' associations to cognition and neuroimaging measures, corrected for education, age, sex and anxiety or depressive symptoms.

Depressive symptoms	HC	SCD	ADC patients
Cognitive measures			
Global cognition	0.313 (-0.163)	0.255 (0.260)	0.112 (0.240)
Episodic memory	0.505 (0.103)	0.725 (-0.038)	**0.012 (0.373)**
Neuroimaging measures			
GM volume	0.462 (-0.160)	0.930 (-0.027)	0.440 (-0.135)
Glucose metabolism	0.481 (0.121)	0.244 (0.309)	**0.032 (0.301)**
Amyloid load	0.422 (0.139)	**0.008 (0.657)**	0.279 (-0.171)
Anxiety symptoms	HC	SCD	ADC patients
Cognitive measures			
Global cognition	0.371 (0.150)	0.725 (-0.088)	*0.083 (0.016)*
Episodic memory	0.506 (-0.106)	0.226 (-0.294)	0.577 (0.088)
Neuroimaging measures			
GM volume	0.954 (0.013)	0.329 (-0.267)	0.985 (-0.003)
Glucose metabolism	0.212 (-0.220)	0.949 (0.016)	0.930 (-0.012)
Amyloid load	0.648 (-0.082)	0.594 (-0.160)	0.868 (0.025)

Values indicate p (r) values of the multiple linear regressions between depressive or anxiety symptoms on the one hand, and the corresponding cognitive or neuroimaging variables on the other hand for each group. All analyses with depressive symptoms were corrected for level of education, age, sex and anxiety symptoms while all analyses with anxiety symptoms were corrected for level of education, age, sex and depressive symptoms. Values in bold correspond to significant p values ($p<0.05$) and values in italic correspond to trends ($0.01<p<0.05$). Abbreviations *ADC* Alzheimer's continuum *GM* grey matter *HC* Healthy controls *SCD* subjective cognitive decline.

Additional Table 2: Non-parametric associations of psychoaffective factors with cognition and neuroimaging measures.

Depressive symptoms	HC	SCD	ADC patients
Cognitive measures			
Global cognition	0.401 (-0.117)	0.185 (0.236)	0.368 (0.124)
Episodic memory	0.996 (0.001)	0.930 (-0.015)	*0.074 (0.258)*
Neuroimaging measures			
GM volume	**0.049 (-0.275)**	0.480 (-0.139)	0.471 (-0.099)
Glucose metabolism	0.116 (0.230)	0.698 (0.078)	*0.073 (0.246)*
Amyloid load	0.279 (0.169)	*0.071 (0.353)*	0.456 (-0.102)
Anxiety symptoms	**HC**	**SCD**	**ADC patients**
Cognitive measures			
Global cognition	0.776 (0.043)	**0.030 (0.411)**	0.572 (-0.079)
Episodic memory	0.961 (0.007)	0.873 (-0.031)	0.162 (0.205)
Neuroimaging measures			
GM volume	0.433 (-0.116)	0.243 (-0.242)	0.419 (0.113)
Glucose metabolism	0.928 (-0.014)	0.404 (0.179)	0.987 (0.002)
Amyloid load	0.982 (-0.004)	0.404 (0.179)	0.489 (0.097)

Values indicate p (r) values of Spearman's correlations between depressive or anxiety symptoms on the one hand, and the corresponding cognitive or neuroimaging variables on the other hand for each group. Values in bold correspond to significant p values ($p<0.05$) and values in italic correspond to trends ($0.01<p<0.05$). Abbreviations *ADC* Alzheimer's continuum *GM* grey matter *HC* Healthy controls *SCD* subjective cognitive decline.

Additional Table 3: Depressive symptoms' associations to cognition and neuroimaging measures in subgroups with at least one depressive symptom.

Non-parametric	HC	SCD	ADC patients
Cognitive measures			
Global cognition	0.206 (-0.295)	0.227 (0.268)	0.259 (0.181)
Episodic memory	0.784 (-0.065)	0.131 (0.325)	0.493 (0.118)
Neuroimaging measures			
GM volume	0.652 (0.111)	0.183 (0.339)	0.752 (0.051)
Glucose metabolism	0.932 (-0.021)	0.699 (0.105)	0.244 (0.188)
Amyloid load	0.971 (0.009)	**0.016 (0.592)**	0.468 (-0.117)
corrected for the level of education, age and sex	HC	SCD	ADC patients
Cognitive measures			
Global cognition	0.377 (-0.192)	0.287 (0.278)	0.102 (0.284)
Episodic memory	0.801 (-0.054)	0.221 (0.345)	0.157 (0.253)
Neuroimaging measures			
GM volume	0.136 (0.442)	0.703 (0.138)	0.453 (-0.147)
Glucose metabolism	*0.071 (-0.516)*	0.147 (0.505)	**0.039 (0.331)**
Amyloid load	0.737 (-0.085)	**0.036 (0.584)**	0.166 (-0.252)
corrected for the level of education, age, sex and anxiety symptoms	HC	SCD	ADC patients
Cognitive measures			
Global cognition	0.280 (-0.256)	0.107 (0.503)	0.117 (0.286)
Episodic memory	0.955 (-0.014)	0.494 (0.231)	0.998 (0.306)
Neuroimaging measures			
GM volume	0.261 (0.358)	0.545 (0.273)	0.586 (-0.113)
Glucose metabolism	0.211 (-0.412)	0.101 (0.750)	**0.040 (0.340)**
Amyloid load	0.795 (0.073)	*0.059 (0.748)*	0.174 (-0.261)

Values indicate p (r) values of the multiple linear regressions between depressive and the corresponding cognitive or neuroimaging variables for each group. Values in bold correspond to significant p values ($p<0.05$) and values in italic correspond to trends ($0.01<p<0.05$). Abbreviations *ADC* Alzheimer's continuum *GM* grey matter *HC* Healthy controls *SCD* subjective cognitive decline.

3.5. Etude 3 : Focus sur le SCD

Le stade de SCD est défini comme un groupe de sujets présentant une plainte cognitive qui n'est pas objectivée par des tests neuropsychologiques, et qui est plus à risque de développer des troubles cognitifs ainsi qu'une démence (Jessen et al., 2014; Kaup et al., 2015; Koppara et al., 2015; Mitchell et al., 2014; Reisberg et al., 2010). La recherche sur la MA s'orientant vers la prévention et la compréhension des stades précliniques ces dernières années, ces individus ont reçu de plus en plus d'attention (Reisberg et al., 2010; Sperling et al., 2011). Cependant, cette plainte cognitive pourrait être liée à d'autres étiologies que la MA, telles que le vieillissement normal (Ponds et al., 1997), les troubles du sommeil, ou la présence de symptômes anxieux ou dépressifs (Clarnette et al., 2001; Comijs et al., 2002; Gamaldo et al., 2019; Kang et al., 2017; Lauriola et al., 2017; Paradise et al., 2011). De plus, les études s'intéressant au SCD recrutent des participants dans la population générale (Mielke et al., 2012; Stewart et al., 2008) et/ou dans des centres mémoire, au cours de consultations médicales au sujet de leur inquiétude concernant leur cognition (Hafkemeijer et al., 2013; Perrotin et al., 2015; Snitz et al., 2015; Striepens et al., 2010), qui pourrait être une source supplémentaire d'hétérogénéité. L'objectif de cette dernière étude est de caractériser les SCD selon leur mode de recrutement, en termes de modifications cognitives et neurobiologiques typiques de la MA, ainsi que d'évaluer les symptômes anxieux et dépressifs en tant que substrats de cette plainte cognitive.

Dans ce contexte, nous avons inclus 50 SCD, 23 provenant de la population générale (SCD-communauté) et 27 recrutés lors de consultation en centre mémoire (SCD-clinique), ainsi que 28 sujets de plus de 50 ans sans déficits ni plainte cognitive en tant que contrôles, tous issus du protocole IMAP+. Ces participants ont effectué plusieurs évaluations cognitives contenant une évaluation de la cognition globale, mesurée à l'aide de la Mattis Dementia Rating Scale (DRS), et de la mémoire épisodique, mesurée à l'aide du sous-score de rappel différé de la tâche d'« Encodage, Stockage et Récupération » (ESR). La plainte cognitive a été évaluée de façon globale chez le participant (auto-questionnaire) et chez son informant (hétéro-questionnaire) à l'aide du questionnaire de *Cognitive Difficulties Scale* (CDS), ainsi que 3 sous-facteurs uniquement en auto-rapporté mesurant la plainte cognitive

d'attention/langage, de mémoire/orientation et de praxies/activités domestiques, déterminés à l'aide d'une analyse factorielle dans une étude précédente réalisée dans le laboratoire (La Joie et al., 2016). Les participants ont également effectué des examens de neuroimagerie d'IRM structurale, de TEP avec le radiotraceur ^{18}F-fluorodeoxyglucose et de TEP avec le radiotraceur ^{18}F-florbetapir. Les symptômes d'anxiété trait ont été mesurés avec le questionnaire *Spielberger State-Trait Anxiety Inventory form Y-B* (STAI-B), et les symptômes dépressifs ont été évalués par un clinicien avec le *Montgomery-Åsberg Depression Rating Scale* (MADRS). Les participants ont été suivis sur ces mêmes mesures pendant 2.4 ans en moyenne. Dans un premier temps, nous avons comparé les groupes sur ces différentes mesures, puis nous avons effectué des analyses de régression entre les scores de plainte cognitive subjective auto-rapportée et la plainte hétéro-rapportée, la cognition, les facteurs psychoaffectifs et la neuroimagerie en « *voxel-wise »* dans chaque groupe. Les analyses longitudinales ont évalué l'évolution des différents scores avec le temps, et des analyses de régression entre les scores baseline de plainte et de symptômes anxieux et dépressifs avec la pente de cognition nous ont permis d'évaluer les prédicteurs du déclin cognitif. Pour finir, nous avons calculé et comparé des cartes d'atrophie cérébrale pour chaque groupe.

Les principaux résultats transversaux de cette étude montrent que les deux groupes de SCD ont des performances cognitives similaires, mais une plainte de l'informant et des symptômes anxieux plus importants comparé aux contrôles. Les SCD-clinique présentent cependant plus de symptômes dépressifs, de plainte de l'informant et d'atrophie avec le temps, comparé aux SCD-communauté. Une augmentation de la plainte cognitive auto-rapportée est associée (i) à une diminution du volume de substance grise ainsi qu'à une augmentation des symptômes d'anxiété chez les SCD-communauté ; (ii) à une augmentation de la plainte rapportée par l'informant chez les SCD-clinique ; et (iii) à une diminution du métabolisme du glucose dans les deux groupes de SCD. Les analyses longitudinales indiquent notamment une augmentation des symptômes dépressifs, ainsi qu'une association entre une plainte auto-rapportée élevée à baseline et un déclin cognitif plus important avec le temps dans le groupe de SCD-communauté. Pour finir, une atrophie de la substance grise plus importante a été

mise en évidence chez les SCD-clinique, comparé aux contrôles et aux SCD-communauté, sans différence entre les deux groupes de SCD en comparaison directe.

Les résultats suggèrent que le groupe de SCD recruté en centre mémoire représente une population plus fragile, et a plus de risque de déclin cognitif subséquent, comparé aux SCD recrutés dans la population générale. En effet, les SCD-clinique ont une plainte de l'informant plus élevée ainsi qu'une atrophie plus importante avec le temps. Cependant ces groupes présentent des similarités sur de nombreux aspects, tels que les symptômes anxieux et la charge amyloïde. Ces deux groupes semblent donc faire partie d'un continuum, puisque les SCD-communauté montrent une augmentation des symptômes dépressifs avec le temps, rejoignant les SCD-clinique qui présentaient plus de symptômes dépressifs que les SCD-population à baseline, ainsi qu'une plainte de l'informant d'un niveau intermédiaire (supérieure à celle des contrôles mais inférieure à celle des SCD-clinique). En conclusion, cette étude met en évidence la pertinence d'un suivi clinique des SCD, notamment les SCD-clinique, et de l'évaluation, voire du traitement des symptômes anxieux et dépressifs infra-cliniques chez les personnes âgées. Plutôt que facteurs confondants du SCD, les facteurs psychoaffectifs pourraient représenter les premiers symptômes du syndrome clinique d'Alzheimer, ou encore l'expression d'un processus pathologique associé à une détresse psychologique et au déclin cognitif chez les SCD-communauté.

Cette étude a fait l'objet d'une communication orale en 2018 (Réunion Francophone sur la Maladie d'Alzheimer et Syndromes Apparentés), avec prix de la meilleure communication orale pour la catégorie « Recherche clinique » (présentée par E. Kuhn, co-premier auteure), ainsi que deux communications affichées en 2019 (*Alzheimer's Imaging Consortium* et *Alzheimer's Association International Conference*), et a été publiée en Juillet 2019 dans la revue *Alzheimer's Research & Therapy*.

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RESEARCH

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Cross-sectional and longitudinal characterization of SCD patients recruited from the community versus from a memory clinic: subjective cognitive decline, psychoaffective factors, cognitive performances, and atrophy progression over time

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Abstract

Background: Subjective cognitive decline (SCD) defines a heterogeneous population, part of which having Alzheimer's disease (AD). We aimed at characterizing SCD populations according to whether or not they referred to a memory clinic, by assessing the factors associated with increased AD risk.

Methods: Seventy-eight cognitively unimpaired older adults from the IMAP+ study (Caen) were included, amongst which 28 healthy controls (HC) and 50 SCD recruited from the community (SCD-community; $n = 23$) or from a memory clinic (SCD-clinic; $n = 27$). Participants underwent cognitive, psychoaffective, structural MRI, FDG-PET, and amyloid-PET assessments. They were followed up over a mean period of 2.4 ± 0.8 years. The groups were compared in terms of baseline and follow-up levels of SCD (self- and informant-reported), cognition, subclinical anxiety and depression, and atrophy progression over time. We also investigated SCD substrates within each SCD group through the correlations between self-reported SCD and other psychometric and brain measures.

Results: Compared to HC, both SCD groups showed similar cognitive performances but higher informant-reported SCD and anxiety. Compared to SCD-community, SCD-clinic showed higher informant-reported SCD, depression score, and atrophy progression over time but similar brain amyloid load. A significant increase over time was found for depression in the SCD-community and for self-reported praxis-domestic activities SCD factor in the SCD-clinic. Higher self-reported SCD correlated with (i) lower grey matter volume and higher anxiety in SCD-community, (ii) greater informant-reported SCD in SCD-clinic, and (iii) lower glucose metabolism in both SCD groups.

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Conclusions: Higher subclinical depression and informant-reported SCD specifically characterize the SCD group that refers to a memory clinic. The same group appears as a frailer population than SCD-community as they show greater atrophy progression over time. Yet, both the SCD groups were quite similar otherwise including for brain amyloid load and the SCD-community showed increased depression score over time. Altogether, our findings highlight the relevance of assessing psychoaffective factors and informant-reported SCD in SCD populations and point to both differences and similarities in SCD populations referring or not to a memory clinic.

Keywords: Neuroimaging, Biomarkers, Pathological ageing, Preclinical Alzheimer's disease, Psychoaffective factors, Subjective cognitive decline

Background

Subjective cognitive decline (SCD) refers to individuals' perceived decline in memory and/or other cognitive abilities relative to their previous level of performance, in the absence of objective neuropsychological deficits [1]. Although these individuals have been described for decades [2], they have received increasing attention over the past few years due to growing interest in characterizing the preclinical stages of Alzheimer's disease (AD) [3, 4]. Recent cross-sectional studies have shown that SCD is associated with neuroimaging biomarkers suggestive of AD such as hippocampal/parahippocampal atrophy [5–17] and/or temporoparietal hypometabolism [5, 18, 19], and cortical amyloid β (Aβ) deposition [18, 20–24] (see [25] for review). Longitudinal investigations have repeatedly shown that SCD is also associated with an increased risk of subsequent cognitive decline [26, 27] or conversion to mild cognitive impairment (MCI) or AD dementia [28–34]. There is thus converging evidence that SCD is associated with an increased risk of AD dementia and might represent, at least for some cases, the first clinically observable sign of Alzheimer's clinical syndrome [35].

However, the links between SCD and AD biomarkers have not been reported in all studies (see [25] for review), which might reflect the fact that SCD is multidetermined. Thus, SCD may be due to AD but also non-AD aetiologies (see [36] for review, [37]) including normal ageing [38], poor general health [38, 39], medication [1], sleep disorders [40–43], or psychoaffective factors such as anxiety and depression [39–41, 44]. The current challenge, as highlighted in an international collaborative working group on SCD called the SCD-Initiative (SCD-I; [1, 45]), is thus to identify the specific characteristics of SCD that are associated with an increased likelihood of AD aetiology [1, 45].

An important source of heterogeneity in the definition and aetiology of SCD patients is their type of recruitment [25] (see [46–48] for review). Indeed, typical research settings include population-based studies [6, 24], volunteer samples [18, 20, 21, 23], and/or medical help-seeking samples [5, 7–12, 22]. In a previous study [25], we showed that SCD patients who refer to a memory clinic, referred to as SCD-clinic, had significant atrophy in AD-sensitive regions compared to SCD individuals recruited from a self-reported SCD questionnaire in volunteers from the community, referred to as SCD-community in what follows. This previous study suggested that SCD-clinic as a group is further along the Alzheimer's clinical syndrome trajectory than SCD-community.

In this study, our aim was to provide further evidence towards this statement with a more complete characterization of both SCD-clinic and SCD-community populations of the substrates of their SCD and of their evolution.

For this purpose, we first highlighted the similarities and differences between the two SCD populations in terms of cognitive performances, psychoaffective measures, informant-reported SCD, and the type of self-reported SCD. Informant-reported SCD is recognized as a feature that influences the likelihood of preclinical AD/Alzheimer's syndrome—confirmation of cognitive decline by an informant being associated with increased risk for preclinical AD/Alzheimer's syndrome [1, 45, 49, 50]. Moreover, subclinical symptoms of anxiety or depression might be related with SCD and may constitute risk factors for subsequent cognitive decline and/or be early manifestations of preclinical Alzheimer's syndrome [51–55]. In addition, a previous study showed that SCD of different cognitive domains were differentially associated with preclinical Alzheimer's syndrome [56].

Second, we investigated the substrates of self-reported SCD within each SCD group by assessing the correlations with informant-reported SCD, psychoaffective and cognitive measures, and neuroimaging biomarkers (grey matter atrophy, cerebral glucose hypometabolism, and amyloid deposition).

Finally, we studied the evolution of the groups over a mean follow-up period of 2.4 years in terms of SCD, psychoaffective and cognitive measures, and atrophy progression over time. We also assessed how baseline variables predicted subsequent cognitive decline.

Methods

Subjects

A total of 78 cognitively unimpaired individuals were included from the *Imagerie Multimodale de la maladie d'Alzheimer à un stade Précoce* (IMAP+) study (Caen, France). The inclusion and exclusion criteria are detailed in previous publications. Briefly, participants were all aged over 50 years; had at least 7 years of education; had no history of alcoholism, drug abuse, head trauma, or psychiatric disorder; and performed in the normal range on a standardized neuropsychological examination [8, 25, 57].

Participants were recruited from two main sources, memory clinic or public advertising (see Fig. 1). The first group of SCD patients was recruited from a local memory clinic consultation (SCD-clinic) that they attended because of memory concerns. The clinical diagnosis was obtained by a multidisciplinary consensus under the supervision of a senior neurologist. The subjective cognitive decline was self-reported to the clinician during the interview and with a 10-item SCD questionnaire, the Cognitive Complaint Questionnaire [58]. Before inclusion, the clinician checked that the SCD was not caused by medication, psychoaffective conditions (including a major depressive disorder or generalized anxiety disorder), or other medical conditions. Amongst the 41 patients who met these criteria, only those for which the main variables of interest (self- and informant-reported SCD questionnaires and objective episodic memory score) were available were included in the present study, resulting in a group of 27 SCD-clinic.

Fifty-one participants were recruited from the community through public advertising, as they volunteered to

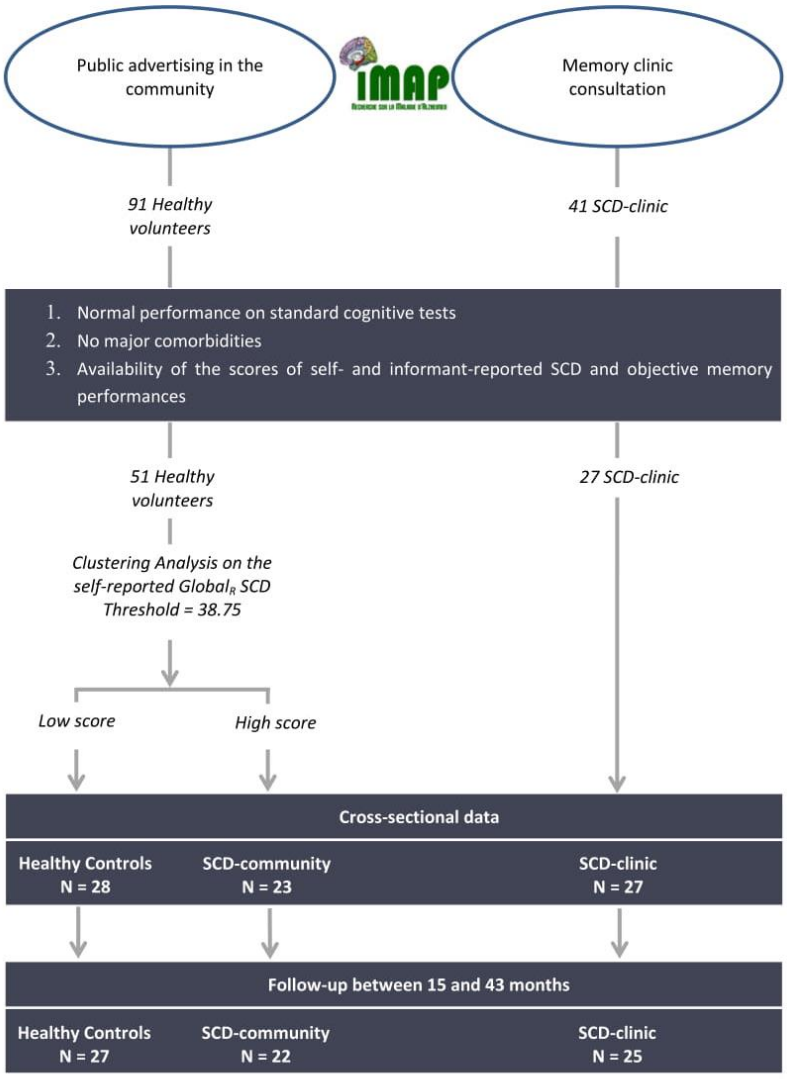

Fig. 1 A flow chart of participant selection and categorization. The graphic shows the steps to select the participants finally included in the three groups of interest of the present study—the healthy controls and the cognitively unimpaired older adults with subjective cognitive decline (SCD) who referred (SCD-clinic) or not (SCD-community) to a memory clinic. All participants were selected from the *Imagerie Multimodale de la maladie d'Alzheimer à un stade Précoce* (IMAP+) study. *N*, sample size

participate in the IMAP+ study. This group was subdivided into two groups based on their score of self-reported SCD (see below and Fig. 1) resulting in 28 participants with a low score considered as the healthy control (HC) and 23 participants with a high score labelled as the SCD-community. As for the SCD-clinic, only the participants for whom the three main measures of interest were available were included in the present study.

The IMAP+ study was approved by the local ethics committee. After the complete description of the study to the participants, written informed consent was obtained from all participants.

Neuropsychological assessment

Neuropsychological assessment was performed on the same site for all participants at baseline and at follow-up. The mean duration between serial neuropsychological assessments was 2.4 (± 0.8) years.

Self- and informant-reported cognitive difficulties

SCD was assessed with the Cognitive Difficulties Scale (CDS) [59], a 39-item self-rated questionnaire that requires participants to rate how often they experience particular cognitive difficulties in everyday life on a 5-point scale (from "never" = 0 to "very often" = 4). This questionnaire was performed by the participant about himself, resulting in a self-reported measure of SCD, and by the participant's informant about the participant, resulting in an informant-reported measure of SCD. Higher scores indicate greater SCD.

In the present study, we used the reduced SCD score of the CDS [59], corresponding to the sum of 34 items, as a measure of self- or informant-reported cognitive difficulties. Five items were removed from the initial questionnaire which correspond to gendered items (e.g. related to cooking or sewing), as they depend on age-specific cultural norms [59]. This score will be referred to as '$global_R$ SCD' in the following article. The self-reported $global_R$ SCD score was used to separate the HC from the SCD-community. More specifically, a hierarchical clustering analysis (2 clusters, 50 iterations) was performed on this score within the cognitively unimpaired volunteers recruited from the community, resulting in 28 participants with a low score (HC) and 23 participants with a high score (SCD-community).

In a previous study by our team, we conducted a factorial analysis on the CDS scale and highlighted three different factors reflecting different types of SCD [56]: (i) the first factor (F1) was composed of 11 items related to attention and language; (ii) the second factor (F2) included 12 items related to memory and orientation; and (iii) the third factor (F3) included 7 items related to praxis and domestic activities [56]. These three factors were computed for each participant using each item weighted according to the results of the factorial analysis from La Joie et al. [56] (for self- and informant-reported SCD) and compared between the groups.

Psychoaffective measures

Depressive symptomatology and trait anxiety were assessed using the Montgomery-Asberg Depression Rating Scale (MADRS) [60] and Spielberger State-Trait Anxiety Inventory (STAI-B), respectively [61]. Higher scores indicated a higher level of depression or anxiety with all scores yet keeping within the subclinical levels as participants were screened for the lack of clinically significant anxiety or depression disorders.

Cognitive measures

Global cognition was assessed using the Mini-Mental State Examination (MMSE) [62] and the global score of the Mattis Dementia Rating Scale (DRS) [63]. Memory was assessed using the Encoding, Storage and Recuperation (ESR) word list delayed recognition subscores [64].

Cross-sectional data: transformation to *w*-scores

For cross-sectional analyses, all continuous raw scores were transformed into *w*-scores, which are age and education-adjusted *z*-scores relative to the control group [65], except for the psychoaffective measures.

Longitudinal data: computation of slope of changes

For longitudinal analyses, a slope of decline was calculated for each measure of each subject with a simple linear regression equation '$y = ax + b$' (where y is the score of interest; x is the number of months from the initial evaluation; a is the slope of the line; b is the intercept) [66].

Neuroimaging assessment

Neuroimaging data acquisition

All participants were scanned on the same magnetic resonance imaging (MRI) and positron emission tomography (PET) cameras at the Cyceron Center (Caen, France): a Philips Achieva 3.0 T scanner and a Discovery RX VCT 64 PET-CT device (General Electric Healthcare), respectively.

High-resolution T1-weighted anatomical volumes were acquired using a 3D fast-field echo sequence (3D-T1-FFE sagittal; repetition time = 20 ms; echo time = 4.6 ms; flip angle = 10°; 180 slices with no gap; slice thickness = 1 mm; field of view = $256 \times 256\ mm^2$; in-plane resolution = $1 \times 1\ mm^2$). In the present study, we used the baseline and the follow-up MRI scans; the mean duration between serial MRI was 2.4 years (± 0.8 years). Follow-up MRI scan was missing in 1 HC, 1 SCD-community, and 3 SCD-clinic participants.

Both ^{18}F-fluorodeoxyglucose (FDG) and florbetapir-PET scans were acquired with a resolution of $3.76 \times 3.76 \times$

4.9 mm^3 (field of view = 157 mm). Forty-seven planes were obtained with a voxel size of 1.95 × 1.95 × 3.2 mm^3. A transmission scan was performed for attenuation correction before the PET acquisition. For ^{18}F-FDG-PET, the participants were fasted for at least 6 h before scanning. After a 30-min resting period in a quiet and dark environment, 180 MBq of ^{18}F-FDG was intravenously injected as a bolus. A 10-min PET acquisition scan began 50 min after the injection. For florbetapir-PET, each participant underwent a 20-min PET scan, beginning 50 min after the intravenous injections of ~ 4 MBq/kg of florbetapir. Two HC and 3 SCD-clinic participants only underwent a 10-min acquisition starting 50 min after the injection. In the present study, we used the baseline PET scans of the participants, which was missing for 1 HC for 18F-FDG-PET and for 3 HC and 1 SCD-community participants for florbetapir-PET (see Additional file 1).

Neuroimaging pre-processing

Cross-sectional data Neuroimaging pre-processing was performed using the Statistical Parametric Mapping version 12 (SPM12) software (Wellcome Trust Centre for Neuroimaging, London, UK).

T1-weighted MRI were segmented using multimodal segmentation (T1-weighted MRI, T2-weighted MRI, and Flair) and spatially normalized to the Montreal Neurological Institute (MNI) space. Then, the normalized grey matter segments were modulated to correct for non-linear warping effects, and the resultant images were smoothed using an 8-mm full-width half-maximum (FWHM) Gaussian kernel [57, 67, 68].

PET data were corrected for partial volume effects using the Muller-Gartner method, coregistered onto their corresponding MRI, and normalized using the deformation parameters defined from the MRI procedure. Resultant images were quantitatively normalized using the cerebellar grey matter as the reference region. PET images were then smoothed using a 10-mm FWHM Gaussian kernel [57, 67–69].

All resultant MRI and PET images were finally masked to exclude non-grey matter voxels as well as the cerebellum from the analyses.

The global neocortical standardized uptake value ratio (SUVr) value was also obtained in each individual from the Florbetapir-PET SUVr images using a neocortex mask (including all regions but the cerebellum, hippocampus, amygdala, and subcortical grey nuclei). The SUVr was used to classify subjects as florbetapir positive or negative, using a threshold derived from an independent group of 41 young individuals from the IMAP project (16 females; age = 28.40 ± 6.06 years) [25, 70]. The positivity threshold was defined by the mean + 2 SD of 41 healthy young controls aged 21 to 39 years old (supposedly devoid of amyloid deposition), corresponding to a Florbetapir SUVr of 0.98. Individuals with values above this threshold were considered as amyloid-positive and those below this threshold as amyloid-negative.

Longitudinal changes For each participant, a brain map of atrophy progression over time, reflecting the progression of atrophy over the follow-up period, was computed using the Jacobian determinants from the pairwise longitudinal registration of the baseline and follow-up MRI scans. The method is detailed in [71] and summarized in Additional file 2.

Statistical analysis

Cross-sectional data To assess whether the control and both SCD groups differ in terms of demographic and clinical variables or self-reported $global_R$ SCD, variance analyses (ANOVAs) with one three-level (group) factor were performed.

To highlight the differences between the three groups regarding the factors of interest potentially related to SCD or memory clinic consultation (i.e. psychoaffective measures, informant-reported SCD, types of SCD), we performed analyses of covariance (ANCOVAs) with one three-level (group) factor correcting for age and education, for all continuous variables—except for *w*-scores where ANOVAs were performed without covariates as age and education were already partialled out. Group differences for categorical variables were assessed using chi-square tests.

The cognitive substrates of self-reported SCD were assessed in each group using correlations, correcting for age and education for all variables but *w*-scores. Correlations were performed between self-reported $global_R$ SCD score and self-reported SCD factors, informant-reported $global_R$ SCD, cognitive performances (global cognition and memory *w*-scores), and psychoaffective measures (anxiety and depression). All statistical analyses of behavioural data were performed using the STATISTICA software (v13.0, StatSoft Inc., Tulsa, OK).

The cerebral substrates were assessed in each group using regression analyses correcting for age and education between the self-reported $global_R$ SCD score and cross-sectional MRI and PET (FDG and Florbetapir) data. All statistical analyses of neuroimaging data were performed using the full factorial design in SPM12.

Longitudinal data To determine whether SCD, cognitive, and psychoaffective measures significantly changed over time, the individual slopes of regression line were compared to zero for each SCD group separately, using one-sample *t* tests. Then, to assess whether the changes in these measures significantly differed between the groups, the slopes of regression line were compared between the groups using ANCOVAs with one two-level

(group) factor, correcting for age and education, for each SCD, cognitive, and psychoaffective measures. Thirdly, to assess whether the atrophy progression over time significantly differed between the groups, an ANCOVA with one three-level (group) factor with age and education as covariates was performed in SPM12. Finally, to improve our understanding of the predictors of cognitive decline, regression analyses were performed within each SCD group between baseline SCD scores or psychoaffective measures and the slope of cognitive decline, correcting for age and education, using general linear models and the STATISTICA software.

Neuroimaging results are examined at $p_{\text{uncorrected}} < 0.005$ and cluster extent $k > 250\,\text{mm}^3$ also indicating results surviving the $p < 0.001$ and $k > 50\,\text{mm}^3$ threshold. This allows to take into account the clusters that were less significant but larger versus more significant but smaller. For behavioural results, when the main effect of the group was significant ($p < 0.05$), post-hoc analyses were performed using the Newman-Keuls method.

Results

Group characteristics

There was no between-group difference in any demographic or cognitive variables; only a trend was found for SCD-clinic to be younger than HC and SCD-community to have a higher amyloid proportion of amyloid-positive individuals (Table 1). The self-reported global_R SCD score was higher in SCD-clinic compared to HC but equivalent in both SCD groups (Fig. 2a).

Cross-sectional data

At baseline, the self-reported SCD differed significantly between the groups for the global_R score and the three factors. HC showed lower self-reported SCD than both SCD groups; note that self-reported global_R SCD was used to separate HC from SCD-community. As for the informant-reported SCD, SCD-clinic had higher scores than SCD-community and HC, and SCD-community had higher scores than HC, for all SCD measures except for the praxis-domestic activities SCD for which no difference was found between the SCD groups (see Fig. 2b). The two psychoaffective measures showed significant between-group differences: for anxiety, scores were significantly higher in SCD-community and SCD-clinic compared to HC; for depression, SCD-clinic had higher scores than SCD-community and HC (see Fig. 2c, d).

Substrates of self-reported SCD

Cognitive and behavioural correlates

Significant relationships were found between self-reported global_R SCD score and each self-reported SCD factors in both SCD groups. Significant correlations were found between self-reported global_R SCD and the corresponding measures of informant-reported SCD only in the SCD-clinic. A significant relationship was also found between the self-reported global_R SCD score and anxiety in the SCD-community group, while no relationship was found with baseline objective measures of cognition or depression in any group (Table 2).

Brain correlates

In the SCD-community group, self-reported global_R SCD negatively correlated with glucose metabolism and grey matter volume in the left insula, right superior frontal, and anterior cingulate cortex (Fig. 3a). Except for the right superior frontal correlation with grey matter volume, all

Table 1 Demographic features of the study populations

	HC	SCD-community	SCD-clinic	ANOVAs, *p* value
N	28	23	27	
Female % (*N*)	46 (13)	61 (14)	41 (11)	(χ^2) NS[¤]
Age	72.25 ± 6.33	71.70 ± 6.60	68.30 ± 7.99	0.09
Level of education	11.50 ± 3.64	12.65 ± 4.13	12.85 ± 3.60	0.37
MMSE	28.68 ± 1.09	28.70 ± 1.18	28.70 ± 1.27	0.99
DRS	0.05 ± 1.02	0.08 ± 0.58	−0.12 ± 0.90	0.68
ESR	− 0 ± 0.71	0.01 ± 0.72	− 0.49 ± 1.70	0.18
APOE ε4 (carrier) % (*N*)	18 (5)	26 (6)	15 (4)	(χ^2) NS[¤]
Amyloid status (pos) % (*N*)	22 (6)	45 (10)	33 (9)	(χ^2) NS[¤]
SUVr	0.97 ± 0.17	1.03 ± 0.18	1.01 ± 0.19	0.46

Values indicate mean ± SD or percentage. When the analyses of variance (ANOVAs) reached significance, Newman-Keuls tests were used. [¤]For gender, HC – SCD-community $p = 0.29$, HC – SCD-clinic $p = 0.71$, SCD-community – SCD-clinic $p = 0.16$; for APOE4 carrier: HC – SCD-community $p = 0.49$, HC – SCD-clinic $p = 0.76$, SCD-community – SCD-clinic $p = 0.33$; for amyloid status: HC – SCD-community 0.09, HC – SCD-clinic $p = 0.37$, SCD-community – SCD-clinic $p = 0.39$
Abbreviations: *APOE* ε4 apolipoprotein E allele 4, *DRS* *w*-score of Mattis Dementia Rating Scale, *ESR* *w*-score of Encoding, Storage and Recuperation, *HC* healthy control, *MMSE* Mini-Mental State Examination, *N* sample size, *NS* not significant, *pos* positive, *SCD* subjective cognitive decline, *SD* standardized deviation

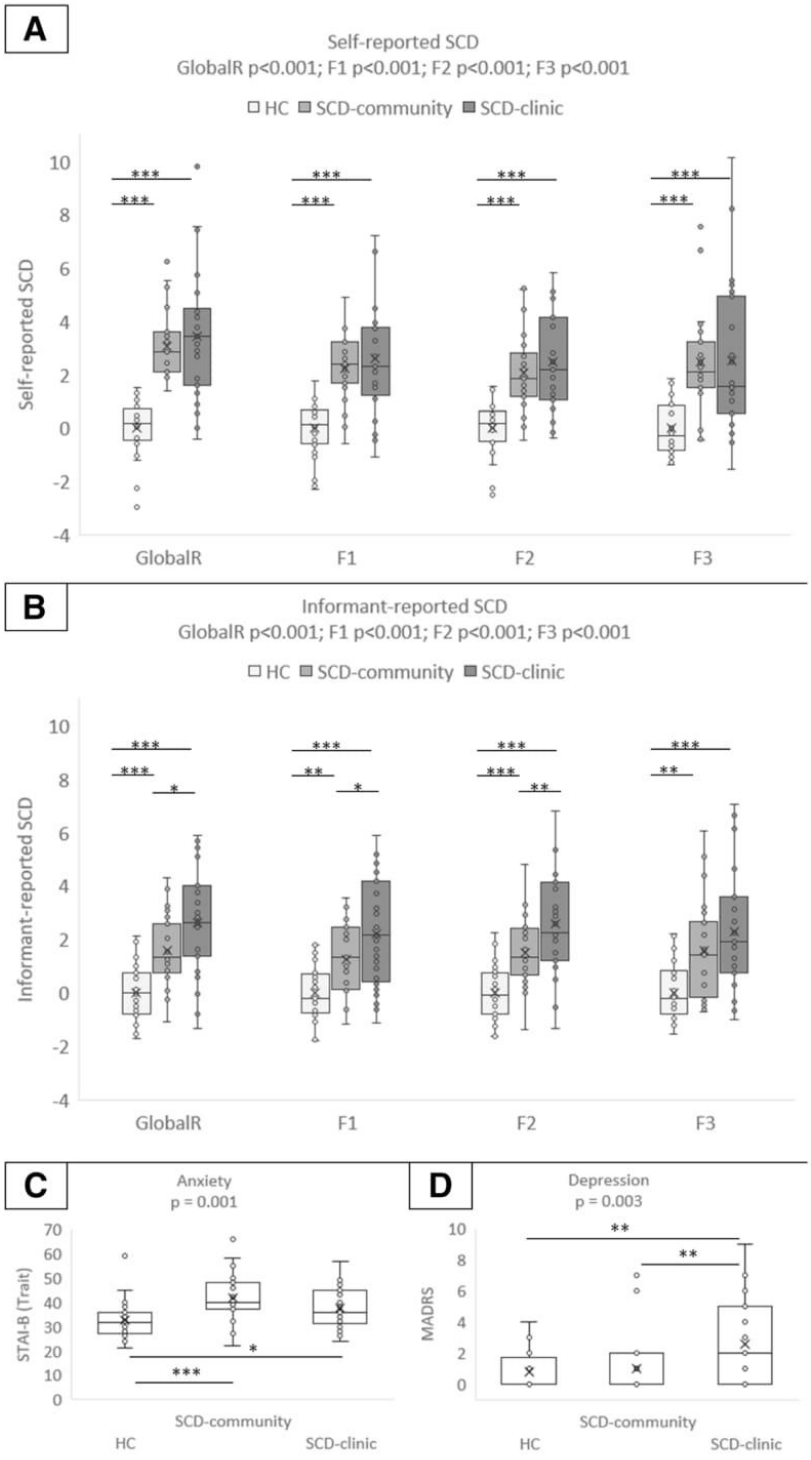

Fig. 2 Group comparisons on subjective cognitive decline (SCD) and psychoaffective measures. The graphs indicate mean values and 95% confidence intervals. **a** Group comparisons on the global$_R$ and the three self-reported SCD factors. **b** Group comparisons on the global$_R$ and the three informant-reported SCD factors. **c** Group comparison on subclinical anxiety. **d** Group comparison on subclinical depression. **a**, **b** *p* corresponds to one-way analysis of variance (ANOVA); post-hoc analyses were performed with the Newman-Keuls difference test. Higher scores indicate greater SCD. **c**, **d** *p* corresponds to one-way analysis of covariance (ANCOVA) correcting for age and education; post-hoc analyses were performed with the Newman-Keuls difference test. Higher scores indicate higher subclinical anxiety or depression. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ between the groups. F1, factor 1 attention-language SCD; F2, factor 2 memory-orientation SCD; F3, factor 3 praxis-domestic activities SCD; MADRS, Montgomery-Asberg Depression Rating Scale; STAI-B, Spielberger State-Anxiety Inventory Trait

Table 2 Results of linear regressions or general linear models between self-reported $global_R$ SCD and cross-sectional measures

	SCD-community		SCD-clinic	
	r	*p*	*r*	*p*
Self-reported SCD				
Attention-language SCD (F1)	*0.62*	*0.003*	*0.88*	*< 0.001*
Memory-orientation SCD (F2)	*0.70*	*< 0.001*	*0.90*	*< 0.001*
Praxis-domestic activities SCD (F3)	*0.56*	*0.008*	*0.67*	*< 0.001*
Informant-reported SCD				
$Global_R$ SCD	0.10	0.66	*0.68*	*< 0.001*
Cognitive measures				
DRS	− 0.10	0.67	0.14	0.48
ESR	− 0.25	0.25	− 0.14	0.48
Psychoaffective measures				
STAI-B	*0.49*	*0.02*	− 0.03	0.90
MADRS	− 0.01	0.96	− 0.15	0.47

For the informant-reported SCD and cognitive measures, values indicate the results of the simple linear regressions (*r* and *p* values) between the self-reported $global_R$ SCD score on the one hand and the corresponding variables on the other hand. For the psychoaffective measures, values indicate the results of the general linear model between the self-reported $global_R$ SCD score and these measures, correcting for age and education. Values indicated in italics correspond to $p < 0.05$

Abbreviations: DRS w-score of Mattis Dementia Rating Scale, *ESR w*-score of Encoding, Storage and Recuperation, *F1 w*-score of cognitive difficulties scale factor 1 attention-language SCD, *F2 w*-score of cognitive difficulties scale factor 2 memory-orientation SCD, *F3 w*-score of cognitive difficulties scale factor 3 praxis-domestic activities SCD, *MADRS* Montgomery-Asberg Depression Rating Scale, *SCD* subjective cognitive decline, *STAI-B* Spielberger State-Anxiety Inventory Trait

clusters were recovered at $p < 0.001$, $k > 50$ voxels (Additional file 3).

In the SCD-clinic group, the self-reported $global_R$ SCD negatively correlated with glucose metabolism in the bilateral insula, left medial prefrontal cortex (encompassing both the ventral and dorsal sections), bilateral superior and middle temporal cortex, and right fusiform gyrus. All clusters were recovered at $p < 0.001$, $k > 50$ voxels, except for the left medial prefrontal cortex (Additional file 3). At the threshold of $p < 0.005$ and $k > 250$ voxels, no correlation was found with amyloid deposition or grey matter volume (see Fig. 3b).

For the sake of comparison, the correlations were also assessed with the SCD factors; they showed that the brain substrates of the self-reported memory SCD score were very similar to those of the $global_R$ SCD score (Additional file 3).

Longitudinal data

Cognitive and behavioural measures

The self-reported praxis-domestic activities SCD slope was significantly higher than zero ($p = 0.04$), i.e. this measure significantly increased over time, only in the SCD-clinic. By contrast, the depression score slope tended to be higher than zero ($p = 0.06$) only in the SCD-community. None of the other slopes significantly differed from zero indicating that none of the other self- and informant-reported SCD factors and cognitive or psychoaffective measures significantly changed over time during the follow-up period of the SCD groups (Table 3).

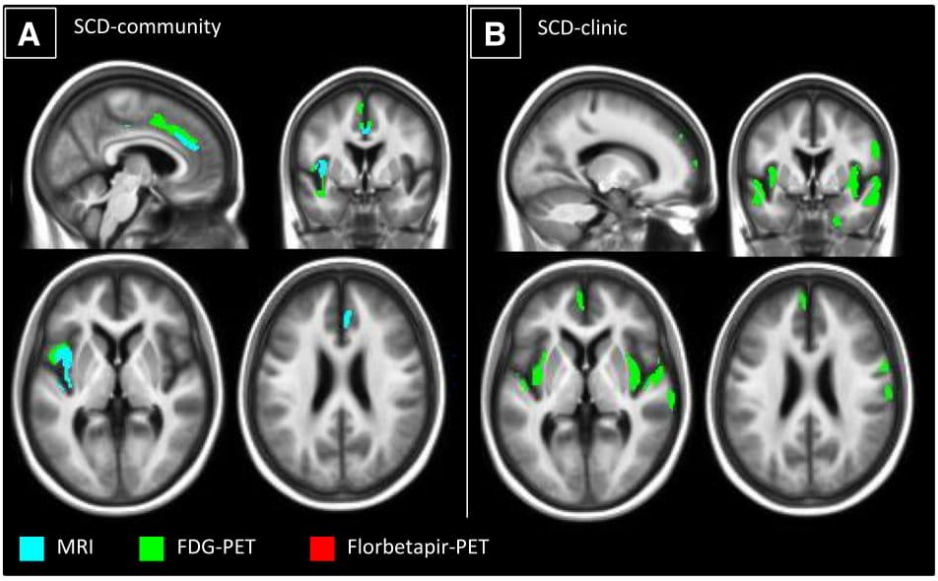

Fig. 3 Results of the voxelwise correlations between self-reported $global_R$ SCD and neuroimaging within each SCD group. The correlations with grey matter volume (blue), glucose metabolism (green), and amyloid deposition (red) are presented within the SCD-community (**a**) and the SCD-clinic (**b**) groups. The results are displayed at uncorrected $p < 0.005$, $k > 250$ voxels. FDG, 18F-fluorodeoxyglucose; PET, positron emission tomography; SCD, subjective cognitive decline

At follow-up, there was no significant group difference for any cognitive, psychoaffective, or SCD slope of changes, except for the self-reported praxis-domestic activities SCD which increased more in the SCD-clinic group than in the SCD-community group (Table 3).

Atrophy progression over time in MRI

Between-group comparisons of brain maps of atrophy progression over time showed that SCD-clinic had higher atrophy progression over time in the dorsal frontal cortex compared to HC (Fig. 4b) and in the middle temporal cortex and dorsal frontal cortex extending to the ventral prefrontal cortex compared to SCD-community (Fig. 4c). There was no significant difference in the atrophy progression over time between HC and SCD-community (Fig. 4a). All clusters were recovered at $p < 0.001$, $k > 50$ voxels (Additional file 4).

Predictors of cognitive decline

Regression analyses between the slope of cognitive decline and baseline measures showed that a high self-reported $global_R$ ($r = -0.59$, $p = 0.007$) or memory ($r = -0.52$, $p = 0.02$) SCD at baseline correlated with a higher global cognitive decline only in the SCD-community group. No baseline measures predicted the evolution of cognitive performances in the SCD-clinic group (Additional file 5).

Discussion

The type of recruitment of SCD patients might have a significant impact on the characteristics, aetiology, and risk of Alzheimer's clinical syndrome of the recruited SCD sample. Yet, the characteristics specifically associated with help-seeking behaviour in SCD have only been assessed in a few studies [25, 72–76], and most of these studies were not restricted to elders with formally assessed normal cognitive performances, few of them included the role of the informant or neuroimaging biomarkers and none included longitudinal data. This study thus aimed at identifying the characteristics of SCD individuals according to their type of recruitment (SCD-community versus SCD-clinic) in terms of cross-sectional and longitudinal self- and informant-reported SCD, subclinical anxiety and depression, cognitive performances, and atrophy progression over time, all known to increase the risk of being at a preclinical stage of Alzheimer's syndrome [1, 43, 49–54, 77, 78]. We also assessed the substrates of self-reported SCD within each group to identify the main respective drivers of their

Table 3 Description of the progression over time of SCD, cognitive, and psychoaffective measures within each group

Scores	*N*	SCD-community	*N*	SCD-clinic	ANCOVAs, *p* value
Follow-up duration, years (behavioural measures)	22	2.45 ± 0.67	25	2.36 ± 0.95	0.32
Follow-up duration, years (neuroimaging measures—MRI)	22	2.55 ± 0.67	24	2.28 ± 0.78	0.22
Self-reported SCD slopes					
$Global_R$	22	− 0.08 ± 0.27	20	0.08 ± 0.35	0.11
Attention-language (F1)	22	0.009 ± 0.06	20	0.02 ± 0.11	0.60
Memory-orientation (F2)	22	− 0.03 ± 0.09	20	0.004 ± 0.12	0.28
Praxis-domestic activities (F3)	22	− 0.009 ± 0.07	20	0.04 ± 0.09[#]	*0.04*
Informant-reported SCD slopes					
$Global_R$	15	0.06 ± 0.46	16	0.07 ± 0.65	0.98
Attention-language (F1)	15	− 0.02 ± 0.13	16	0.01 ± 0.2	0.65
Memory-orientation (F2)	15	0.02 ± 0.12	16	− 0.007 ± 0.12	0.61
Praxis-domestic activities (F3)	15	0.03 ± 0.15	16	0.02 ± 0.1	0.94
Slope of cognitive change					
DRS	22	− 0.02 ± 0.14	25	− 0.03 ± 0.11	0.74
ESR	22	0.0005 ± 0.03	24	− 0.02 ± 0.09	0.27
Slope of psychoaffective changes					
STAI-B	22	− 0.04 ± 0.21	25	0.05 ± 0.22	0.16
MADRS	22	0.09 ± 0.20	23	0.08 ± 0.26	0.92

The values indicate the mean ± SD of the slope of evolution between baseline and follow-up. When ANCOVAs correcting for age and education reached significance, values are indicated in italics ($p < 0.05$)

Abbreviations: *ANCOVAs* analyses of covariance correcting for age and education, *CDS* Cognitive Difficulties Scale, *DRS* Mattis Dementia Rating Scale, *ESR* Encoding, Storage and Recuperation, *F1* factor 1 attention-language SCD, *F2* factor 2 memory-orientation SCD, *F3* factor 3 praxis-domestic activities SCD, *HC* healthy control, *MADRS* Montgomery-Asberg Depression Rating Scale, *MRI* magnetic resonance imaging, *N* sample size, *SCD* subjective cognitive decline, *SD* standardized deviation, *STAI-B* Spielberger State-Anxiety Inventory Trait

[#]The slope is significantly different from zero ($p < 0.05$)

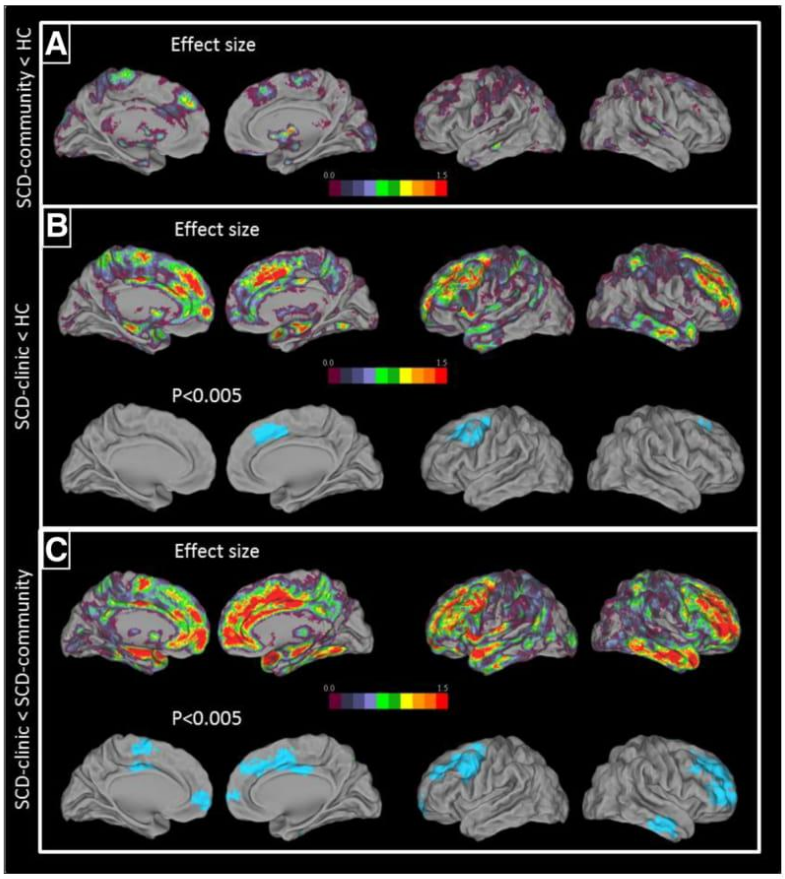

Fig. 4 Results of the between-group comparisons of brain maps of atrophy progression over time. Voxelwise comparisons showed the regions of significantly higher atrophy progression over time in SCD-community as compared to healthy control (HC) (**a**) and in SCD-clinic as compared to HC (**b**) and to SCD-community (**c**). The results are displayed as *T* value maps thresholded at uncorrected $p < 0.005$, $k > 250$ voxels and as effect size maps. SCD, subjective cognitive decline

SCD which could include risk factor of Alzheimer's clinical syndrome [25] or psychological distress [39].

Common points between the SCD groups

The two SCD groups presented similar characteristics, although the recruitment setting differs. Thus, at a comparable level of self-reported $global_R$ SCD, both SCD groups showed a higher level of subclinical anxiety and a higher level of informant-reported $global_R$ SCD but similar cognitive performances compared to controls. Hence, in both SCD groups, the self-reported $global_R$ SCD correlated to the three factors—suggesting that they are not driven by the subjective decline in the distinct cognitive domain—but surprisingly not to any objective measure of cognition. This highlights the relevance of the self- and informant-reported SCD, which might be sensitive to subtle cognitive changes not yet detectable using objective measures [46, 49, 50]. No significant change in cognition was found in any group, which might reflect the fact that the follow-up period (2.4 ± 0.8 years) was too short to capture subtle cognitive decline.

Surprisingly, our findings also showed no difference between the groups in term of amyloid status or SUVr uptake values. In contrast to previous studies, the self-reported SCD was not associated with the presence of amyloid deposition in cognitively unimpaired elders recruited from the community [18, 20, 21, 23, 25] or in SCD-clinic patients [22, 25]. However, this effect seems subtle and might depend on the sample and the measurement used [21, 22], as other studies have reported negative results like ours [79, 80] compared with controls, or found an association only in APOE ε4 carriers [81, 82]. Interestingly, when merging our two SCD groups together, a significant between-group difference was found with higher amyloid SUVr in the SCD compared to the controls ($p = 0.044$, Additional file 6). The lack of difference between the SCD groups might also be due to the fact that the SCD-clinic tended to be younger (about 68.3 years old in SCD-clinic against 71.70 in SCD-community and 72.25 in controls), and the proportion of APOE ε4 carriers was relatively small in the SCD-clinic (15%) compared to the SCD-community (26%) or the controls (18%); when the analyses were

corrected for age, level of education, and APOE ε4 status, a general trend appeared in the between-group comparison of amyloid SUVr ($p = 0.096$, Additional file 6).

Specificities of both SCD groups

Specificities of the SCD-community

While the SCD-community share similarities with the SCD-clinic, our findings also highlight the differences. Thus, the SCD-community showed a higher subclinical anxiety than older adults without subjective cognitive decline. Moreover, their anxiety score correlated with their level of self-reported $global_R$ SCD which itself predicted their subsequent cognitive decline. This suggests that anxiety contributes to the level of SCD only in the SCD-community group, while psychoaffective factors do not influence SCD in the SCD-clinic group. Neuroimaging correlates confirmed this view in showing a link between SCD and frontal grey matter volume and glucose metabolism in SCD-community, while it rather involved the temporal and parietal brain regions sensitive to AD [19, 57, 83] in the SCD-clinic group. As suggested in previous studies [39, 84–86], the subjective cognitive decline of SCD-community thus seems to be more strongly related to the psychoaffective factors.

SCD-clinic seems to be a frailer population than SCD-community

By contrast, a few evidence suggest that SCD-clinic might be a frailer population than SCD-community. Thus, cognitively unimpaired older adults with subjective cognitive decline who referred to a memory clinic were characterized by higher informant-reported $global_R$ SCD, higher depressive symptoms, and greater subsequent atrophy progression over time than those with the same level of SCD but who did not refer to a memory clinic. Moreover, SCD-clinic tended to show a more generalized profile of SCD. Indeed, while their level of self-reported SCD was similar to SCD-community, they showed a significant increase in praxis-domestic activities SCD over the follow-up period.

In a previous study [25], we showed that subclinical depression and (notably hippocampal) atrophy were specifically associated with medical help-seeking, suggesting that those who consult are at a higher risk of developing Alzheimer's clinical syndrome, as indicated in another study which compared the rates of incident dementia [37]. In the present study, our findings reinforced this view by showing greater atrophy progression over time. The atrophy progression over time was significantly higher in the frontal cortex and tended to be higher in the temporal lobe and particularly in the hippocampus (see effect size on Fig. 4). It might thus reflect accelerated brain ageing related to psychoaffective factors, as the frontal areas are known to be sensitive to ageing [84–86] and commonly associated with subclinical anxiety [87] and depression [88]—themselves associated with increased risk for cognitive decline or dementia [27, 33]. These findings might also reflect, to a lesser extent, increased risk for dementia, as greater hippocampal atrophy progression over time is known to be associated with subsequent cognitive decline [89] and dementia [90]. Similarly, the fact that they showed greater praxis-domestic activities SCD over time might also represent an additional evidence for this statement. Thus, as multi-domain amnestic MCI are known to be more at risk of AD than single-domain MCI [91], the generalization of SCD in the SCD-clinic group might alike indicate that they are in a more advanced stage of SCD and possibly represent a frailer population than SCD-community, with an increased risk of cognitive decline, and potentially Alzheimer's clinical syndrome. These are yet only indirect evidences and longer-term follow-up in larger samples are needed to confirm this hypothesis.

SCD-community and SCD-clinic: a continuum or distinct entities?

One possible interpretation of our findings is that SCD-community represents an intermediate stage in a continuum leading to SCD-clinic. Indeed, they showed intermediate levels of informant-reported $global_R$ SCD, and their level of subclinical depression tended to increase at follow-up ($p = 0.06$), reaching the level of depression of the SCD-clinic ($p = 0.25$, data not shown). While their neural correlates for self-reported $global_R$ SCD were different from SCD-clinic for some brain regions, there were also common functional brain correlates (in the insula and frontal cortex) between both SCD groups.

The intermediate level of informant-reported $global_R$ SCD in the SCD-community highlights the sensitivity of this measure to capture subtle differences between the SCD groups that refer or not to a memory clinic. Previous studies have shown that the informant-reported SCD can be associated with longitudinal cognitive decline [49] and a higher risk of subsequent conversion to MCI or AD dementia [50, 92]; suggesting that both groups show risk factors for Alzheimer's clinical syndrome. Moreover, this is consistent with the fact that the self-reported SCD measure predicted the level of subsequent cognitive decline in the SCD-community, adding to the risk.

As regards to psychoaffective factors, a higher level of subclinical anxiety compared to controls characterized both SCD groups, while the level of subclinical depression was higher only in the SCD-clinic group at baseline and increased from baseline to follow-up in the SCD-community. As a whole, our findings suggest that referring to a memory clinic is associated with subclinical depression rather than with the level of subclinical

anxiety or self-reported SCD. Interestingly, both psychoaffective factors (depressive symptoms and subclinical anxiety) are frequently associated with early cognitive deficits [53, 93, 94] or subsequent dementia [51, 54] and could be a prodromal sign of Alzheimer's clinical syndrome [55]. However, the causal link between self- and informant-reported SCD, psychoaffective factors, and cognitive or brain changes is unclear. SCD and frontal atrophy might lead to an increase in subclinical anxiety and depression, themselves associated with an increase in informant-reported SCD, leading to memory consultation. Alternatively, psychoaffective factors might lead to, or exacerbate, brain and cognitive decline underlying self- and informant-reported SCD and stimulating memory consultation. Further studies are needed to better understand the sequence of events and causal relationships between these different factors. Specifically, a better understanding of the role of psychoaffective factors is important for the development of non-pharmacological interventions targeting emotional regulation processes [95].

Altogether, our results suggest that the two SCD groups have specificities but may represent in fact different stages of progressive cognitive decline that may lead to Alzheimer's clinical syndrome. As for early and late MCI [28, 96], SCD-community and SCD-clinic might represent two stages of SCD in a continuum that would lead, for part of them, to Alzheimer's clinical syndrome. However, we cannot exclude the alternative hypothesis that, instead of a continuum, the two groups represent distinct selections of individuals with SCD where underlying neuropsychiatric/non-AD aetiologies versus AD pathology are differently represented.

Strengths, limitations, and perspectives

The major strengths of this study are its multimodal dimension and the combination of cross-sectional and longitudinal setup. Indeed, the availability of standardized assessment of a broad range of factors potentially related to SCD, including various biomarkers, provides novel insights into the integrated characterization of SCD in the context of preclinical AD/Alzheimer's syndrome. However, although based on the recommendations of Jessen et al., 2014, which list the specific features that increase the likelihood of the presence of preclinical AD/Alzheimer's syndrome in individuals with SCD [1, 45] and a previous study [56], the threshold used to separate SCD-community from controls was somewhat arbitrary. In addition, all the questionnaires were self-completed, and the sample sizes and follow-up time were relatively limited, resulting in a limited statistical power. Consequently, the statistics were not corrected for multiple comparisons which increase the risk for false positive. Therefore, our results should be interpreted with caution and validated in future studies with larger group sizes and longer follow-up time. This would also allow the assessment of the sequential and causal relationships between the different factors to understand the role of psychoaffective factors and informant-reported SCD, but also to confirm that SCD-community and SCD-clinic are two stages of a continuum in preclinical Alzheimer's syndrome. Nowadays, characterizing and discriminating preclinical Alzheimer's syndrome from the 'worried well' seems especially important for the early detection of persons in the preclinical stage of dementia, the prevention, and the development of efficient therapies. Given the heterogeneity of the aetiology and presentation of SCD [1, 25, 45, 46], a better understanding of these two populations might help us to identify the potential targets for pharmacological or non-pharmacological interventions.

Conclusions

As a whole, our results point to the SCD-clinic as a frailer population showing faster atrophy over time, compared to HC and SCD-community, which might reflect an increased risk for later cognitive decline. Depression symptoms were also higher in the SCD-clinic, but they increased over time in the SCD-community, suggesting a continuity between SCD groups. Alternatively, they might reflect distinct populations with different proportion of possible aetiologies (AD pathology, neuropsychiatric aetiologies, etc.). From a clinical standpoint, SCD patients might thus benefit from a closer clinical follow-up; from a research standpoint, this population could enrich interventional clinical trials on SCD with more participants at risk of AD/dementia. Finally, our findings highlight the relevance of psychoaffective factors, including both subclinical anxiety and depression, at this stage. Rather than confounding factors of SCD, psychoaffective factors might represent early symptoms of Alzheimer's clinical syndrome, or even the expression of a pathological process associated with psychological distress and related to subsequent cognitive decline in the SCD-community. This, along with the fact that they are associated with increased risk of dementia, highlights the relevance of treating these symptoms in the elderly. Further studies are yet needed to better understand their causal and/or consequent role within the different SCD stages.

Additional files

Additional file 1: Population sizes at the various imaging examination time points: cross-sectional and longitudinal neuroimaging assessments. Abbreviations: HC healthy control, SCD subjective cognitive decline, *N* sample size, MRI magnetic resonance imaging, PET positron emission tomography, FDG 18F-fluorodeoxyglucose. (DOCX 46 kb)

Additional file 2: Description of the methodology of the longitudinal neuroimaging data processing. (DOCX 16 kb)

Additional file 3: Glass brain of the voxelwise correlations between self-reported SCD and neuroimaging within each SCD group. The correlations between self-reported SCD measures (1, $Global_R$ SCD; 2, Attention/Language SCD; 3, Memory/Orientation SCD; 4, Praxis/Domestic Activities SCD) and grey matter volume (MRI), glucose metabolism (FDG-PET), or amyloid deposition (Florbetapir-PET) are presented within the SCD-community (A) and the SCD-clinic (B) groups. The results are displayed at uncorrected $p < 0.005$, $k > 250$ voxels and $p < 0.001$, $k > 50$ voxels for all analyses. FDG 18F-fluorodeoxyglucose, PET positron emission tomography, SCD subjective cognitive decline. (DOCX 538 kb)

Additional file 4: Glass brains of the between-group comparisons of brain maps of atrophy progression over time. Voxelwise comparisons show the regions of significantly higher atrophy progression over time in SCD-community as compared to healthy control (HC) (A), and in SCD-clinic as compared to HC (B) and to SCD-community (C). The results are displayed as *T* value maps thresholded at uncorrected $p < 0.005$, $k > 250$ voxels and $p < 0.001$, $k > 50$ voxels. SCD Subjective cognitive decline. (DOCX 267 kb)

Additional file 5: Results of the general linear model assessing the links between baseline variables and cognitive decline slopes. The values indicate the results of the general linear model assessing the links between baseline self- and informant-reported SCD factors or psychoaffective measures and the slope of cognitive decline, corrected for age and education. Values indicated in bold correspond to $p < 0.05$. Abbreviations: DRS Mattis Dementia Rating Scale, ESR Encoding, Storage and Recuperation, *F1* score of cognitive difficulties scale factor 1 attention-language SCD, *F2* score of cognitive difficulties scale factor 2 memory-orientation SCD, *F3* score of cognitive difficulties scale factor 3 praxis-domestic activities SCD, MADRS Montgomery-Asberg Depression Rating Scale, SCD subjective cognitive decline, STAI-B Spielberger State-Anxiety Inventory Trait. (DOCX 21 kb)

Additional file 6: Group comparisons on amyloid SUVr. Graphs indicate mean values and 95% confidence intervals. A: three-group comparisons on the amyloid SUVr and post-hoc analyses performed with the Newman-Keuls test; B: two-group comparisons on the amyloid SUVr, when SCD groups were merged. ANCOVA analysis of variance corrected, APOE apolipoprotein E, HC healthy control, SCD subjective cognitive decline, SUVr standardized uptake value ratio. (DOCX 77 kb)

Abbreviations

AD: Alzheimer's disease; ANCOVA: Analysis of covariance; ANOVA: Analysis of variance; APOE ε4: Apolipoprotein E allele 4; Aβ: Amyloid deposition; CDS: Cognitive Difficulties Scale; DRS: Mattis Dementia Rating Scale; ESR: Encoding, Storage and Recuperation; F1: Factor 1 of CDS corresponding to attention-language SCD; F2: Factor 2 of CDS corresponding to memory-orientation SCD; F3: Factor 3 of CDS corresponding to praxis-domestic activities SCD; FDG: 18F-fluorodeoxyglucose; FWHM: Full-width half-maximum; HC: Healthy controls; IMAP+: *Imagerie Multimodale de la maladie d'Alzheimer Précoce*; MADRS: Montgomery-Asberg Depression Rating Scale; MCI: Mild cognitive impairment; MMSE: Mini-Mental State Examination; MNI: Montreal Neurological Institute; MRI: Magnetic resonance imaging; *N*: Size; NS: Not significant; PET: Positron emission tomography; Pos: Positive; SCD: Subjective cognitive decline; SCD-clinic: Subjective cognitive decline recruited from a memory clinic; SCD-community: Subjective cognitive decline recruited from volunteers from the community; SCD-I: Subjective Cognitive Decline Initiative; SD: Standard deviation; SPM12: Statistical Parametric Mapping version 12; STAI-B: Spielberger State-Trait Anxiety Inventory-B; SUVr: Standardized uptake value ratio

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Authors' contributions

EK and IM performed the analyses, contributed to the data interpretation, and wrote the first draft of the manuscript. AP, BL, CT, and RLJ contributed to the design of the study, data acquisition and interpretation, and manuscript revision. AB and SS contributed to the neuroimaging data processing, interpretation, and manuscript revision. VDLS is the main MD investigator, he supervised the recruitment of the patients, and participated in the study design and data interpretation. BD, DV, and GP participated in study design, data interpretation, and/or manuscript revision. GC is the principal investigator of IMAP and she supervised the study, the interpretation of data, and the writing of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due to local privacy regulations but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The IMAP study was approved by the regional ethics committee (Comité de Protection des Personnes Nord-Ouest III) and registered with ClinicalTrials.gov (number NCT01638949). All participants gave written informed consent to the study prior to the investigation.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Additional material

Additional files 1: Population sizes at the various imaging examination time points: cross-sectional and longitudinal neuroimaging assessments.

N	HC	SCD-community	SCD-clinic
Cross-sectional neuroimaging assessment			
MRI	27	24	27
FDG-PET	26	24	27
Florbetapir-PET	25	22	27
Longitudinal neuroimaging assessment			
Atrophy rate maps	25	24	24

Abbreviations: *HC* healthy control, *SCD* subjective cognitive decline, *N* sample size, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *FDG* 18F-fluorodeoxyglucose.

Additional files 2: Description of the methodology of the longitudinal neuroimaging data processing.

For each participant, a pairwise longitudinal registration was computed between the baseline and follow-up anatomical MRI resulting in a mid-point average anatomical MRI image (anatomical MRI average) and the Jacobians. The Jacobian rates were computed by differences between the Jacobian determinants, divided by the time interval between the two scans, and reflect a rate of change between baseline and follow-up MRI scans. Values of Jacobian rates less than zero indicate contraction (over time), whereas values greater than zero indicate expansion [1]. The anatomical MRI average was segmented into grey matter, white matter and cerebrospinal fluid. The resulting grey matter segment (reflecting an average grey matter density probability map) was then (i) multiplied by the Jacobian rates resulting in the grey matter change map (reflecting a map of grey matter probability changes between baseline and follow-up); and (ii) normalized to the DARTEL template (Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra; the Template was obtained from healthy volunteers and patients from IMAP+); the resulting deformation field was then applied to the grey matter change map. The normalized grey matter change map, smoothed with an 8mm full-width at half-maximum isotropic Gaussian kernel, was used as a reflect of atrophy propagation progression (i.e. atrophy rate maps) over the follow-up period for each subject [2].

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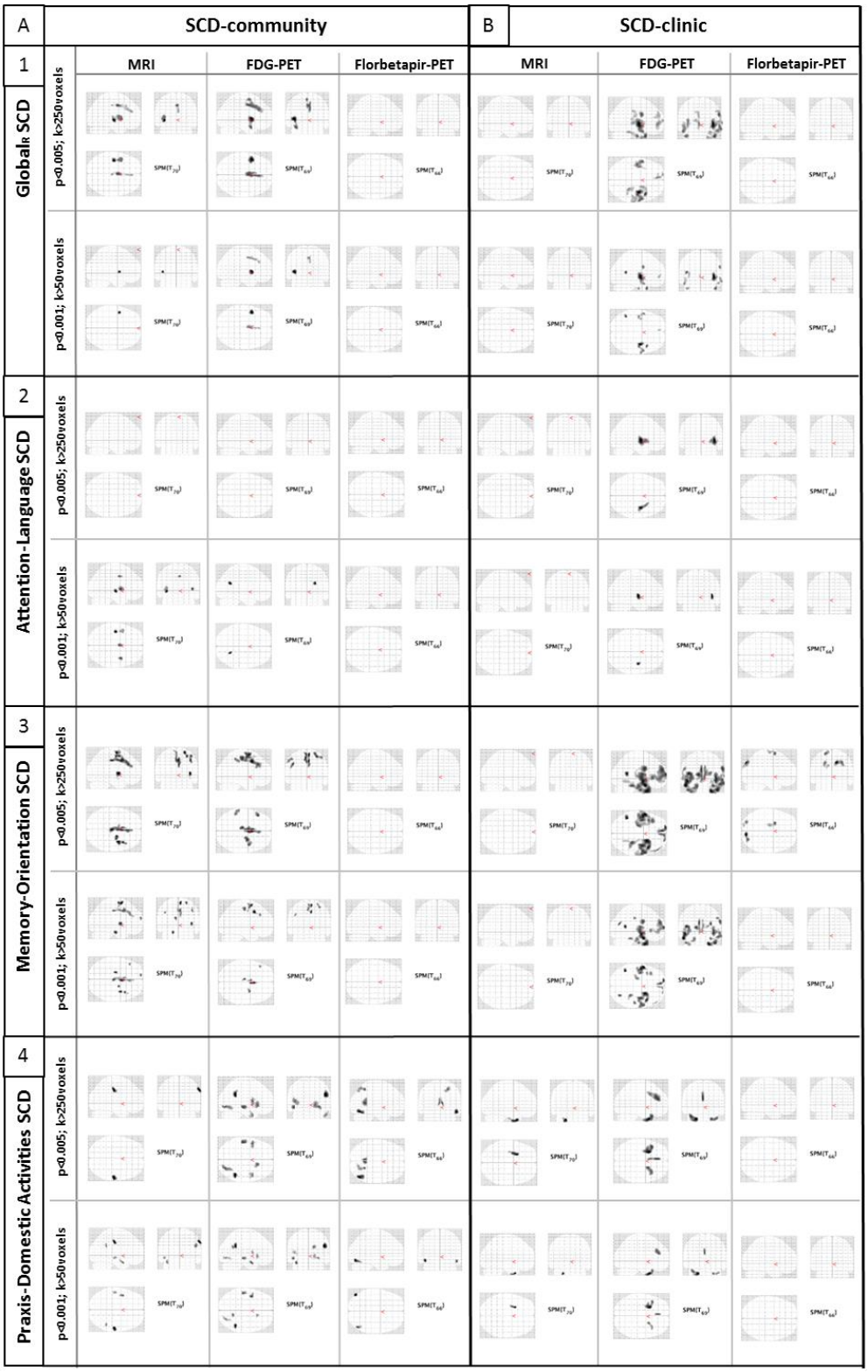
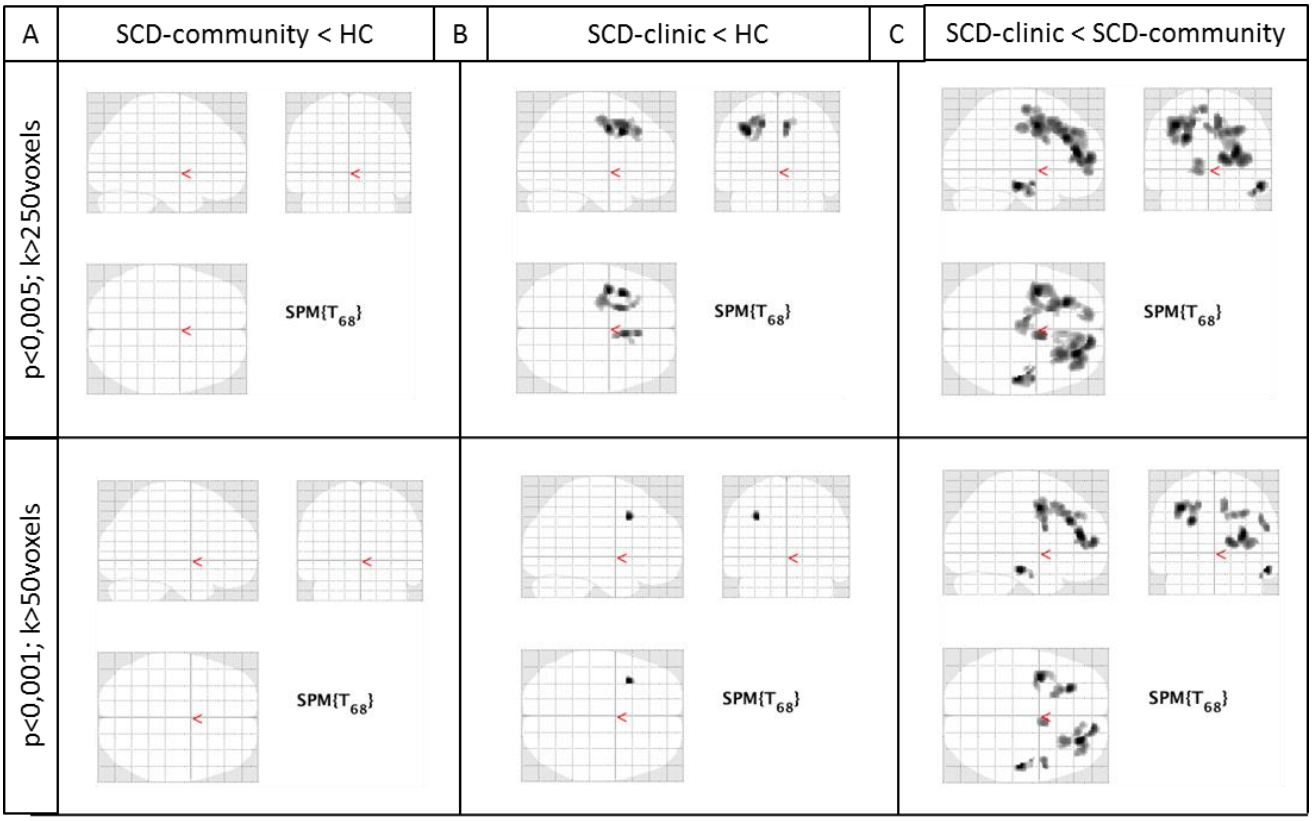


Additional file 3: Glass brain of the voxelwise correlations between self-reported SCD and neuroimaging within each SCD group. The correlations between self-reported SCD measures (1, Global$_R$ SCD; 2, Attention/Language SCD; 3, Memory/Orientation SCD; 4, Praxis/Domestic Activities SCD) and grey matter volume (MRI), glucose metabolism (FDG-PET), or amyloid deposition (Florbetapir-PET) are presented within the SCD-community (A) and the SCD-clinic (B) groups. The results are displayed at uncorrected $p < 0.005$, $k > 250$ voxels and $p < 0.001$, $k > 50$ voxels for all analyses. *FDG* 18F-fluorodeoxyglucose, *PET* positron emission tomography, *SCD* subjective cognitive decline.

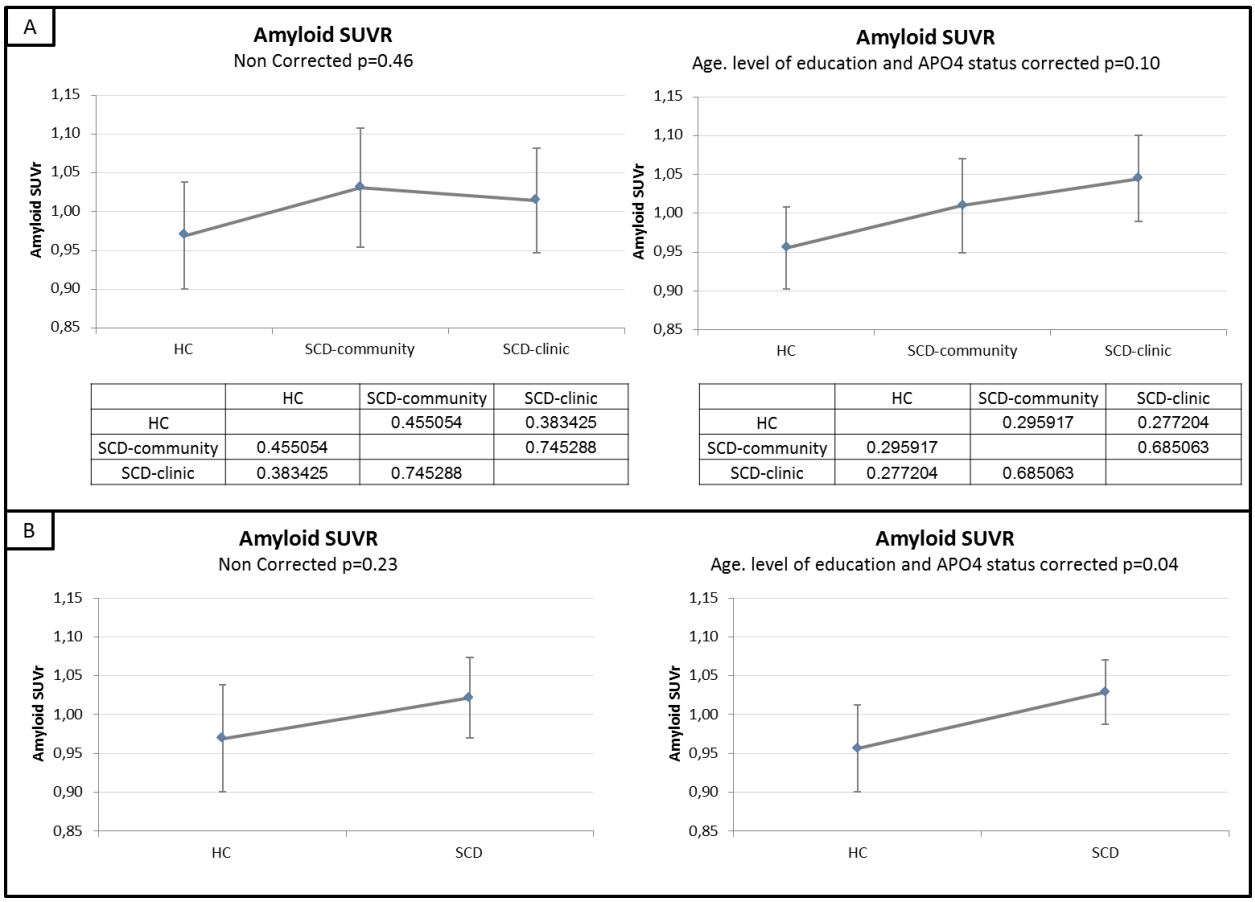


Additional file 4: Glass brains of the between-group comparisons of brain maps of atrophy progression over time. Voxelwise comparisons show the regions of significantly higher atrophy progression over time in SCD-community as compared to healthy control (HC) (A), and in SCD-clinic as compared to HC (B) and to SCD-community (C). The results are displayed as *T* value maps thresholded at uncorrected $p < 0.005$, $k > 250$ voxels and $p < 0.001$, $k > 50$ voxels. *SCD* Subjective cognitive decline.

Additional file 5: Results of the general linear model assessing the links between baseline variables and cognitive decline slopes.

	Slope of decline DRS		Slope of decline ESR	
	r	p	r	p
SCD-community				
Baseline self-reported SCD				
$Global_R$ SCD	**-0,59**	**0.007**	-0.13	0.57
Attention-language SCD (F1)	-0.37	0.11	-0.34	0.15
Memory-Orientation SCD (F2)	**-0.52**	**0.02**	0.02	0.94
Praxis-Domestic Activities SCD (F3)	-0.22	0.35	0.18	0.46
Baseline informant-reported SCD				
$Global_R$ SCD	-0.21	0.57	0.28	0.44
Attention-language SCD (F1)	-0.14	0.69	0.40	0.26
Memory-Orientation SCD (F2)	-0.05	0.89	0.09	0.81
Praxis-Domestic Activities SCD (F3)	0.31	0.39	0.43	0.22
Baseline psychoaffective measures				
STAI-B	-0.36	0.12	0.11	0.65
MADRS	0.15	0.52	0.20	0.40
SCD-clinic				
Baseline self-reported SCD				
$Global_R$ SCD	-0.07	0.76	0.15	0.52
Attention-language SCD (F1)	-0.05	0.84	0.19	0.39
Memory-Orientation SCD (F2)	-0.02	0.93	0.04	0.85
Praxis-Domestic Activities SCD (F3)	-0.08	0.70	0.14	0.53
Baseline informant-reported SCD				
$Global_R$ SCD	0.21	0.39	0.22	0.39
Attention-language SCD (F1)	0.17	0.48	0.25	0.16
Memory-Orientation SCD (F2)	0.24	0.32	0.10	0.71
Praxis-Domestic Activities SCD (F3)	-0.07	0.78	0.35	0.16
Baseline psychoaffective measures				
STAI-B	0.01	0.95	-0.27	0.23
MADRS	0.08	0.73	-0.15	0.52

The values indicate the results of the general linear model assessing the links between baseline self- and informant-reported SCD factors or psychoaffective measures and the slope of cognitive decline, corrected for age and education. Values indicated in bold correspond to $p < 0.05$. Abbreviations: *DRS* Mattis Dementia Rating Scale, *ESR* Encoding, Storage and Recuperation, *F1* score of cognitive difficulties scale factor 1 attention-language SCD, *F2* score of cognitive difficulties scale factor 2 memory-orientation SCD, *F3* score of cognitive difficulties scale factor 3 praxis-domestic activities SCD, *MADRS* Montgomery-Asberg Depression Rating Scale, *SCD* subjective cognitive decline, *STAI-B* Spielberger State-Anxiety Inventory Trait.



	HC	SCD-community	SCD-clinic
HC		0.455054	0.383425
SCD-community	0.455054		0.745288
SCD-clinic	0.383425	0.745288	

	HC	SCD-community	SCD-clinic
HC		0.295917	0.277204
SCD-community	0.295917		0.685063
SCD-clinic	0.277204	0.685063	

Additional file 6: Group comparisons on amyloid SUVr. Graphs indicate mean values and 95% confidence intervals. A: three-group comparisons on the amyloid SUVr and post-hoc analyses performed with the Newman-Keuls test; B: two-group comparisons on the amyloid SUVr, when SCD groups were merged. *ANCOVA* analysis of variance corrected, *APOE* apolipoprotein E, *HC* healthy control, *SCD* subjective cognitive decline, *SUVr* standardized uptake value ratio.

4. Discussion générale

4.1. Synthèse des résultats

L'objectif de cette thèse était de contribuer à caractériser les liens des symptômes psychoaffectifs (i.e. symptômes anxieux et dépressifs) avec la cognition de façon globale, et avec la neuroimagerie. Ces liens ont été évalués de façon multimodale au cours du vieillissement normal et chez des patients du continuum Alzheimer. Ils ont également été analysés chez des patients présentant des déficits cognitifs subjectifs en l'absence de déficit cognitif objectifs (i.e. SCD), de façon différentielle chez des personnes de la population générale et des personnes ayant consulté en centre mémoire, puisque le type de recrutement est une source d'hétérogénéité et un biais majeur dans les études actuelles sur cette population.

Les résultats recueillis au cours de ces trois travaux de thèse ont tout d'abord permis de mettre en évidence une diminution des symptômes anxieux avec l'âge uniquement chez les femmes, ainsi qu'une association entre une augmentation de ces symptômes anxieux et une diminution du volume de substance grise et du métabolisme du glucose dans le cerveau de cette même population. Les analyses longitudinales nous ont ensuite permis de montrer qu'un faible volume de substance grise était associé à une augmentation de l'anxiété au cours du temps, tandis que le lien inverse n'a pas été démontré. Nous avons également montré une diminution des symptômes dépressifs avec l'âge, sans liens avec la cognition et la neuroimagerie au cours du vieillissement normal. Dans le cadre de la démence de type Alzheimer, nous avons mis en évidence des symptômes dépressifs plus élevés chez les patients, mais pas de différence de symptômes anxieux. De même, ces symptômes dépressifs plus élevés sont associés à une meilleure mémoire et cognition globale, ainsi qu'à plus de métabolisme du glucose cérébral chez les patients, ce qui semble lié à une meilleure conscience des troubles cognitifs. Pour finir, les SCD recrutés dans les centres mémoire présentent plus d'atrophie de la substance grise avec le temps que les autres SCD et que les contrôles, ainsi que de symptômes dépressifs. Ces derniers sont associés à plus de dépôts amyloïdes dans ce même groupe, et leur plainte subjective est corrélée au métabolisme du glucose cérébral et à la plainte de leur informant. Quant aux SCD recrutés dans la

population générale, ils présentent plus de symptômes anxieux que les contrôles, mais autant que les SCD-clinique, et une augmentation de leur plainte est corrélée à une augmentation de ces symptômes anxieux et une diminution du métabolisme du glucose. Avec le temps, les symptômes dépressifs dans ce groupe semblent augmenter pour atteindre le niveau des SCD-clinique.

Dans cette discussion générale nous proposons une présentation de ces résultats indépendamment dans chaque groupe de participants, puis dans leur ensemble pour une interprétation intégrée, également schématisée dans la figure 15.

4.2. Les Facteurs psychoaffectifs

4.2.1. Au cours du vieillissement normal

Dans notre première étude, nous avons pu observer que les symptômes anxieux augmentent avec l'âge, et ce uniquement chez les femmes, tandis que les symptômes dépressifs diminuent avec l'âge, et ne sont pas corrélés à la cognition et la neuroimagerie. Bien que des études aient montré que les symptômes anxieux sont liés à de moins bonnes performances cognitives (Beaudreau & O'Hara, 2009; Booth et al., 2006; Ganguli et al., 2009; Köhler et al., 2010; Wilson et al., 2011; Yochim et al., 2013; Zhang et al., 2020), ces études se focalisent sur les personnes âgées, et ne couvrent pas tout le spectre d'âge. Au sujet de la neuroimagerie, les études sont conflictuelles et montrent à la fois des associations positives et négatives avec la substance grise, ce qui pourrait refléter des associations régions-spécifiques qui ne seraient pas visibles dans des analyses globales, ou encore des associations non-linéaires avec l'âge qui seraient différentes selon la tranche d'âge considérée. La littérature montre une diminution du métabolisme du glucose (Donovan et al., 2015; Krell-Roesch et al., 2016), ainsi qu'une augmentation de la pathologie amyloïde (Krell-Roesch et al., 2018), associée aux symptômes dépressifs légers, mais qui n'ont été évalués que chez des sujets âgés. Cette association pourrait alors ne survenir qu'avec l'avancée en âge.

De façon intéressante, les symptômes anxieux sont associés à un plus petit volume de substance grise uniquement chez les femmes, comme montré dans une étude sur des seniors (Yamasue et al., 2008), mais aussi à un plus bas métabolisme du glucose dans cette même population. Bien que la diminution de substance grise et du métabolisme du glucose cérébral soient exacerbées dans la MA et ne concernent pas tout à fait les mêmes régions cérébrales (Apostolova et al., 2007; Chételat et al., 2008; La Joie et al., 2012; Nestor et al., 2003; Pini et al., 2016), ces modifications ne lui sont pas spécifiques, puisqu'elles sont également associées au vieillissement normal (Chételat et al., 2013; Fjell et al., 2009, 2014; Hsieh et al., 2012; Kakimoto et al., 2016; Kalpouzos et al., 2009; Raz et al., 2005; Yoshizawa et al., 2014). Cependant, ces résultats pourraient, au moins partiellement, expliquer que les personnes âgées présentant des symptômes anxieux, soient plus à risque de démence (Petkus et al., 2016). De plus, des analyses longitudinales nous ont permis d'établir que c'est une substance grise basse à baseline qui prédit une augmentation de l'anxiété, qui serait donc une manifestation ou une conséquence de cette vulnérabilité cérébrale.

On peut donc voir que les symptômes anxieux ne sont pas spécifiquement liés à la maladie d'Alzheimer puisqu'ils ne sont pas associés à l'amyloïde, mais semblent être une manifestation d'un vieillissement cérébral plus sévère, et donc d'une vulnérabilité accrue aux maladies neurodégénératives liées à l'âge telles que les démences, et ce principalement chez les femmes.

4.2.2. Dans le continuum Alzheimer

Dans le cadre de notre deuxième étude, nous avons voulu décrire les liens cognitifs et cérébraux des symptômes anxieux et dépressifs dans le cadre de la maladie d'Alzheimer. Dans le groupe du continuum Alzheimer avec MCI ou MA, c'est-à-dire qui présente à la fois des déficits cognitifs et une charge amyloïde cérébrale positive, on observe plus de symptômes dépressifs que chez les sujets sains, mais pas de différences en terme d'anxiété. Ce résultat semble en accord avec la littérature, qui montre une fréquence plus importante de symptômes dépressifs chez des patients MCI et MA clinique

comparés à des contrôles, tandis que les symptômes anxieux ne diffèrent qu'entre les patients avec démence moyenne et sévère (Fernández-Martínez et al., 2010). Les symptômes anxieux ne sont d'ailleurs associés ni à la cognition, ni à la neuroimagerie dans notre étude, ce qui est contraire aux quelques études précédentes sur le sujet, qui montraient que ces symptômes seraient associés à moins de substance grise (Hayata et al., 2015; Tagai et al., 2014) et de métabolisme du glucose cérébral (Hashimoto et al., 2006) dans cette population. Cependant, ces études ont sélectionné leurs participants selon le syndrome clinique et non selon les critères biologiques, et se sont focalisées sur l'anxiété dite « trait » tandis que nous nous sommes intéressés à l'anxiété « état », qui n'a pas été évaluée dans cette population. Ces deux types d'anxiété pourraient donc avoir des substrats différents dans la MA.

Les symptômes dépressifs sont associés à une meilleure cognition, une meilleure mémoire et un plus haut métabolisme du glucose cérébral, mais pas à la charge amyloïde. Ces résultats concordent avec la littérature qui, bien que conflictuelle, ne montre principalement pas de liens entre les symptômes dépressifs et l'amyloïde (Bensamoun et al., 2016; Chung et al., 2015; Mori et al., 2014). Les résultats cognitifs semblent, quant à eux, contraires à la littérature, qui montre que les symptômes dépressifs seraient plutôt associés à un déclin cognitif chez des patients MCI (Chan et al., 2011; Poulin et al., 2017). Cependant, une récente étude a également montré que des patients MCI présentant moins de symptômes dépressifs à baseline avaient un déclin cognitif plus marqué un an et demi plus tard (Cerbone et al., 2020). Les auteurs ont alors émis l'hypothèse que la conscience de ses propres troubles cognitifs pourrait être associée à cet affect négatif, tandis que les patients qui ne présentent pas de symptômes dépressifs pourraient ne pas apprécier l'ampleur de leur déficit cognitif. Dans notre deuxième étude, nous avons donc évalué cette hypothèse qui semblait concorder avec nos résultats, et nous avons pu montrer que des symptômes dépressifs élevés étaient effectivement associés à une meilleure conscience des troubles.

Notre étude montre donc que les symptômes dépressifs ne sont pas liés directement à la pathologie Alzheimer, puisqu'ils ne sont pas corrélés à la charge amyloïde, mais ils sont plutôt associés à une moins grande sévérité des atteintes cognitives et fonctionnelles résultants de cette pathologie. En effet, ils sont associés à une meilleure conscience de ses troubles et à plus de métabolisme du glucose cérébral dans notre étude, faisant le lien entre les études précédentes montrant que l'anosognosie est à la fois associée à plus de symptômes dépressifs chez les patients MA (Kashiwa et al., 2005), et à plus de métabolisme du glucose chez les MCI (Nobili et al., 2010; Perrotin et al., 2015; Vannini et al., 2017). On pourrait donc émettre l'hypothèse que lorsque la démence est moins sévère, les atteintes fonctionnelles sont moindres et la cognition est meilleure, résultant en une meilleure conscience de ses propres troubles et donc une manifestation de symptômes dépressifs.

4.2.3. Le SCD, une ou plusieurs populations ?

Dans le cadre de notre troisième étude, nous avons pu mettre en évidence des points communs, mais aussi des différences entre les deux groupes de SCD, séparés selon leur type de recrutement. En effet, les deux groupes présentent, en plus d'un niveau de plainte subjective équivalente, une plainte de l'informant et un niveau d'anxiété supérieurs aux contrôles, bien que leurs mesures objectives de cognition soient similaires. De plus, la plainte subjective est associée à un plus bas métabolisme du glucose dans les deux groupes, bien que les régions associées soient différentes. En effet, chez les SCD-communauté, une plainte subjective plus élevé est associé à une anxiété et un déclin cognitif, ainsi qu'à une diminution du volume de substance grise et de métabolisme du glucose cérébral dans des régions frontales. Ces régions sont couramment associées aux facteurs psychoaffectifs (Baur et al., 2012; Besteher et al., 2017; Carlson et al., 2015; Spampinato et al., 2009; Webb et al., 2014), ce qui pourrait indiquer que, comme suggéré dans des études précédentes (Comijs et al., 2002; Fjell & Walhovd, 2010; Kalpouzos et al., 2009), le déclin cognitif subjectif serait plus fortement associé aux facteurs psychoaffectifs qu'à une démence préclinique dans cette population.

Chez les SCD-cliniques, la plainte n'est pas corrélée aux facteurs psychoaffectifs, mais est associée à une diminution de métabolisme du glucose cérébral dans des régions temporales et pariétales, qui sont des régions sensibles à la MA (Chételat et al., 2008; La Joie et al., 2012; Minoshima et al., 1997; Nestor et al., 2003; Pini et al., 2016; Salmon et al., 2000). Ce groupe présente également une atrophie de la substance grise cérébrale plus importante avec le temps, ainsi que plus de symptômes dépressifs que les SCD-communauté et les contrôles – symptômes dépressifs que l'on sait par ailleurs être associés à un risque plus élevé de déclin cognitif et de démence (Barnes et al., 2006; Chan et al., 2011; Donovan et al., 2014; Palmer et al., 2007). La littérature est conflictuelle quant au lien de la plainte subjective avec l'amyloïde, puisque certaines études montrent une charge amyloïde plus importante chez des SCD-communauté et chez des SCD-clinique (Amariglio et al., 2015; Perrotin et al., 2017; Snitz et al., 2015), tandis que d'autres n'en montrent pas (Buckley et al., 2013; Hollands et al., 2015). Bien que dans notre étude nous n'ayons pas trouvé de différence de charge amyloïde entre les deux groupes de SCD et avec les contrôles, nous avons mis en évidence dans notre deuxième étude que des symptômes dépressifs élevés sont associés à une charge amyloïde plus élevée dans le groupe de SCD-clinique, sans liens avec la cognition ou la plainte subjective. La plainte subjective et les symptômes dépressifs pourraient donc être une manifestation comportementale d'un changement pathologique sous-jacent dans le groupe de SCD-clinique. Cependant, nos études ne montrent pas de liens de causalité, c'est pourquoi ces symptômes pourraient également être un facteur de risque d'atrophie et d'agrégation de protéine Aβ, ou même être causés par un facteur commun extérieur encore inconnu.

De façon intéressante, ces deux groupes présentent des similarités et des différences, et bien que le groupe de SCD-clinique soit plus à risque, les SCD-communauté semblent être un stade intermédiaire dans ce continuum. En effet, ces derniers ont un niveau intermédiaire de plainte de l'informant, et les symptômes dépressifs tendent à augmenter avec le temps dans ce groupe, jusqu'au niveau des symptômes dépressifs des SCD-clinique. De même, ces deux groupes montrent des modifications cérébrales associées à la plainte dans des régions similaires telles que l'insula et des régions frontales, bien qu'elles s'étendent à des régions temporales chez les SCD-clinique. Il semblerait également y avoir

une transition en termes psychoaffectifs entre ces groupes. En effet, les symptômes anxieux, bien que comparables dans les deux groupes de SCD, ne sont associés à la plainte que chez les sujets SCD-communauté. Ensuite, l'apparition des symptômes dépressifs dans le groupe de SCD-clinique, est associée à la pathologie amyloïde, et semble donc être un symptôme de MA préclinique. Dans l'ensemble, nos résultats suggèrent que les deux groupes de SCD peuvent représenter des stades de déclin cognitif progressif, avec des manifestations psychoaffectives spécifiques, qui peuvent conduire au syndrome clinique d'Alzheimer.

4.3. Schéma général

L'ensemble de ce travail de thèse a montré que les symptômes psychoaffectifs semblent avoir un rôle changeant dans la transition du vieillissement normal au vieillissement pathologique de type Alzheimer, schématisé dans la figure 15. En effet, au cours du vieillissement normal et chez les SCD-communauté, les symptômes anxieux sont associés à la neurodégénérescence, tandis qu'ils ne semblent plus avoir de substrats chez les SCD-clinique et les patients. Les symptômes dépressifs sont tout d'abord associés à plus de pathologie amyloïde et donc de risque de MA, tandis que lorsque la démence est installée, au stade de MCI ou MA, ils sont associés à une meilleure santé puisqu'à une meilleure cognition et conscience des troubles.

De façon intéressante, Les SCD-communauté semblent être plus proches des sujets sains en termes de facteurs psychoaffectifs et de leurs corrélats, puisque dans les deux groupes les symptômes anxieux sont associés directement ou indirectement à un volume de substance grise et un métabolisme du glucose plus bas. De plus, dans ce groupe, la plainte et la neurodégénérescence semblent plus associées aux symptômes anxieux et au vieillissement normal qu'à la maladie d'Alzheimer, au vu des régions impliquées (Baur et al., 2012; Besteher et al., 2017; Kalpouzos et al., 2009; La Joie et al., 2012; Spampinato et al., 2009; Webb et al., 2014) et de l'absence de liens avec l'amyloïde. Au contraire chez les SCD-clinique et les patients déments, les symptômes anxieux ne sont plus associés à la

neuromimagerie, tandis que les symptômes dépressifs augmentent. Ces derniers sont tout d'abord signe de prodrome et risque de MA chez les SCD-clinique, puisqu'associés à une charge amyloïde plus importante, puis chez les sujets du continuum Alzheimer (MCI et MA positifs pour l'amyloïde) ils seraient signes de moindre sévérité de la démence, puisqu'associés à une meilleure mémoire et conscience de ses propres troubles. De façon générale, les symptômes psychoaffectifs semblent être des manifestations de vulnérabilité et de risque, puis de prodrome, et enfin de conscience de la démence de type Alzheimer.

Cependant, les symptômes anxieux et dépressifs sont souvent considérés comme un ensemble, en tant que symptômes neuropsychiatriques. Notamment, les hypothèses liant ces symptômes aux biomarqueurs ou au risque de MA les décrivent comme une seule entité (Gallagher et al., 2017; Geda et al., 2013). Si l'on fait le parallèle avec les hypothèses présentées précédemment (voir section 2.4.1), au cours du vieillissement et chez les SCD-communauté, les symptômes anxieux pourraient suivre la voie dite « étiologique » (Geda et al., 2013) : les symptômes anxieux représenteraient un état cérébral sous-jacent (volume de SG plus petit), notamment chez la femme. Cet état cérébral serait associé au développement d'une MA et de ses symptômes cognitifs associés. Puis chez les SCD-clinique, bien que nous ne connaissions pas le sens de causalité, les symptômes dépressifs pourraient suivre l'hypothèse d'« interaction » (Geda et al., 2013). L'amyloïde et les symptômes dépressifs pourraient donc interagir pour conduire à la MA. Enfin au stade démentiel, les symptômes dépressifs seraient une réaction psychologique au déclin cognitif causé par la MA, selon la troisième hypothèse de « SNP causés par la MA » (Geda et al., 2013). Ces résultats montrent que les symptômes neuropsychiatriques ont des substrats et des évolutions différentes au cours du vieillissement normal et pathologique. Ils devraient donc être considérés et étudiés à la fois séparément pour comprendre leurs spécificités, et à la fois ensembles afin d'évaluer leurs potentielles synergies et interactions.

Dans le cadre de la recherche, les études cliniques peuvent également enrichir leurs populations d'Alzheimer préclinique avec des patients SCD-clinique présentant des symptômes dépressifs, qui,

comme nous l'avons montré précédemment, sont plus à risque de démence. En termes cliniques, cette thèse montre également l'intérêt de surveiller les symptômes anxieux et dépressifs, notamment chez la femme, pour mieux évaluer et gérer les risques de développer une démence, ainsi que de traiter les symptômes anxieux des patients présentant une démence légère, afin d'améliorer leur qualité de vie et diminuer leur risque de conversion ou d'aggravation.

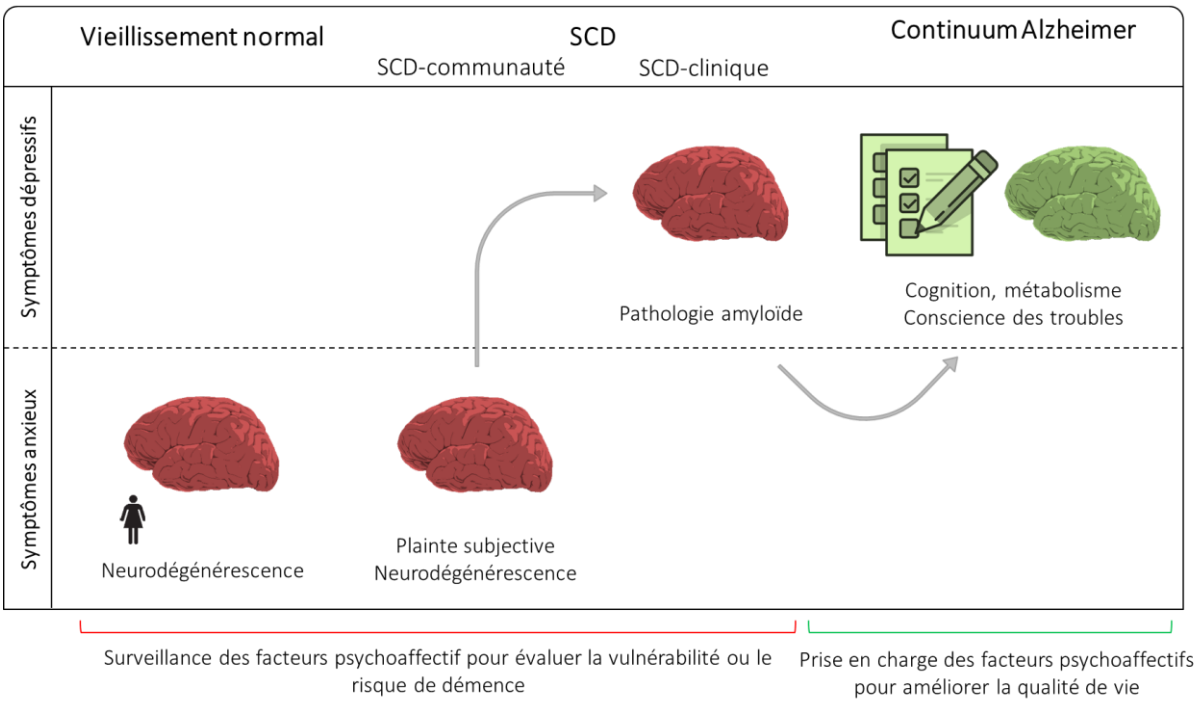


Figure 15 : Schéma de synthèse des principaux résultats de cette thèse.
Abréviations : SCD *Subjective Cognitive Decline.*

4.4. Limites et perspectives

Ce travail de thèse a permis de mieux comprendre les substrats cérébraux des symptômes anxieux et dépressifs au cours du vieillissement normal et du vieillissement pathologique. Une force de ce travail réside dans son caractère multimodal et dans l'analyse simultanée des symptômes anxieux et dépressifs. Ce travail présente néanmoins un certain nombre de limites. Notamment, la faible variabilité du score de symptômes dépressifs a pu limiter notre capacité à détecter des liens avec les autres mesures. En effet, autour de 40% de nos populations de l'étude 1 et 2 n'avait aucuns symptômes

dépressifs. Pour pallier à cela, nous avons effectué des analyses complémentaires non paramétriques et dans un sous-groupe comprenant uniquement les participants rapportant au moins un symptôme dépressif. Il est également à noter que cette thèse n'est pas généralisable à l'ensemble de la population puisque nos participants ont un niveau d'éducation élevé, et ne présentent pas de comorbidités en termes de santé. Or, les symptômes anxieux et dépressifs sont notamment plus prévalents dans des populations cliniques ou moins éduquées (pour revue Bryant et al., 2008; Craig & Van Natta, 1979; Himmelfarb & Murrell, 1984; Vasiliadis et al., 2013). De plus, elle ne permet pas de certifier les liens de causalité des associations mises en évidence, c'est pourquoi des études sur des populations plus diverses et des suivis longs pourraient être pertinentes pour compléter ces résultats.

Cette thèse rapporte les liens entre les symptômes anxieux et une vulnérabilité cérébrale chez les sujets âgés sains et les SCD-communauté, ainsi que les liens des symptômes dépressifs avec le risque de développer une MA chez les SCD-clinique. Elle met donc en évidence l'importance de traiter les symptômes anxieux et dépressifs pour prévenir le déclin cognitif à un stade asymptomatique. Une intervention non-pharmacologique de réduction de ces symptômes, tel qu'un programme de méditation, permettrait d'évaluer l'impact et la pertinence de leur prise en charge chez des SCD et des sujets âgés cognitivement sains.

Ce travail de thèse s'inclut donc de façon plus globale dans la mise en place du projet européen *Medit-Ageing*, qui comprend un essai clinique randomisé nommé *Age-Well* et fait suite au projet IMAP+ dans le laboratoire de recherche qui m'a accueilli. Cette nouvelle étude commencée en 2016 est dirigé par la Dr Gaëlle Chételat, coordinatrice scientifique, et le Pr Vincent de la Sayette, médecin investigateur, dans l'unité de recherche INSERM U1237 dirigée par le Pr Denis Vivien. Elle se propose d'évaluer l'impact neurobiologique et cognitif d'un entrainement mental de 18 mois de méditation ou d'anglais, chez des personnes âgées de plus de 65 ans. En effet, comme détaillé dans l'annexe 6.1 (Poisnel et al., 2018), 137 participants ont effectué des examens sanguins, neuropsychologiques, psychoaffectifs (i.e.

questionnaires de symptômes dépressifs et anxieux, de rumination) de neuroimagerie et de sommeil, à baseline et 18 mois après le début de l'intervention. Pour ma part, j'ai eu l'opportunité d'être au contact des sujets et de participer au screening, aux acquisitions, et au prétraitement des mesures de neuroimagerie, à la fois à l'inclusion et au suivi.

Complémentaire à l'étude *Age-Well*, l'étude *SCD-Well,* détaillée en annexe 6.2 (Marchant et al., 2018), est une étude multicentrique dans 4 pays européens mise en place dans le cadre du protocole Medit-Ageing, et dirigée par la Dr. Natalie Marchant au *University College* de Londres. Elle vise à mesurer l'effet d'un programme de méditation MBI (*Mindfullness Based Intervention*) de 8 semaines (Kabat-Zinn, 1990), comparé à un programme d'éducation à la santé de même durée, sur des mesures sanguines, neuropsychologiques et psychoaffectives, chez 147 participants SCD de plus de 60 ans recrutés dans des centres mémoire. Une troisième étude a également été menée sur des méditants experts, qui ne sera pas détaillée dans le cadre de cette thèse.

Des études ont montré que la méditation avait un impact bénéfique dans le cadre du vieillissement, notamment en diminuant les symptômes anxieux et dépressifs, et ce même dans des populations cliniques (pour revue Moulinet et al., 2018). C'est pourquoi, l'une des perspectives évidentes de cette thèse est d'évaluer l'impact d'un entraînement de méditation de 18 mois dans le cadre de l'étude *Age-Well*, sur les liens entre anxiété et substance grise que nous avons mis en évidence dans notre première et troisième étude. Le protocole *SCD-Well* nous permettra d'évaluer l'impact d'une intervention de méditation MBI sur le lien entre les symptômes dépressifs et la charge amyloïde cérébrale, mis en évidence dans notre deuxième étude chez les SCD recrutés en centre mémoire. De façon intéressante, quelques études ont également montré une amélioration des symptômes anxieux et dépressifs dans des populations SCD (Innes et al., 2016), MCI et MA (pour revue Russell-Williams et al., 2018), le plus souvent dans le cadre d'une intervention de méditation standardisée de type MBSR (*Mindfullness Based Stress Reduction* ; Kabat-Zinn, 1982). Il serait donc intéressant d'évaluer aussi si cela modifierait les liens entre la cognition, la conscience des troubles et les symptômes anxieux que nous avons mis en évidence dans notre deuxième étude.

D'autres perspectives, plus directement en lien avec les résultats de cette thèse, seraient d'approfondir les recherches de l'effet interactif du sexe, et plus spécifiquement de regarder si cette hypersensibilité des femmes est également présente dans les populations SCD, MCI et MA. Pour finir, nous avons évalué dans cette thèse les associations entre les symptômes anxieux et dépressifs avec les atteintes structurales, fonctionnelles et moléculaires de la MA, excepté la pathologie tau. En effet, pour le moment, seule une étude chez des sujets MCI a mis en évidence une association entre des symptômes dépressifs élevés et un marquage important de la pathologie Alzheimer dans le temporal médian, mais à l'aide d'un radiotraceur marquant à la fois les dépôts amyloïdes et les DNF (Lavretsky et al., 2009). Il serait donc intéressant de compléter ces résultats, dans chaque groupe, avec une mesure de TEP-tau telle que le radiotraceur ^{18}Flortaucipir.

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6. Annexes

6.1. Protocole Age-Well (Poisnel et al., 2018)

ELSEVIER

Alzheimer's & Dementia: Translational Research & Clinical Interventions 4 (2018) 714-723

Alzheimer's & Dementia

Featured Article

The Age-Well randomized controlled trial of the Medit-Ageing European project: Effect of meditation or foreign language training on brain and mental health in older adults

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Abstract

Introduction: The Age-Well clinical trial is an ongoing monocentric, randomized, controlled trial aiming to assess an 18-month preventive meditation-based intervention directly targeting the attentional and emotional dimensions of aging to promote mental health and well-being in elderly people.
Methods: One hundred thirty-seven cognitively unimpaired older adults are randomized to either an 18-month meditation-based intervention, a structurally matched foreign language training, or a passive control arm. The impact of the intervention and underlying mechanisms are assessed with detailed cognitive, behavioral, biological, neuroimaging and sleep examinations.
Results: Recruitment began in late 2016 and ended in May 2018. The interventions are ongoing and will be completed by early 2020.
Discussion: This is the first trial addressing the emotional and cognitive dimension of aging with a long-term nonpharmacological approach and using comprehensive assessments to investigate the mechanisms. Results are expected to foster the development of preventive strategies reducing the negative impact of mental conditions and disorders.
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Keywords: Aging; Alzheimer's disease; Dementia; Prevention; Cognition; Reserve; Attention; Meditation; Mindfulness; Compassion; Foreign language training; Emotion; Lifestyle; Neuroimaging; Blood markers; Sleep

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1. Introduction

As the number of older people grows, increasing healthy life years is a priority. The main drivers of decreased mental health and well-being in aging populations include dementia, depression, anxiety, insomnia, and even subclinical conditions such as stress, worry, sleep disturbances, and cognitive decline [1,2]. Moreover, these conditions interact and promote each other. For instance, anxiety, depression, and sleep difficulties are associated with increased risk of Alzheimer's disease (AD).

The reduction of modifiable risk factors represents a true opportunity to prevent AD [3,4]. Indeed, around a third of AD cases may be attributable to potentially modifiable risk factors, and the future prevalence of AD could be reduced by 8% to 15% if each of the main risk factors (e.g., cardiovascular risk factors, depression, physical, and cognitive inactivity) is reduced by 10 to 20% [3,5]. Several lifestyle interventions in nondemented older adults have thus been investigated with mixed results before larger-scale trials with long-term (>1 year) follow-up and using multidomain interventions simultaneously targeting various risk factors were launched [6]. Examples of such multidomain prevention randomized controlled trials (RCTs) include the Multidomain Alzheimer Prevention Trial (MAPT) [7], the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial [8], and the Prevention of Dementia by Intensive Vascular Care (PreDIVA) trial [9]. Positive effects on cognitive function were found in Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability [10], which has evolved toward a worldwide consortium, World Wide Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability, including, for example, the U.S. equivalent U.S. POINTER (https://alz.org/us-pointer/). These trials target most of the main modifiable risk factors (cardiovascular risk factors, physical and cognitive inactivity). Yet although very important, psychoaffective risk factors have so far not been directly targeted.

A promising way of targeting psychoaffective risk factors consists in mental training for the reduction of stress, the regulation of attention and the cultivation of positive emotions through meditation practice. Such interventions might be beneficial to improve mental health and well-being in the aging population and reduce AD risks. Promising evidence exists that mindfulness meditation improves cognition in young adults (mainly attention, metacognition and memory, which are cognitive processes sensitive to aging and AD) [11–13], and reduces stress, anxiety, depression, insomnia [14–17] and cardiovascular risk factors [18,19]. Moreover, meditation has also been associated with brain structural and functional changes that persist beyond the time of actual practice and mainly impact frontal and limbic networks [20–23]. In a recent cross-sectional pilot study, we showed that elderly expert meditators had higher gray matter volume and/or fluorodeoxyglucose metabolism compared with age-matched non-meditators in frontal, insula and posterior associative regions [24]. These findings suggest that meditation might have a beneficial effect in brain regions sensitive to aging and AD and subtending reserve processes, thereby reducing the risk or delaying the onset of dementia/AD.

To test this hypothesis, we need an RCT including an adequate active control comparison condition to estimate the specific effects of a meditation intervention. The duration of the intervention should exceed that of the commonly used 8-week mindfulness-based stress reduction program to demonstrate an effect not only on behavioral, but also on protracted age-related biological processes. Moreover, complementary outcome measures allowing to investigate the mechanisms of action and to assess the multidimensional aspect of aging should be used.

Medit-Ageing (public name: Silver Santé Study; www.silversantestudy.eu) is a European research project focusing on mental health and well-being in aging populations. It includes two independent clinical studies (SCD-Well and Age-Well) and the Age-Well study includes an RCT and an observational cross-sectional study on older expert long-term meditators. The present article will focus on the design and progress of the Age-Well RCT.

The Age-Well RCT is the first trial addressing the emotional and cognitive dimension of aging with a long-term nonpharmacological approach and including both an active and a passive control conditions. A complete set of unique measurements will be used to investigate the mechanisms of action, including cognitive tests particularly focusing on memory and attention, scales and questionnaires assessing well-being, quality of life, psychoaffective factors and lifestyle, but also complementary neuroimaging measures of brain structural and functional integrity, emotion and attention-related neural activity, biological blood measures and gold-standard measures of sleep with polysomnography. Finally, on the level of social relations, measurements in participants' partners will allow to investigate their perception of the participant's changes and their own perceived social support. Objective biomarkers of brain integrity will be used as primary outcomes.

We hypothesize that meditation training will be associated with an increase in positive emotions and improved cognitive control which will in turn enhance health and well-being, and promote brain and cognitive reserve processes that are protective of dementia. Qualitative and quantitative differences are expected in the effects of meditation versus foreign language training interventions as they are thought to involve overlapping but partly distinct mechanisms (Fig. 1).

2. Methods/design

2.1. Clinical trial setting and design

The Age-Well clinical trial is a monocentric, randomized, controlled superiority clinical trial with blinded endpoint assessment and with three parallel arms: an 18-month

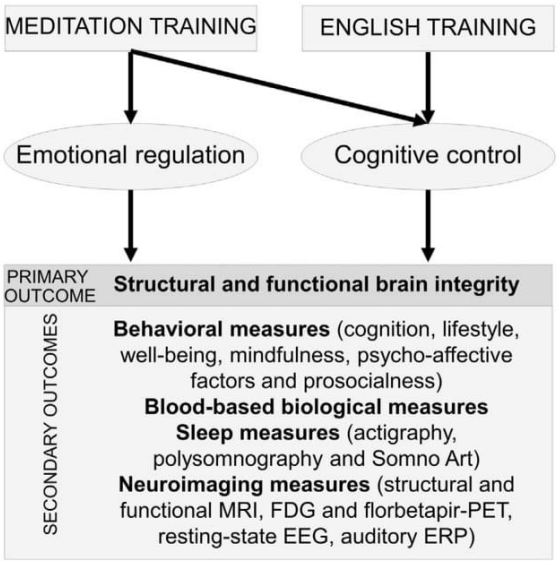

Fig. 1. Hypothetical model of the expected effects and mechanisms of the meditation and foreign language training interventions included in the Age-Well RCT. Meditation training is thought to promote both emotional regulation/positive affect and cognitive control. Foreign language training is expected to act mainly through cognitive stimulation. Consequently, while both the meditation and foreign language training interventions are expected to have a positive impact on markers of mental health and well-being in aging, the nature and degree of these effects are expected to differ between both interventions. Abbreviations: EEG, electroencephalography; ERP, event-related potential; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.

meditation arm, an 18-month foreign language (English) training intervention arm (the active control) and a no-intervention passive control arm. The Age-Well RCT includes 137 cognitively unimpaired older adults. Participants were recruited in three successive cohorts of 43, 50 and 44 participants, respectively, spaced about 6 months apart. The general design of the trial is depicted in Fig. 2 and the different steps are detailed in the Supplementary Material. In brief, participants were recruited from the general population, prescreened, and then invited to a screening visit (V0) at which the diagnostic battery depicted in Table 1 was performed. Participants fulfilling eligibility criteria (Table 2) were invited to the baseline pre-intervention visit (V1), then randomized to one of the three arms (groups) at a ratio of 1:1:1, and the 18-month intervention period starts. A mid-intervention intermediate visit (V2) is performed 9 months after the start of the intervention, and the post-intervention visit (V3) is performed at the end of the 18-month intervention period.

2.2. Measures collected at the baseline and follow-up visits (V1, V2, and V3)

V1 and V3 comprise a multidisciplinary assessment of a wide range of behavioral and biological measures collected within a maximum of 3 months before (V1) and after (V3) the start of the intervention. The detailed biological, behavioral, neuroimaging and sleep measures collected at the pre-intervention and post-intervention visits (V1 and V3) are listed in Table 3; the mid-intervention intermediate visit (V2) includes a selected set of the behavioral measures collected at V1 and V3 as indicated in Supplementary Table 1. Briefly, behavioral measures are neuropsychological tests assessing different cognitive functions (e.g. episodic memory, attention, executive function), scales and questionnaires assessing, for example, sleep quality, lifetime and current engagement in cognitive, social and physical activities; Mediterranean diet adherence, health-related behaviors such as self-medication, smoking and alcohol consumption, quality of life and well-being, psychoaffective factors such as anxiety and depression, and prosocialness (Supplementary Table 1 for details). Some of the questionnaires are also given to a participant's close relative or friend (subsequently referred to as the "partner"). Neuroimaging measures include a series of structural and functional (resting-state and task-related) MRI scans, fluorodeoxyglucose (Glucotep) and florbetapir (AV45, Amyvid) positron emission tomography scans, and resting-state electroencephalography and auditory event related potential recording (Supplementary Table 2 for details). Objective measures of sleep include actigraphy, an ambulatory monitoring device using heart rate and body movements to score sleep (SomnoArt) and polysomnography. Biological measures are obtained from blood sampling (Supplementary Table 3). All procedures for data acquisition were discussed and audited by experienced and skilled study staff to ensure standardization of the procedures.

2.3. Interventions

The 18-month intervention period starts just after the randomization step for each of the three cohorts of 43, 50, and 44 participants, each subdivided in three groups (meditation, foreign language, control) of 14–17 participants.

During the study, participants are strongly encouraged not to practice the activity proposed in the other arms (groups). The meditation and the foreign language training interventions are structurally equivalent in overall course length, class time, and home activities and matched in administration, dosage, and duration. The number of teachers per class and their level of expertise are equal in both interventions. Participants are encouraged to participate in all those activities during the whole period of the intervention (i.e., 18 months).

In addition to being structurally equivalent, we actively tried to balance researcher allegiance to the two interventions as this might have significant impact on the findings [4–6,32,33]. A well-designed control should also include a rationale for the positive expectation for intervention success by both the teachers and participants [34]. We thus tried to keep all communications about the study fully balanced as regard to expected effects of both the meditation and the foreign language training interventions and underpinning

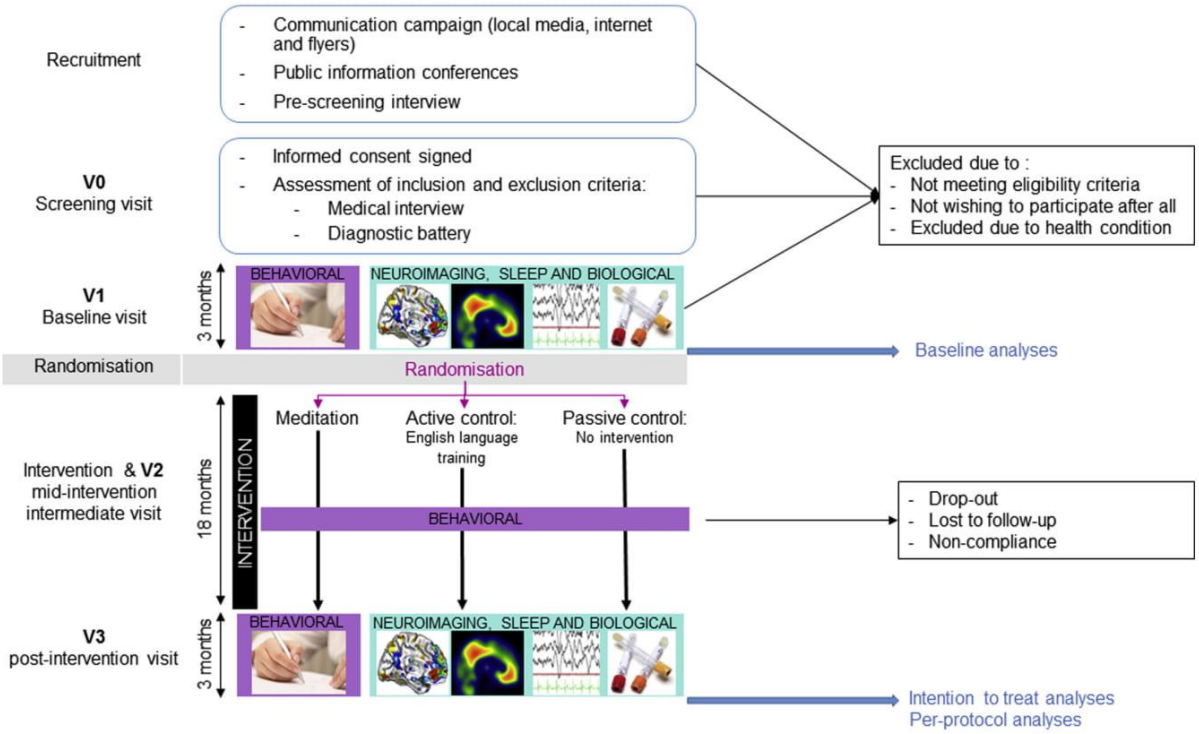

Fig. 2. Flow chart of the Age-Well RCT participants. The different steps are detailed in the text. The boxes at V1 and V3 depict the types of measurements that are collected. Abbreviation: RCT, randomized controlled trial.

the equipoise regarding their use. To assess participants' expectations regarding the intervention, a questionnaire was proposed to them at the beginning of the intervention (Credibility and Expectancy questionnaire, [35]).

For both the meditation-based and the foreign language training interventions, participants follow:

- 2-hour weekly group sessions,
- daily home practice (at least 20 minutes per day),
- one day of more intense practice during the intervention (5 hours during the day).

Both interventions have been fully described a priori in respective manuals.

The meditation intervention consists of an original secular program of meditation training labeled "The Silver Santé Study Meditation Programme" especially designed for this study based on pre-existing interventions (as detailed in the Supplementary Materials) with the objective of personal development and healthy aging, and is provided by expert meditator instructors in Caen. The objective of this 18-month intervention program is to develop mindfulness, kindness and compassion abilities as additional psychological resources to cope with challenges related with aging on physical, cognitive and psychological aspects. The first 9 months of the intervention are dedicated to the teaching of mindfulness meditation whereas the 9 following months

Table 1
Tests included in the diagnostic battery performed during the screening visit V0

Diagnostic battery				
Domains evaluated	Tests	Score(s)	References	Expected performances
Manual laterality	Edinburgh Questionnaire	Unique	[25]	Not applicable
Global cognitive functioning	MMSE	Unique	[26]	Norms according to age, sex, and education level
Depression	Montgomery and Asberg Depression Rating Scale	Unique	[27]	Score < 19
Executive functions	Wisconsin Card Sorting Test	Multiple	[28]	Z score > -1.65 (norms according to age, sex, and education level)
Verbal episodic memory	RL-RI16	Multiple	[29]	Z score > -1.65 (norms according to age, sex, and education level)
English test	Evaluation of oral and written comprehension.	Unique	Original test	Score $<16/18$

Table 2
Inclusion and exclusion criteria for the Age-Well clinical trial

Inclusion criteria	Exclusion criteria
- Age ≥65 years - Autonomous - Living at home - Educational level ≥7 years (from the Preparatory Course—1st grade—included) - Registered to the social security system - Motivated to effectively participate in the project and signing the informed consent form - Performance within the normal range on standardized cognitive tests according to agreed study-specific standards (age, sex and education level when available) - Native French speaker - Available to attend the intervention for the trial duration (24 months) - Retired for at least one year - No strong preference or aversion for an intervention group - No present or past regular or intensive practice of meditation or comparable practices; the practice is considered as regular and/or intensive if i) it occurs more than one day per week for more than six consecutive months over the last 10 years, and/or in case of more than five consecutive days of intensive practice (internship or retreat) over the past 10 years, and/or of more than 25 days of retreats (cumulatively) within the last 10 years - Not speaking fluent English	- Safety concerns in relation to MR scanning (claustrophobia, ferromagnetic object) or PET scanning (blood sampling to check hepatic and renal functions are performed before the PET scans; known hypersensibility to Amyvid or Glucotep) - Presence of a major neurological or psychiatric disorder (including an addiction to alcohol or drugs) - History of cerebral disease (vascular, degenerative, physical malformation, tumor, or head trauma with loss of consciousness for more than an hour) - Presence of a chronic disease or acute unstable illness (respiratory, cardiovascular, digestive, renal, metabolic, hematologic, endocrine or infectious) - Current or recent medication that may interfere with cognitive functioning (psychotropic, antihistaminic with anticholinergic action, anti-Parkinson's, benzodiazepines, steroidal anti-inflammatory long-term treatment, antiepileptic or analgesic drugs), the interfering nature of the different treatments being at the discretion of the investigating doctor - Being under legal guardianship or incapacitation - Participation in another biomedical research protocol including the injection of radiopharmaceuticals - Physical or behavioral inability to perform the follow-up visits as planned in the study protocol

are dedicated to the teaching of the meditation on loving kindness and compassion. Each session contains moments of group meditation, sitting, or walking and moments of sharing and teaching.

The foreign language training program is a cognitively stimulating intervention structurally matched to the meditation intervention and hypothesized to have no specific effect on emotional measures. It consists of English exercises designed to reinforce each participant's abilities in understanding, writing and speaking. Sessions are held by mixing oral comprehension and expression activities to work in priority, the acquisition of new vocabulary and new grammatical structures.

Participants in the passive control group are requested not to change their habit and continue living as they used to before engaging in the study and until the end of V3. They are specifically asked not to engage in meditation or foreign language training.

More details on the interventions can be found in the Supplementary Material.

2.4. Outcome measures

The main objective of the Age-Well RCT is to test, whether an 18-month meditation-based intervention in cognitively unimpaired older adults is superior to i) a passive control group on changes in volume and perfusion of the anterior cingulate cortex (ACC); ii) an 18-month foreign language training program on changes in volume and perfusion of the insula. Accordingly, the primary outcomes are the mean change in the volume and perfusion of both the ACC and the insula, as measured with structural T1-weighted MRI and early florbetapir positron emission tomography scan respectively from the baseline pre-intervention to the 18-month post-intervention follow-up visits.

The secondary objectives will focus on the effects of the interventions on cognition, well-being, quality of life, psychoaffective factors and lifestyle; complementary neuroimaging measures of brain integrity, emotion and attention-related neural activity; sleep quality with polysomnography; and biological blood measures in the aging population. Sex-specific effects of the interventions and effects on participants' partners (perception of participant's changes and their own perceived social support) will also be assessed, together with exploratory analyses unrelated to the clinical trial intervention (e.g., aiming to further understand the impact of lifestyle factors and the physiopathological mechanisms of AD). The secondary outcomes used to assess these questions are listed in Table 3. Adverse events and measures collected during the intervention by the teachers and self-report of participants will be used to assess safety, acceptance and adherence.

2.5. Statistical considerations

2.5.1. Sample size calculation

The comparison of the meditation versus passive control arms will focus on the mean change in (1) volume and (2) perfusion of the ACC from the baseline pre-intervention visit to the end of the 18-month intervention, with an expected relevant effect size of 0.75, as suggested by a meta-analysis of meditation effects on neuroimaging markers

Table 3
List of collected measures and corresponding outcomes

Measures collected at V1 and V3 (and V2 for a selected set of behavioral measures)	Outcomes
Behavioral measures (Supplementary Table 1 for details): Series of neuropsychological tests,scales and questionnaires selected as they are particularly sensitive to aging and AD (e.g., assessing episodicmemory, attention, executive functions and metacognition) and/or meditation practices (e.g., assessing mindfulness, compassion, and interoception), emotions (e.g., assessing anxiety, depression, empathy, emotion regulation, positive and negative emotions), or as they allow to assess different aspects of sleep quality, lifestyle, well-being, prosociality, loneliness, social support and quality of life. Questionnaires are also proposed to a partner (i.e., a participant's close relative or friend) to assess how the partner perceives the mindfulness, compassion, depression, anxiety, and prosocialness of the participant as well as questions on the social support and the role ofan informal carer of the partner.	Composite scores and raw individual measures of cognitive performance, well-being, mindfulness and meta-cognition, emotion-related questionnaires, altruism, prosociality, sleep quality, lifestyle, and quality of life of the participants. Partner perception of the participant's mindfulness, compassion, depression, anxiety, and prosocialness as well as questions on the social support and the role of an informal carer of the partner.
Neuroimaging measures (Supplementary Table 2 for details): 1) Structural MRI a) 3D T1 and fluid-attenuated inversion recovery—FLAIR b) High-resolution proton-density focused on the hippocampus c) Diffusion Kurtosis Imaging—DKI d) Quantitative Susceptibility Mapping—QSM 2) Functional MRI—fMRI a) Resting-state fMRI b) Task-related fMRI i) The AX-CPT task [30] ii) The SoVT-Rest task 3) Resting-state EEG 4) Auditory event-related potential (ERP) using a mismatch negativity protocol sensitive to aging [31] 5) PET scans a) FDG (Glucotep) PET scan b) Florbetapir (AV45, Amyvid) PET scan	- Gray and white matter volumes - White matter lesions (number and size per type and location) - Hippocampal subfield volumes - Fractional anisotropy and mean diffusivity - Magnetic susceptibility index - Brain functional connectivity - Behavioral and brain activity measures associated with attentional processes (alertness, inhibition, sustained attention) - Behavioral and brain activity and connectivity changes associated with emotions and emotional inertia - Resting-state spontaneous oscillatory activity - ERP measures of brain activity associated with auditory mismatch negativity - Resting-state brain glucose consumption - Brain perfusion from early florbetapir-PET acquisition - Brain amyloid load from late florbetapir-PET acquisition
Biological measures from blood (Supplementary Table 3 for details): Fasting sampling performed in the morning and after one day of diet excluding ich food (tomatoes, avocados, pineapple, chocolate, bananas…). 18 tubes (68 mL) of blood collected at V1 and 16 tubes (62 mL) at V3.	- Global health: blood count, glucose, cholesterol/lipid profile, urea, creatinine, Gamma-GlutamylTransferase, Glutamic Oxaloacetic Transaminase, Glutamic Pyruvic Transaminase, Brain Natriuretic Peptide, Thyroid Stimulating Hormone, - Stress/inflammation: high-sensible C-Reactive Protein, cytokines, cortisol, Superoxide Dismutase - Aging/AD (telomere length, telomerase activity, β-amyloid (Aβ) 1-40/42, Total Tau, Phospho-Tau, tissue Plasminogen Activator, Plasminogen Activator Inhibitor-1, Brain Derived Neurotrophic Factor, insulin, Insulin Growth Factor-1, lymphocyte immunophenotyping, Repressor Element 1-Silencing Transcription factor, Neurofilament, - Mood: serotonin, - Sex/gender: bioavailable testosterone, estradiol, Sex Hormone Binding Globulin, DeHydroEpiAndrosterone Sulfate - Genetic: Apolipoprotein E, Genome Wild Association Study - Epigenetics
Objective measures of sleep: 1) 1-week wrist actigraphy recording 2) 2-nights at-home polysomnography with 2D-object location task performed before and after night sleep 3) 5-nights recording with Somno-Art	- Indices of mean sleep duration, sleep fragmentation and regularity of the rest-activity cycle - Multiple indices of sleep quality derived from EEG analyses and behavioral measures of overnight memory consolidation - Indices of night-to-night variability of sleep quality and quantity.

More details can be found in the Supplementary Material.

[20]. To demonstrate an effect size of 0.75 for each of the four comparisons, with 80% power and a two-sided type I error of 1.25% (Bonferroni correction for test multiplicity), 42 participants per arm (126 in total) need to be included. The total number of participants included in the Age-Well RCT (n = 137) is higher than this required minimum of 126.

2.5.2. Statistical analyses

The planned statistical analyses are detailed in a statistical analysis plan and summarized in the Supplementary Material. Briefly, statistical analyses related to the primary outcome will be conducted on an intent-to-treat principle and missing primary endpoint data will be handled with a "missing = failure" strategy. Additional analyses conducted on both primary and secondary outcomes will include sensitivity analyses, per-protocol analyses and analyses of exposure/dose effects.

2.6. Ethics, safety, and study monitoring

The Age-Well RCT was approved by the ethics committee (Comité de Protection des Personnes CPP Nord-Ouest III, Caen; trial registration number: EudraCT: 2016-002441-36; IDRCB: 2016-A01767-44; ClinicalTrials.gov Identifier: NCT02977819) and adheres to Standard Protocol Items: Recommendations for Interventional Trials guidelines for clinical trial protocols [36].

The management structure of Medit-Ageing is illustrated in Fig. 3 and includes the coordinator (G.C.), the executive committee and 9 work packages (including the management work package). In addition, the sponsor (Inserm) has established a trial steering committee in line with Good Clinic Practice guidelines, and an external Data and Safety Monitoring Board, independent of the sponsor, was appointed.

More details on ethics and safety, study governance and monitoring, as well as study progress can be found in the Supplementary Material.

2.7. Clinical trial progress

From May 2016 to May 2018, about 900 individuals came to public conferences and filled in the online prescreening questionnaire. Among those, 157 participants were screened. Thirteen did not fulfill the inclusion criteria (the main reason being abnormal performance in the diagnostic battery), 6 participants were excluded during V1 because of artifacts or claustrophobia attack during the MRI scan or high level of glycemia and 1 participant withdrew. Finally, 137 participants (40/60% men/women) were randomized to the three experimental groups. Participants from the first and second cohort had their 9-month intermediate follow-up visit—at that time only 1 participant dropped out (death).

The 18-month follow-up post-intervention visits will end in early 2020. Electronic data entry, monitoring and processing are currently ongoing.

3. Discussion

Age-Well is the first RCT to comprehensively assess the long-term efficacy of meditation on well-being and aging through a multidisciplinary approach. The strength and originality of the Age-Well RCT relies, first, in the nature, dose and duration of the proposed interventions. Thus, this meditation intervention is especially designed to target not only cognitive control via the regulation of attention, but also psychoaffective factors through the reduction of stress and the cultivation of positive emotions. This is crucial as stress, anxiety and depression significantly contribute to reduced quality of life and increased risk for dementia in older adults [2]. Current lifestyle preventive trials tend to include multidomain interventions as recommended [6] but most often do not focus on the emotional dimension of aging; thus they target the main risk factors for dementia (cardiovascular risk, diet, cognitive and physical activity) except the psychoaffective ones (e.g., depression). Moreover, interventions

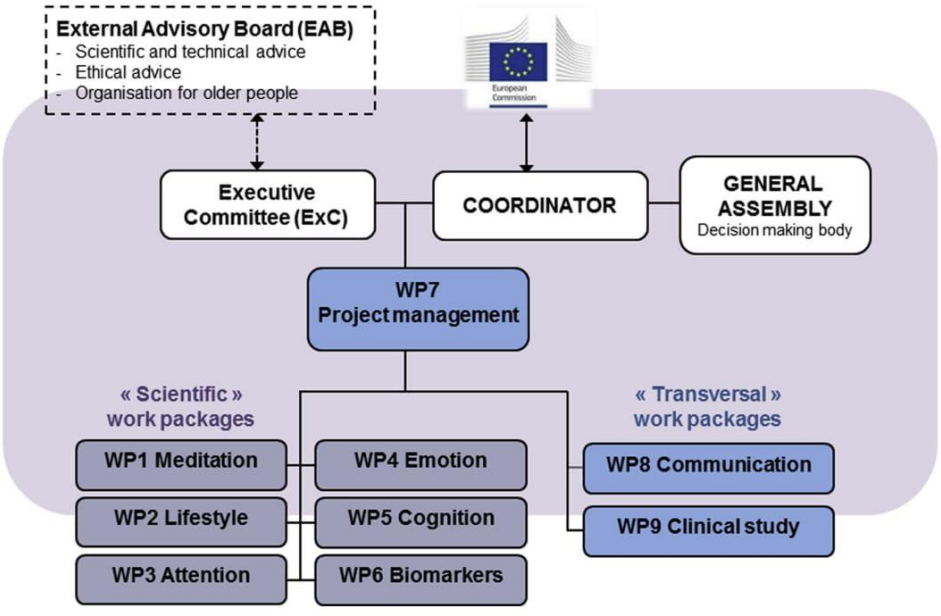

Fig. 3. Management structure of Medit-Ageing.

in Age-Well include weekly 2-h group practice monitored by highly experienced teachers and daily individual home practice collected over the 18 months of the interventions. They might have the potential to induce long-term effects on brain and biological markers of healthy aging.

Second, the Age-Well RCT assesses a wide range of complementary outcomes including cognitive tests, scales and questionnaires assessing well-being, quality of life, psychoaffective factors and lifestyle, but also complementary MRI and positron emission tomography neuroimaging measures of brain structural and functional integrity, emotion and attention-related neural activity, biological blood measures and gold-standard measures of sleep with polysomnography. In addition to being useful to provide a comprehensive overview of the effects and to monitor the effectiveness of the intervention [6], this multidisciplinary approach will allow for the investigation of mechanisms underlying the possible effects of the intervention. A better understanding of the mechanisms of action of meditation will facilitate sensitivity to intervention analysis and help refine and tailor future meditation-based interventions. The Age-Well RCT is monocentric thus avoiding intersite variability, which often limits the inclusion of certain biomarkers in multisite clinical trials.

A further strength of this study to estimate specific meditation effects is the ability to use the foreign language intervention as an active control condition. Many of the previous studies of mindfulness-based interventions have suffered from a lack of an adequate comparison condition. As mindfulness-based interventions contain a number of nonspecific elements, such as social interaction, light exercise, or the provision of treatment expectancies, the use of an active control condition is important. Foreign language training was selected as the active control condition for several reasons. Like meditation, it involves cognitive mental training. It can easily be matched structurally to the meditation intervention (e.g., group sessions and daily practices with audio and video supports). Positive effects are expected given that the learning of a new language has been shown to impact on cognitive functions and brain structures sensitive to aging and AD [33,34]. In addition to being useful as an active control condition, this intervention has its own scientific interest as the first RCT to date on language training in older adults over 18 months and with multidisciplinary outcomes including multimodal neuroimaging. Note that, while both interventions are expected to have a positive impact in aging populations, they are expected to target distinct aspects of mental health and well-being and to involve distinct mechanisms (Fig. 1). In particular, foreign language training is not expected to directly impact on emotional states, contrary to meditation training. It will thus be interesting to compare the relative effects of both interventions on the different outcome measures.

As for the choice of the primary endpoint, most previous long-term preventive trials used clinical/cognitive measures. Here we think that the use of neuroimaging biomarker is more appropriate as we are interested in the earliest stages where clinical and cognitive decline is not expected to be significant within 18 months, while neuroplasticity is likely to occur and be translated in measurable brain changes. Neuroimaging biomarkers are increasingly used in ongoing trials, especially in preventive trials or early disease stages and when the goal is to show an effect on the pathophysiology of the disease [37]. More specifically, the ACC and insula emerge as the most appropriate endpoints for the following reasons: the ACC is both i) a brain area with known relevance to maintain cognitive function in older people [36–39] and ii) one of the brain regions most sensitive to meditation [20,22]. The insula has been selected to assess the effects of the meditation intervention compared with the foreign language training intervention as it is a region related to interoceptive awareness, emotional and empathic processing, also most frequently involved in meditation studies [20,22] but less likely to be involved in cognitive training and to be impacted by the foreign language training intervention.

A side effect of most clinical studies and especially those that are highly demanding (in terms of examinations and intervention), is that individuals interested in participating are likely to be particularly active and educated. They might thus not be representative of the general population. Future studies should develop specific strategies to stimulate enrollment of under-represented populations in such clinical trials and increase generality of findings. In addition, the Age-Well RCT is interested in assessing the effects of the interventions on brain structure and function and investigating the mechanisms underlying these effects. Future studies could focus on estimating impact on clinical outcomes such as conversion to mild cognitive impairment or dementia using comparative trials with a sufficient duration of follow-up.

The results of the Age-Well RCT are expected to further the understanding of the factors preventing and delaying age-related diseases and disabilities to promote healthy aging and older adults' well-being and to propose innovative therapeutic approaches. Our objectives are expected to reduce stress, to improve the maintenance of cognitive abilities and the regulation of emotion in older adults through meditation practice, to establish a preventive strategy favoring the emotional dimension of healthy aging and to reduce the negative impact of mental conditions and disorders. The Age-Well RCT, and Medit-Ageing at large, should help shape and optimize future lifestyle-based and meditation-based clinical trials and facilitate the integration of meditation practice into existing and future prevention programs and clinical interventions in older people. Future trials would be needed to confirm the long-term clinical impact on aging populations.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.trci.2018.10.011.

RESEARCH IN CONTEXT

1. Systematic review: We reviewed previously published literature and existing randomized controlled trials (RCTs) in the fields of aging, prevention of dementia or Alzheimer's disease, and nonpharmacological interventions from PubMed and clinicaltrials.gov. Previous RCT-evaluated individualized programs of physical activities or technology-based solutions to improve the quality of life of older people. The largest ongoing nonpharmacological prevention RCT use multidomain interventions simultaneously targeting various vascular and lifestyle-related risk factors.
2. Interpretation: Age-Well is the first RCT in aging to propose a long-term intervention addressing the plasticity of emotional and cognitive dimensions during aging. It will assess the effects and mechanisms of a long-term meditation-based intervention compared with a foreign language training and a passive control condition on behavioral, neuroimaging, sleep and biological blood markers of mental health and well-being in the aging population.
3. Future directions: The Age-Well clinical trial might facilitate the integration of meditation practice and foreign language learning into existing and future preventive programs in older people and contribute to the design of larger multinational prevention RCTs.

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6.2. Protocole SCD-Well (Marchant et al., 2018)

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Alzheimer's & Dementia

Featured Article

The SCD-Well randomized controlled trial: Effects of a mindfulness-based intervention versus health education on mental health in patients with subjective cognitive decline (SCD)

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Abstract

Introduction: Subjectively experienced cognitive decline in older adults is an indicator of increased risk for dementia and is also associated with increased levels of anxiety symptoms. As anxiety is itself emerging as a risk factor for cognitive decline and dementia, the primary question of the present study is whether an 8-week mindfulness-based intervention can significantly reduce anxiety symptoms in patients with subjective cognitive decline (SCD). The secondary questions pertain to whether such changes extend to other domains of psychological, social, and biological functioning (including cognition, self-regulation, lifestyle, well-being and quality of life, sleep, and selected blood-based biomarkers) associated with mental health, older age, and risk for dementia.

Methods: SCD-Well is a multicenter, observer-blinded, randomized, controlled, superiority trial, which is part of the Horizon 2020 European Union-funded "Medit-Ageing" project. SCD-Well compares an 8-week mindfulness- and compassion-based intervention specifically adapted for older

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T.B. has received honoraria for workshops on mindfulness-based interventions and is the co-author of a book on mindfulness-based cognitive therapy. All other authors declare that they have no competing interests.

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adults with SCD with a validated 8-week health education program. Participants were recruited from memory clinics in four European sites (Cologne, Germany; London, United Kingdom; Barcelona, Spain; and Lyon, France) and randomized with a 1:1 allocation, stratified by site.
Results: The primary outcome, change in anxiety symptoms, and secondary outcomes reflecting psychological, cognitive, social, and biological functioning are assessed at baseline, postintervention, and 4 months after the end of the intervention.
Discussion: The study will provide evidence on whether a mindfulness-based intervention can effect changes in anxiety and other risk factors for cognitive decline and dementia in older adults with SCD and will inform the establishment of intervention strategies targeted at improving mental health in older adults.
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Keywords: Dementia; Meditation; Subjective cognitive decline; Alzheimer's disease; Anxiety; Cognition; Emotion; Mindfulness; Compassion; Psychoeducation; Medit-Ageing; Silver Santé Study

1. Introduction

1.1. Background

Owing to aging populations, incidence of dementia is estimated to triple by 2050, representing the greatest challenge for health care in the 21st century [1]. In addition to affecting the individual living with dementia, there are considerable consequences for wider society given the associated emotional, health, and social care costs. Effective approaches to treating the underlying illnesses that cause dementia are still largely absent, thus emphasizing the need for prevention.

Most neuropathological processes start years before the onset of dementia [2,3]; hence, there is a growing need to target modifiable risk factors in individuals in the earliest stages for intervention when neurodegeneration is still limited [4]. In support of advancing preventative strategies, research shows that approximately a third of dementia cases worldwide might be attributable to potentially modifiable risk factors [5]. Indeed, the risk of dementia increases when adverse factors, including anxiety, depression, stress, and sleep disturbances, are present. Sleep disorders are known to promote dementia-related pathological processes [6], and in older adults, each depressive symptom increases dementia risk by approximately 20% [7]. Importantly, longitudinal studies show that anxiety increases the rate of cognitive decline in individuals at risk of dementia [8], and a recent meta-analysis implicated late-life levels of anxiety symptoms as a predictor of dementia [9]. Increasing evidence supports that subjectively experienced cognitive decline, even when performance on cognitive tests is in the normal range, is also associated with an increased risk for future cognitive decline and dementia [10,11]. A high level of anxiety is a characteristic feature of patients living with subjective cognitive decline (SCD) [12], which may further exacerbate risk for dementia and reduced well-being.

1.2. Mindfulness-based intervention

Although mindfulness-based research in older adults is still in its infancy, there is considerable evidence that these interventions can reduce anxiety in a number of populations, including preliminary studies in older adults [13,14]. Mindfulness-based interventions (MBIs), derived from the generic mindfulness-based stress reduction program developed by Dr. Jon Kabat-Zinn [15], combine intensive training in mindfulness meditation with psychoeducational components and provide individuals with sustainable skills that remain at their disposal beyond the intervention period. MBIs use a secular form of meditation training that emphasizes focused, nonjudgmental awareness of present moment experiences. Participants typically meet for weekly group-based sessions for 8 weeks and engage in home practices between sessions.

In addition to reducing anxiety, promising evidence also shows that MBIs improve cognitive function in areas most sensitive to aging and dementia (such as attention and memory) [16,17]. Further research shows that these interventions can reduce stress, depression, insomnia, feelings of loneliness, and social exclusion [14,18,19], as well as cardiovascular risk factors [20]—all of which are associated with increased risk for dementia [21,22]. Indeed, recent evidence suggests that an MBI altered levels of a blood-based biological marker associated with both stress and dementia in at-risk older adults [23]. Importantly, mindfulness-based training is a scalable, community-based, and low-cost intervention that is broadly available.

1.3. Choice of comparator

Many of the previous studies of MBIs have suffered from a lack of an adequate comparison condition and lack of follow-up to know whether initial benefits are maintained. As MBIs contain a number of nonspecific elements, such as social interaction, light exercise, or the provision of treatment expectancies, the use of active control or comparison interventions is important. Based on the assumption that training in mindfulness is the crucial active component of the intervention and to control for effects due to other aspects of the program, we selected a health education program as the comparison condition. The health education

program is structurally equivalent to the mindfulness-based training in overall course length, class time and home activities, and matched to the training in administration, dosage, and duration. It is a facilitator-led, group-based program, based on a published book [24], and developed and validated in an SCD population by colleagues in the United States [25]. The program was designed to equalize treatment expectancy across conditions, parallel psychoeducational components, and to control for the nonspecific effects of increased social interaction and light physical activity. Moreover, the health education program may have a positive impact on well-being in the SCD population by fostering self-efficacy. Participants with SCD and comorbid clinical anxiety and/or depression in the trial by Wetherell et al. believed this program was a credible intervention and showed nonsignificant improvements in memory, as expected in a comparison condition [25]. However, participants in this condition did not show significant improvement in anxiety symptoms compared with those in the mindfulness-based condition [26].

1.4. Trial objectives and purpose

The SCD-Well trial is part of the "Medit-Ageing" project (public name: Silver Santé Study; www.silversantestudy.eu) funded through the European Union as part of the Horizon 2020 program. SCD-Well will use an MBI that is specifically tailored to the needs of older adults building on modifications suggested by Zellner Keller et al. [27] together with a particular focus on compassion and loving kindness practices. This upgrade takes into account emerging clinical evidence showing a complementary and beneficial role of this style of meditation on anxiety and depression [27–30].

The primary objective of the trial is to test whether an 8-week MBI is superior to an 8-week health education program on reducing anxiety in older adults with SCD in a multicenter randomized controlled trial. We will further examine whether any changes in anxiety symptoms are maintained 4 months after the end of the intervention, and whether the intervention affects a series of outcomes including mental health and cognitive functions, social relations, and biological markers.

2. Methods/design

2.1. Trial design and setting

SCD-Well is a European multicenter, observer-blind, randomized, controlled, superiority trial with two parallel groups: an MBI or a validated health-educational program. The trial includes 8 weeks of intervention and 16 weeks of follow-up (total of 24 weeks) and is designed to compare outcomes from the two intervention groups. The intervention takes place in group settings at four sites, and randomization is performed with a 1:1 allocation, stratified by study site. The study schedule is summarized in Table 1, and detailed descriptions of participant visits are provided in Supplementary Material 1. Briefly, participants are recruited from medical facilities, prescreened, and then invited to a screening visit (V0) where the diagnostic battery is performed (Table 2) and eligibility is assessed. Participants fulfilling eligibility criteria (Table 3) are invited to the baseline visit (V1) and then randomized to one of the two intervention groups. Allocation and assignment of interventions are described in Supplementary Material 1. A postintervention visit (V2) is conducted after the end of the intervention, and a follow-up visit (V3) is held 4 months after the end of the intervention. The primary outcome is change in symptoms of anxiety from V1 to V2. For secondary outcomes, treatment effects are assessed as change from V1 to V2 or V3.

Participants are recruited from medical facilities (e.g., memory clinics) at the four centers where the trial assessments and delivery of the interventions take place (London, UK; Cologne, Germany; Lyon, France; Barcelona, Spain). More detail about the sites is provided in Supplementary Material 1. Participants are patients who are either referred to a memory clinic by a physician or who are self-referrals.

2.2. Data collection

Validated behavioral measures chosen for their sensitivity to aging and early dementia and/or meditation were selected for the trial (see Supplementary Table 1 for details). Briefly, behavioral measures include neuropsychological tests that assess different cognitive functions (e.g., episodic memory, attention, executive function) and questionnaires that include assessments of personality traits; sleep quality; lifetime and current engagement in cognitive, social, and physical activities; Mediterranean diet adherence; health-related behaviors such as self-medication, smoking and alcohol consumption; quality of life and well-being; and mental health indicators such as anxiety and depression and loneliness. Some questionnaires are also given to a participant's close relative or friend (subsequently referred to as the "partner"). Behavioral measures and blood sampling are conducted at V1, V2, and/or V3. Details regarding the collection of blood specimens can be found in Supplementary Material 2.

To standardize the administration and scoring of neuropsychological tests and questionnaires, psychometrists from all sites completed a standardized administration and scoring training that was developed specifically for the study.

2.3. Interventions

The *MBI* uses meditation and yoga practices adapted for older adults [27] and, in line with the standard format of mindfulness-based stress reduction, consists of a pre-class meeting with the facilitator in which the participants are socialized to the treatment, eight weekly group-based sessions of 2 to 2½ hours duration, a half-day of meditation practice after the sixth session of the program (9 sessions

Table 1
Study schedule

Schedule of events	Screening V0	Baseline assessment and randomization V1	Intervention period (8 weeks)	Postintervention assessment V2	4-month follow-up assessment V3
Enrollment					
Eligibility screen	X	X			
Oral and written information	X				
Signed informed consent		X			
Randomization		X			
Assessments					
Baseline characteristics		X			
Primary outcome					
State-Trait Anxiety Inventory (STAI)		X		X	X
Secondary and exploratory outcomes (see Supplementary Table 1 for detailed measures)					
Medical background		X		X	X
Global cognition		X		X	X
Thinking and reasoning				X	
Attention/executive function		X		X	X
Memory		X		X	X
Language		X		X	X
Psychoaffective/emotion		X		X	X
Compassion, support, mindfulness		X		X	X
Sleep		X		X	X
Personality		X			
Lifestyle		X		X	X
Quality of life and well-being		X		X	X
Biological measures		X		X	X
Partner questionnaires		X		X	X
Intervention					
Mindfulness-based intervention			◆———		
Health education program			◆———		
Completion of workbook/questionnaires to monitor intervention adherence and response			◆———		

X indicates that the event occurred during that time in the study schedule. The symbol in question indicates that the intervention period was ongoing for 8 weeks.

in total), and home practices. The intervention combines intensive training in mindfulness and compassion meditation and gentle yoga practices with psychoeducational components targeted at helping individuals to deal more effectively with emotional difficulties and stressors commonly encountered in older age, particularly stressors related to concerns about cognitive functioning and health. The program has a particular emphasis on cultivating wholesome attitudes toward oneself and others. Meditation and yoga practices focus on strengthening attentional capacities and bodily awareness during the first half of the program. Practices in the second half of the program build on these skills to establish more effective ways of responding to difficult experiences. Participants are asked to engage in home practice for approximately an hour per day, 6 days per week. Home practice consists of formal meditation practices guided by meditation recordings and informal practices aimed at helping participants to generalize mindfulness skills to their daily life. Participants receive a workbook that explains the home practices and that is used to record adherence to them.

Table 2
Diagnostic battery

Domains evaluated	Tests
Global cognitive functioning	Cognitive assessment according to site-specific memory clinical standards to diagnose SCD (if needed) MMSE [31]
Depression and anxiety	Standardized questions to assess generalized anxiety and major depression (DSM-5 [32]/ICD-10 checklist [33][p10])
SCD criteria	Meets research criteria for SCD [11]
Memory concern	Expressed concern about memory (either by visiting a memory clinic or assessed via a question at screening)

Abbreviations: DSM-5, Diagnostic and Statistical Manual of Mental Disorders, fifth edition; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; MMSE, Mini–Mental State Examination; SCD, subjective cognitive decline.

The *health education control* intervention follows the same format and structure as the MBI and is matched to

Table 3
Eligibility criteria

Inclusion criteria	Exclusion criteria

• Aged ≥60 years.
• Meets research criteria proposed by the SCD-I working group [11].
• Performance within the normal range on standardized cognitive tests already administered at each site as part of standard clinical assessments according to research criteria based on those defined by Jak and Bondi [34,35] for exclusion of MCI as recommended by Molinuevo et al. [36].
  • Participants are excluded if they score below the normative range on two tests within a single cognitive domain (i.e., memory, executive function, language) or if they score below the normative range on one test within each cognitive domain.
  • Results from prespecified tests in memory, executive function, and language from the baseline cognitive assessment are examined as an additional check to ensure comparable cognitive performance across sites using the same measures and criteria.
• Being referred to the memory clinic by a physician or self-referral because of memory concerns.
• Ability to provide informed consent in accordance with International Conference on Harmonization of Good Clinical Practice (GCP/ICH) guidelines and local regulations.
• Stating that they are available for the trial duration (39 weeks).
	• Presence of a major neurological or psychiatric disorder (including anxiety disorders, major depressive disorder, or an addiction to alcohol or drugs) according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision [33] and/or Diagnostic and Statistical Manual of Mental Disorders, fifth edition [32] criteria.
	• Under legal guardianship or incapacitation.
	• History of cerebral disease (vascular, degenerative, physical malformation, tumor, or head trauma with loss of consciousness for more than an hour), which interferes with the aims of the study protocol.
	• Visual or auditory impairment sufficient to interfere with the aims of the study protocol.
	• Presence of a chronic disease or acute unstable illness (respiratory, cardiovascular, digestive, renal, metabolic, hematologic, endocrine, or infectious), which interferes with the aims of the study protocol.
	• Current or recent medication that may interfere with cognitive action (psychotropic, systemic corticosteroid, anti-Parkinson's, or analgesic drugs). The interfering nature of the different treatments is at the discretion of the investigating doctor.
	• Regular or intensive practice of meditation or comparable practices (yoga, Qigong, Alexander technique), that is, more than 1 day per week for more than 6 months consecutively over the last 10 years, intensive practice (internship or retreat > five consecutive days) over the past 10 years, or more than 25 days of retreats (cumulatively) before the last 10 years.

the MBI in administration, dosage, and duration. More specifically, it consists of a pre-class meeting with the facilitator, eight weekly group-based sessions of 2 to 2½ hours duration, a half-day of practice after the sixth session of the program (9 sessions in total), and home practices. The treatment is based on a published manual [24], with every session of the program covering different subjects, including self-management; problem-solving; sleep; stress; exercise; managing medicines and memory; communicating with family, friends, and health care professionals; eating; weight management; and planning for the future. Participants are provided with information about these subjects and engage in group exercises and discussions about them. They are given a workbook and asked to actively engage in activities described in the workbook to improve health and well-being on 6 days each week, matching home assignments in the MBI. The workbook summarizes the most important points of each session, and participants are asked to record engagement in health-related activities on protocol sheets in the workbook.

Each site has two facilitators, each with a psychology/psychotherapy degree and/or significant experience in leading group-based therapies. One facilitator, who has undergone formal training to match criteria of the good practice guidelines of the UK network of mindfulness-based teacher trainers, delivers the MBI. The other facilitator who has at least 3 years' experience leading group-based clinical programs and/or psychoeducational interventions (e.g., a clinical psychologist or equivalent) leads the health education intervention. Both sets of facilitators received the intervention protocol, instruction, and a day-long training about their respective intervention before the start of the study to promote standardization of the intervention delivery across sites. To document manual adherence, facilitators of both interventions complete self-report checklists after each class. Facilitators are supervised in weekly individual sessions by the intervention leads. The two interventions are delivered to groups of approximately 10 participants and take place in a designated room at the memory clinic or investigator-affiliated facility.

After the first session of the intervention, participants of both intervention groups complete a questionnaire to record their expectations for the credibility and efficacy of their intervention [37]. They also report levels of depression over the past week at the beginning of each intervention session. Participants are also encouraged to record any important comments they might have about the practice to provide qualitative information. Adherence (i.e., class attendance) is collected by facilitators. Participants who choose to drop out of the intervention are invited to continue taking part in assessments.

2.4. Outcomes

Given its prevalence in SCD and relation to objective cognitive decline and dementia risk, the primary outcome is the mean change in anxiety from V1 to V2, in each group.

Mean change in anxiety will be measured by the trait version of the State-Trait Anxiety Inventory (STAI) [38]. We had initially intended to use the state version of the STAI as a primary outcome but took the decision to use the trait version for two reasons—(1) the state version assesses transient anxiety symptoms that are more susceptible to situational variation and (2) intermediate reports indicated floor effects of baseline data for the state, but not the trait-STAI, potentially due to entry to treatment in the trial. Trait-STAI scores are more representative of a person's general level of anxiety and less dependent on situational factors, which may not be fully standardized across sites. Previous research has shown that increased trait anxiety is a characteristic of SCD samples [39]. The change in primary outcome measure from state-STAI to trait-STAI was approved by the Trial Steering Committee, before any statistical analyses. Although trait-STAI will be the primary outcome of this trial, the effects of the interventions on state-STAI will be assessed as a secondary outcome. Other secondary outcomes include

- mean change in anxiety (measured by the trait-STAI) from V1 to V3,
- mean change in behavioral measures (see Supplementary Table 1 for specific outcomes) observed (a) from V1 to V2 and (b) from V1 to V3,
- mean change in blood-based markers of stress and dementia risk observed (a) from V1 to V2 and (b) from V1 to V3,
- change in mean numbers of visits to general practitioners/medical doctors and the medication use during and after the intervention, and
- mean changes in measures of emotions/psychoaffective functioning, compassion, support, and mindfulness assessed by partners of participants.

Moderator analyses will establish whether factors including sex, personality characteristics, genetic phenotypes, general thinking and reasoning skills, and life experiences and diet affect the outcomes of the intervention. Study data will also be used for exploratory analyses unrelated to the intervention.

2.5. Statistical considerations

2.5.1. Sample size

As the STAI anxiety score has no absolute cutoff levels, sample size consideration is based on effect size (i.e., the ratio between the expected interarm differences to the common standard deviation). With a minimum effect size of 0.50 (indicated as a reasonable expectation from a meta-analysis summarizing the efficacy of meditative therapies for reducing anxiety) [13], 64 participants per arm need to be included to demonstrate a significant difference in the primary endpoint (mean difference in the change of the trait-STAI score in each trial arm between baseline and the end of the intervention) in a t-test with 80% power and a two-sided type I error of 5%. As the minimum relevant effect size was considered to be the same for the state- and trait-STAI, sample size remained unchanged after the change of the primary endpoint.

2.5.2. Statistical methods

The planned statistical analyses are described in a trial statistical analysis plan and summarized in Supplementary Material 1. Briefly, the primary outcome analyses will be conducted on an intent-to-treat principle, and missing primary endpoint data will be handled with a conservative a "missing = failure" strategy. Additional analyses conducted on both primary and secondary outcomes will include sensitivity analyses, undertreatment and per protocol analyses, and analyses of exposure/dose effects. For exploratory non-comparative analyses, complete case analyses or imputation methods will be considered on a case-by-case basis, depending on the amount of missing data and the specific research question.

2.6. Ethics, safety, and study monitoring

The SCD-Well trial was approved by the necessary ethics committees and regulatory agencies in London, UK (Queen Square Research Ethics Committee and Health Research Authority); Lyon, France (Comité de Protection des Personnes CPP Sud-Est II Groupement Hospitalier and Agence Nationale de Sécurité du Médicament et des Produits de Santé); Cologne, Germany (Ethikkommission der Medizinischen Fakultät der Universität zu Köln); and Barcelona, Spain (Comité Etico de Investigacion Clinica del Hospital Clinic de Barcelona), registered on ClinicalTrials.gov (Identifier: NCT03005652), and adheres to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines for clinical trial protocols [40] (see Supplementary Material 1 for further details and Supplementary Table 2 for SPIRIT checklist).

The sponsor established a Trial Steering Committee according to Good Clinical Practice guidelines with the responsibility to provide oversight on the conduct of the trial, advise on scientific credibility on behalf of the sponsor and the funder, and assess the progress of the protocol. More details on data management, monitoring, dissemination and access, and study governance (blinding, safety, auditing) are contained in the Supplementary Material 1.

3. Discussion

The primary aim of the SCD-Well study is to establish whether an 8-week MBI as compared to 8-week health education training can reduce anxiety levels in older adults with SCD. This will be assessed through the use of a multicenter randomized superiority trial. As anxiety symptoms are not

only prevalent among patients with SCD [12,41] but may also represent a risk factor for dementia [8,21,42], this study aims to provide an initial step toward testing the potential of mindfulness-based training as a new form of intervention to improve well-being and prevent cognitive decline and ultimately delay the onset of dementia. Furthermore, the study is aimed at providing rigorous evidence regarding the immediate and sustained effects of mindfulness training on a range of other psychological and biological factors that are indicators of health, well-being, and cognitive functions.

3.1. Practical issues

The SCD-Well trial is conducted in several countries with the aim of establishing whether an MBI is broadly applicable for older persons with SCD. However, if there are strong cultural differences in the response to the training, this could increase the heterogeneity across sites in the overall expected effect. Analyses of responder characteristics could help to address such biases in future studies. We have excluded participants with anxiety levels reaching clinical significance to limit potential confounding from psychiatric illness, but we have not set a lower limit for anxiety levels as it is well documented that anxiety is a common symptom in people with SCD. This criterion does however create the possibility that we may not detect an effect of the intervention because of participants' low levels of baseline anxiety symptoms.

Although this study benefits from a 4-month follow-up assessment to examine whether any changes due to the intervention are maintained, future studies would profit from still longer-term follow-up assessment(s), which could examine the duration of possible effects and include monitoring of conversion to dementia. Finally, we have included an active comparison condition that will be used to examine whether mindfulness-based training confers a specific advantage over another form of behavioral intervention; however, we did not include a passive control condition due to recruitment and financial constraints. If no difference is found between the mindfulness-based and comparison interventions, it will therefore be difficult to show whether this is because neither or both were effective at reducing anxiety.

3.2. Operational issues

Although great care was taken in the conceptualization and preparation of the SCD-Well trial, there are some operational issues that are inherent in the dependent measures. First, the main endpoint, anxiety, is only assessed through a questionnaire and is thus not blinded to the allocated intervention. Although the employed questionnaire has been extensively validated, our endpoint relies on participants' capacity to give an accurate report of their anxiety levels. To complement potential biases through self-reports in relation to our secondary objectives, participants' partners (for example, spouses, children, neighbors, close friends) are also invited to fill in a set of questionnaires. A second operational issue is encountered by the fact that we only have few objective risk markers for dementia (e.g., apolipoprotein E [*APOE*] ε4 genotype, hypertension) and that neuroimaging-based dementia markers (such as β-amyloid levels, hippocampal volume) are not collected in this study due to feasibility and cost issues. Those measures will, however, be collected in the AGE-Well Study, which is also part of the Medit-Ageing project. Despite minimal collection of biomarkers, we will store whole blood and plasma samples for future analyses as novel blood-based biomarkers are found and refined and will make use of a number of behavioral and psychiatric risk factors that will be measured in SCD-Well (e.g., depressive symptoms, poor sleep).

In summary, the SCD-Well study aims to test whether mindfulness-based training can be regarded as an alternative approach to reduce anxiety and maintain mental health and well-being in older age. If mindfulness-based training can promote healthy aging in people with SCD, it will offer a novel and alternative therapeutic and preventive approach for a population who currently lacks treatment options.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.trci.2018.10.010.

RESEARCH IN CONTEXT

1. Systematic review: Older adults with subjective cognitive decline (SCD) report concerns about self-perceived cognitive decline but appear normal on assessment. SCD is associated with increased risk for dementia and also increased anxiety symptoms. Database searches for clinical trials indicate that few nonpharmacologic interventions have been trialed for patients with SCD, and those that have are often unicentric, small, have no active control condition, and/or no longitudinal follow-up.
2. Interpretation: SCD-Well is the first large-scale, multicountry randomized controlled trial with a long-term follow-up in older adults with SCD. It assesses for the first time the effects of an 8-week mindfulness-based intervention compared to a health education program on anxiety symptoms and measures of psychological, cognitive, social, and biological functioning.
3. Future directions: SCD-Well will provide evidence on whether a mindfulness-based intervention can reduce anxiety and other dementia risks. It will inform future trials and strategies to improve mental health and prevent cognitive decline in SCD.

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6.3. La méditation dans le vieillissement (Moulinet et al., 2018)

Article de synthèse

Rev Neuropsychol

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La méditation dans le vieillissement : impact sur le bien-être, la cognition et le cerveau de la personne âgée

Meditation and ageing: potential impact on well-being, cognition and brain integrity of older adults

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Résumé

Dans le contexte du vieillissement de la population, augmenter l'espérance de vie en bonne santé est une priorité. Un entraînement mental à la régulation de l'attention et des émotions *via* la méditation pourrait s'avérer particulièrement bénéfique en ciblant notamment les aspects émotionnels du vieillissement. Cet article de synthèse présente les résultats des premières études ayant investigué les effets de la pratique de la méditation chez le sujet âgé, dans différents domaines impactés dans le vieillissement tels que les facteurs psychoaffectifs, la cognition, ainsi que l'anatomie et le fonctionnement cérébral. Ces études montrent dans l'ensemble un impact bénéfique de la méditation sur ces différents domaines, avec une réduction du stress, de l'anxiété, des symptômes dépressifs et des troubles du sommeil, une amélioration des performances cognitives et des modifications cérébrales. Cependant, ces études préliminaires présentent un certain nombre de limites. Des essais cliniques contrôlés et randomisés, portant sur des groupes de taille suffisante, et intégrant des mesures complémentaires des effets et de leurs substrats sont donc nécessaires. Le programme de recherche européen Medit-ageing a été développé dans ce cadre pour mieux comprendre les mécanismes de la méditation ainsi que ses bénéfices dans le contexte du vieillissement.

Mots clés : méditation • vieillissement • cognition • neuro-imagerie • mode de vie

Abstract

As the population is ageing, expanding the healthy life years is a priority. Mental training for emotion and attention regulation through meditation practice could be particularly beneficial, especially as it targets the emotional dimension of ageing. This review article describes the results of the first studies investigating the effects of meditation practice in elderly participants, especially on aspects known to be impacted by ageing such as psycho-affective factors, cognition, and brain structure and function. These studies generally show a beneficial impact of meditation on these different areas, with a reduction of stress, anxiety, depressive symptoms and sleep disorders, as well as an improvement of cognitive performances and brain changes. However, these preliminary studies have several limitations. Randomized controlled clinical trials including large samples, an active control condition and complementary measures of the effects of meditation and their substrates are therefore necessary. The European research program Medit-ageing has been developed in this context to better understand the impacts of meditation and their underlying mechanisms in the ageing population.

Key words: meditation • ageing • cognition • neuroimaging • lifestyle

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Introduction

La population mondiale vieillit rapidement, du fait de l'augmentation de l'espérance de vie mais aussi du vieillissement de la génération des *baby boomers* dans les pays développés. On observe donc à la fois une augmentation du nombre des seniors, qui atteindrait 1,4 milliard en 2030 selon l'OMS, et une augmentation de leur proportion dans la population.

Il est nécessaire que cette augmentation de l'espérance de vie s'accompagne d'un maintien de la qualité de vie et de la santé. En effet, le vieillissement s'accompagne de modifications cognitives et cérébrales, ainsi que d'une diminution de la qualité du sommeil. Ces facteurs, associés à des symptômes de stress, d'anxiété ou de dépression, diminuent la qualité de vie des seniors et augmentent le risque de développer une démence telle que la maladie d'Alzheimer [1, 2]. Face à ce constat et aux conséquences socioéconomiques qui en découlent, des mesures favorisant un vieillissement en bonne santé et prévenant une perte d'autonomie deviennent des enjeux majeurs dans notre société.

Le vieillissement biologique n'est pas lié de façon absolue au vieillissement chronologique. Des études ont montré que la modification de certaines habitudes de vie, telles qu'une alimentation saine ou une activité physique régulière, pourrait favoriser le bien-vieillir, notamment cognitif et cérébral, et réduire ainsi le risque de développer certaines maladies liées à l'âge telles que les maladies neurodégénératives [1, 3]. Le bien-être psychologique, encore très peu considéré dans les mesures de prévention sanitaire, jouerait pourtant un rôle protecteur dans le maintien de la santé, et prendrait davantage d'importance à un âge avancé où la prévalence des maladies chroniques est plus élevée [3, 4]. Dans ce contexte, les chercheurs s'intéressent à la réduction du stress et à la régulation des émotions et de l'attention, *via* un entraînement à la méditation, afin d'améliorer le bien-être et la santé – mentale et physique – des personnes âgées.

Dans cette revue de la littérature, nous présenterons brièvement les modifications liées à l'âge et les facteurs de vie contribuant à un vieillissement en bonne santé. Nous détaillerons ensuite les résultats des études ayant évalué l'impact de la méditation sur les facteurs psychoaffectifs et de bien-être, ainsi que sur la cognition, avant d'aborder les modifications cérébrales, anatomiques et fonctionnelles, associées à cette pratique. Nous nous intéresserons principalement aux résultats obtenus chez le sujet âgé, même si certains résultats obtenus chez le sujet jeune seront également discutés. Pour finir, nous discuterons des limites des études précédentes, et des perspectives de ce domaine de recherche encore novateur.

Vieillissement

Modifications psychoaffectives, cognitives et cérébrales liées à l'âge

Le vieillissement est un processus physiologique naturel associé à de nombreuses modifications à la fois émotionnelles, cognitives, anatomiques et fonctionnelles.

Le vieillissement s'accompagne de perturbations pouvant avoir un impact négatif sur le bien-être et la santé mentale. Ainsi, environ 50 % des personnes âgées ont des problèmes de sommeil, tandis que la dépression touche 10 à 15 % des plus de 60 ans. Des études suggèrent que les symptômes anxieux et dépressifs pourraient être sous-diagnostiqués dans les populations âgées, notamment parce que les seniors semblent moins susceptibles d'exprimer leurs émotions négatives que les plus jeunes. Les personnes âgées pourraient également avoir des sujets d'inquiétude différents, plus orientés par exemple vers leur santé ou leur autonomie [5]. Les perturbations du sommeil et de l'humeur entraînent à leur tour une accélération du déclin cognitif normal, un risque de démence plus élevé, et, de façon plus générale, une détérioration de la santé physique et mentale chez les seniors [4].

Les changements cognitifs font partie du processus normal de vieillissement. Certaines fonctions cognitives sont préservées, telles que le langage et la mémoire sémantique, tandis que d'autres déclinent avec l'âge. Les fonctions les plus sensibles au vieillissement sont les fonctions exécutives, l'attention et la vitesse de traitement des informations. Le vieillissement est alors associé à une diminution de la capacité de résolution de problèmes ainsi que du traitement et de l'apprentissage de nouvelles informations. Il est à noter que la plainte cognitive la plus courante chez le sujet âgé est la plainte de mémoire. Une diminution des performances en mémoire épisodique est effectivement retrouvée dans le vieillissement, reflétant des difficultés de récupération de l'information. De façon générale, le vieillissement cognitif se caractérise par un maintien de l'intelligence cristallisée, c'est-à-dire les connaissances et l'expérience, et un déclin de l'intelligence fluide, c'est-à-dire le raisonnement et la résolution de problème [6].

D'un point de vue cérébral, les études *post-mortem* et en imagerie par résonance magnétique (IRM) structurale ont révélé au cours du vieillissement une atrophie générale de 0,4 à 0,5 % de tissu cérébral par an. Cette atrophie se traduit par une diminution de volume et de poids du cerveau, ainsi que par une expansion ventriculaire et un élargissement des sillons [7]. L'amplitude de l'atrophie diffère en fonction des régions, les plus touchées étant les régions frontales, préfrontales, temporales et pariétales médianes [8]. Ces modifications cérébrales, notamment l'atrophie importante du cortex préfrontal et la préservation du cortex

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occipital, sont cohérentes avec les changements cognitifs observés dans le vieillissement [3]. En plus de ces modifications anatomiques, le vieillissement s'accompagne d'une diminution du métabolisme cérébral du glucose mesuré en tomographie par émission de positons (TEP) avec le traceur FDG (^{18}F-fluorodésoxyglucose). Les régions cérébrales concernées sont similaires à celles touchées par l'atrophie, incluant notamment le cortex frontal, le cortex cingulaire antérieur et moyen et l'insula [9]. En termes fonctionnels, une diminution de la connectivité des régions du réseau du mode par défaut (RMD), ainsi que du désengagement de ce réseau durant des tâches cognitives, a été observée avec l'âge. Le RMD est un réseau fonctionnel actif pendant les états mentaux dirigés vers soi, tels que les états introspectifs, la mémorisation et la planification, qui a tendance à se désengager au cours de tâches cognitives notamment attentionnelles [10]. Un défaut de désengagement de ce réseau pendant ce type de tâches est associé à de moins bonnes performances cognitives et pourrait refléter un vagabondage de l'esprit. Ce réseau semble atteint à la fois structurellement et fonctionnellement au cours du vieillissement normal. En effet, les régions composant ce réseau font partie de celles qui présentent les taux d'atrophie les plus élevés par an [8]. Elles présentent également une diminution de connectivité entre elles, au repos et durant des tâches cognitives, associée à de moins bonnes performances [7]. Préserver l'intégrité de ce réseau semble donc être un enjeu important dans le cadre du vieillissement.

En résumé, le vieillissement s'accompagne de nombreuses modifications cognitives et cérébrales. Favoriser le bien-vieillir, tant au niveau de la santé que du bien-être, représente un enjeu majeur autant pour l'individu (meilleure qualité de vie des seniors) que pour la société (diminution du coût des soins de santé), au vu du vieillissement de la population.

Facteurs de vie contribuant à un vieillissement en bonne santé

De plus en plus d'études reconnaissent l'influence non négligeable des facteurs environnementaux sur la santé mentale et physique. Elles suggèrent notamment qu'une modification du mode de vie contribuerait au vieillissement en bonne santé, en prévenant ou retardant le déclin cognitif et la survenue d'une démence telle que la maladie d'Alzheimer. Parmi ces facteurs de vie sont principalement retrouvées la pratique d'une activité physique régulière, la gestion des facteurs de risques cardiovasculaires (diabète, obésité, tabagisme et hypertension), une alimentation saine, ainsi que l'activité cognitive et sociale [2, 11]. Ainsi, un à trois millions de cas de maladie d'Alzheimer dans le monde pourraient être évités grâce à la réduction de 10 à 25 % de facteurs de risque, tels qu'un faible niveau d'éducation, l'inactivité physique, les facteurs de risques cardiovasculaires et la dépression [12].

Ces facteurs de vie pourraient jouer un rôle de protection ou de compensation *via* des mécanismes physiologiques et cérébraux qui ne sont pas encore clairement définis. Cependant, il semblerait que des modifications cérébrales à la fois structurales, métaboliques et fonctionnelles fassent partie de ces mécanismes [2, 13]. En effet, il a été montré que la pratique d'activités physique et cognitive, à un âge avancé, est associée à une augmentation du volume de substance grise dans des régions particulièrement vulnérables dans le vieillissement et la maladie d'Alzheimer, telles que les régions frontales et temporales, dont l'hippocampe [14]. De plus, un niveau d'éducation élevé chez le sujet âgé sain serait lié à une augmentation du volume de substance grise et du métabolisme du glucose spécifiquement dans le cortex cingulaire antérieur. L'augmentation de substance grise dans cette région est également associée à une connectivité fonctionnelle plus élevée entre cette dernière et l'hippocampe, ainsi que le cortex cingulaire postérieur, deux régions précocement atteintes dans la maladie d'Alzheimer [15]. Ces résultats semblent donc indiquer que l'enrichissement intellectuel précoce et tardif, ainsi que l'activité physique participent à des mécanismes de réserve cérébrale chez les personnes âgées sans déficit cognitif.

Plusieurs programmes de prévention, sous formes d'interventions non pharmacologiques (voir, par exemple, FINGER [16], MAPT [17] ou encore PreDIVA [18]) visent à modifier ces facteurs de vie chez le sujet âgé. Ces programmes couvrent surtout les domaines cognitifs, cardiovasculaires, alimentaires, sociaux et physiques identifiés, mais ne considèrent pas directement la sphère affective du vieillissement. Un entraînement mental tel que la méditation pourrait compléter ce type d'intervention en ciblant non seulement la régulation attentionnelle, mais aussi plus directement les facteurs psychoaffectifs.

Méditation et vieillissement

Brève définition de la méditation

La méditation fait partie intégrante de nombreuses traditions spirituelles et curatives depuis plus de 5000 ans. Le terme « méditation » englobe une large variété de pratiques, telles que la méditation zen, transcendantale, *vihangan*, *kirtan kriya*, ou encore la pleine conscience [19]. Dans ce qui suit, nous définissons la méditation comme une famille de stratégies complexes de régulation attentionnelle et émotionnelle cultivées à des fins diverses incluant le développement de l'équilibre émotionnel et du bien-être [20].

Parmi ces différentes pratiques de méditation, la méditation de pleine conscience est la plus étudiée [19]. La pleine conscience, ou présence attentive, consiste à développer une vigilance consciente de ses propres pensées, actions, émotions et motivations. Elle permet de reprendre le contrôle de ses pensées et d'éviter le « pilotage automatique », afin de ne pas laisser dériver ou ruminer ses pensées. En effet, cette pratique cible directement les

capacités de régulation attentionnelle et émotionnelle, qui sont particulièrement importantes dans le cadre du vieillissement. En pratique, cet entraînement consiste par exemple à se concentrer d'abord sur un objet spécifique (communément le cycle d'inspirations et d'expirations), jusqu'à ce que l'attention soit relativement stable. Ensuite, le méditant ouvre son champ d'attention (généralement par étapes) pour inclure, à la fin, tous les événements physiques et mentaux – les sensations corporelles, les pensées, les souvenirs, les émotions, les perceptions, les intuitions, les fantasmes – au moment où ils se présentent [21]. Il est crucial que cette méditation soit pratiquée avec une attitude d'acceptation sans jugement. Autrement dit, tout stimulus qui entre dans la conscience du méditant durant la pratique de la pleine conscience, tel que les perceptions, les pensées, les émotions ou les sensations, est observé soigneusement mais n'est pas jugé bon ou mauvais, vrai ou faux. Toutes les pensées sont traitées de la même façon, elles sont simplement notées au moment où elles apparaissent. Ainsi, la pleine conscience est l'observation sans jugement du flux continu de stimuli internes et externes à mesure qu'ils se présentent [21, 22].

Ainsi, bien qu'elle tire son origine de pratiques religieuses telles que le bouddhisme, la méditation s'est inscrite dans le domaine scientifique et culturel occidental sous une forme laïque dès le début des années 1980, grâce au chercheur américain John Kabat-Zinn [21]. En effet, ce chercheur a développé un programme standardisé de méditation de pleine conscience de huit semaines, le *Mindfulness-Based Stress Reduction* (MBSR) ayant pour but de réduire le stress dû notamment à la maladie, aux douleurs chroniques et aux traitements pénibles [21]. Cette méthode a ensuite été adaptée pour d'autres applications cliniques, telles que la thérapie cognitive basée sur la pleine conscience (TCBPC), qui couple la méditation de pleine conscience à une thérapie cognitivocomportementale, dans un but de prévention des rechutes dans le cas d'épisodes dépressifs [22].

L'impact de la méditation a tout d'abord été étudié, au moyen de ces programmes standardisés, dans le cadre de pathologies telles que les douleurs chroniques, l'anxiété généralisée, ou encore la boulimie, puis chez des populations non cliniques. Les résultats positifs observés ont ensuite encouragé les chercheurs à s'intéresser à cette méthode dans le vieillissement normal, notamment pour la prévention des pathologies liées à l'âge [22]. Dans cet article de synthèse, nous parlerons principalement de la méditation de pleine conscience, la plupart des études interventionnelles utilisant le protocole MBSR.

Impact de la méditation sur la santé mentale et le bien-être des personnes âgées

Comme décrit précédemment, les premières études sur l'impact de la méditation ont été réalisées à l'aide d'une intervention MBSR et se sont intéressées à son potentiel de régulation émotionnelle dans des populations cliniques [21]. Elles montrent une diminution de la détresse associée à la douleur et une amélioration de l'humeur chez des patients atteints de douleurs chroniques, ainsi qu'une amélioration des scores de dépression et d'anxiété dans des populations atteintes d'anxiété généralisée ou de troubles de panique [22].

Des études transversales indiquent que, chez les personnes âgées, une meilleure capacité à entrer dans un état de pleine conscience de façon naturelle (mesurée au moyen d'un score de « pleine conscience trait ») est associée à une amélioration du bien-être psychologique, qui est mesuré au moyen d'autoquestionnaires des symptômes dépressifs, de qualité de vie ou encore de stress [10]. Cette association serait médiée par la capacité de régulation des émotions dans cette population [10]. De façon générale, les études rapportent une amélioration du sentiment de bien-être grâce à la méditation de pleine conscience, que ce soit en montrant une corrélation entre score de pleine conscience trait et score de bien-être mesurés au moyen d'autoquestionnaires, ou dans des essais cliniques comportant une intervention MBSR. Ces scores de pleine conscience trait ont été associés à un meilleur équilibre affectif et moins de difficultés de régulation émotionnelle [23]. Différentes études montrent également une diminution du sentiment de solitude chez des seniors après une intervention MBSR, ainsi qu'une diminution de 50 % du nombre de seniors présentant une dépression et une anxiété cliniques significatives [10].

De façon générale, les résultats des différentes études, bien qu'encore préliminaires, suggèrent que la méditation réduit le stress, l'anxiété et les symptômes dépressifs, et diminue également les troubles du sommeil [4] dans des populations cliniques ou non cliniques. Cet effet bénéfique a été observé directement après une intervention de méditation mais aussi à l'issue de suivis (de 6 ou 36 mois) [22].

Impact de la méditation sur la cognition dans le vieillissement

La méditation permet la régulation des émotions, mais c'est également un entraînement mental, qui mobilise notamment les capacités attentionnelles. Les chercheurs se sont donc intéressés à l'impact d'une pratique de méditation sur la cognition.

La première étude sur l'effet de la méditation sur la cognition chez le sujet âgé a été menée en 1989 par Alexander *et al.* [24]. Une population de 73 seniors recrutés dans des maisons de retraite a suivi une intervention de 12 semaines dans différents groupes, répartis de façon aléatoire : deux groupes de méditation, un groupe de relaxation et un groupe témoin. Ces premiers résultats ont montré une amélioration significative des variables étudiées dans les deux groupes de méditation, par rapport aux autres groupes, notamment en termes de flexibilité mentale. Les auteurs suggèrent qu'un changement d'état de conscience au travers de techniques mentales pourrait médier les améliorations en termes de santé et de fonctionnement cognitif chez la personne âgée, qui ne sont pas unique-

ment explicables par la relaxation ou un effet placebo (*i.e.* effets espérés par les participants à l'étude). De plus, un suivi a montré que les effets observés dans l'étude étaient maintenus à trois ans chez plus de 85 % des sujets faisant partie des groupes de méditation. Cette étude présente des forces, telles que son caractère longitudinal et la répartition aléatoire des sujets dans les différents groupes d'études, mais également des limites. En effet, les effectifs sont réduits dans chaque groupe (11 à 20 sujets), et les groupes sont très hétérogènes (en termes d'autonomie et de degré d'atteinte cognitive). Cette étude est donc le précurseur de ce domaine de recherche, mais nécessite des investigations complémentaires pour pallier ses limitations.

Bien que l'étude d'Alexander *et al.* [24] suggère un impact positif de la méditation sur la cognition chez le sujet âgé, il a fallu plus de dix ans pour que de nouvelles études soient conduites dans ce domaine. Ces dernières tendent à mettre en évidence que la méditation, quel que soit le type de pratique, a un impact positif sur la cognition chez le sujet âgé. Il s'agit à la fois d'études transversales (comparant les performances de méditants à celles de non-méditants) et d'études longitudinales (comparant les performances de personnes avant et après un entraînement à la méditation). Ces études rapportent le plus souvent de meilleures performances associées à la pratique de la méditation, principalement dans des tâches évaluant l'attention, les fonctions exécutives, la vitesse de traitement des informations, mais aussi les fluences verbales, la flexibilité cognitive et la mémoire, notamment la mémoire épisodique et la mémoire de travail [19, 25]. Une étude suggère que les performances des méditants âgés à une tâche de clignement attentionnel, qui évalue l'attention soutenue, sont meilleures que celles des non-méditants du même âge, et seraient même équivalentes à celles des non-méditants jeunes [26].

Dans l'ensemble, ces études fournissent donc des résultats préliminaires encourageants, suggérant que la pratique de la méditation pourrait permettre de compenser le déclin cognitif lié à l'âge, au moins en partie et pour certains domaines cognitifs. Des études cliniques randomisées, longitudinales et portant sur des échantillons plus importants sont cependant nécessaires pour confirmer ces résultats.

Modifications cérébrales, structurales et métaboliques liées à la pratique de la méditation

Les études en IRM anatomique et TEP-FDG se sont intéressées aux effets de la méditation sur la structure et le métabolisme cérébral. Ces études conduites surtout chez le sujet jeune et d'âge intermédiaire rapportent que la méditation, sous diverses formes, est associée à des changements principalement dans les régions frontales et limbiques, ainsi que dans l'insula [27]. En effet, une méta-analyse regroupant 21 études d'imagerie structurale a montré qu'à la suite d'une courte intervention de méditation, ou encore chez des méditants expérimentés, le volume de substance grise serait plus élevé dans le cortex préfrontal et somatosensoriel, l'insula, l'hippocampe, le cortex cingulaire antérieur et moyen, ainsi que le cortex orbitofrontal [27]. Ces régions sont connues pour être impliquées dans des processus mentaux qui sont spécifiquement engagés lors de la pratique de la méditation tels que la métacognition et l'introspection (cortex préfrontal), l'intéroception – c'est-à-dire la conscience des états internes du corps (insula), le traitement des stimuli sensoriels externes (cortex somatosensoriel), les processus mnésiques (hippocampe), ainsi que le contrôle de soi et la régulation des émotions (cortex cingulaire antérieur et moyen, cortex orbitofrontal) [27].

De façon intéressante, une étude princeps, menée en 2005 par Lazar *et al.* [28] chez des participants âgés de 25 à 50 ans, a montré une diminution moins importante de l'épaisseur corticale avec l'âge dans le cortex préfrontal, chez des méditants expérimentés pratiquant la méditation de pleine conscience, comparés à des sujets témoins appariés en âge. Ces résultats préliminaires suggèrent que la pratique régulière de la méditation pouvait ralentir l'amincissement cortical lié à l'âge dans cette région.

Seules deux équipes de recherche se sont intéressées à cette question dans le contexte d'une population âgée. Une première étude a mis en évidence, chez une population de 20 à 77 ans, une diminution moindre du volume de substance grise avec l'âge chez les méditants expérimentés par rapport aux sujets témoins. Cette préservation du volume de substance grise s'observait surtout dans des régions frontales et temporales telles que le cortex cingulaire antérieur et orbitofrontal, l'hippocampe, ainsi que dans d'autres régions comme le cortex temporopariétal, cingulaire postérieur et somatosensoriel, l'insula, l'amygdale et le thalamus [29].

Une étude pilote réalisée par Chételat *et al.* en 2017 [30] a, quant à elle, rapporté des différences entre un groupe de six méditants expérimentés de plus de 60 ans comparés à un groupe de 67 sujets témoins non méditants d'âge équivalent, non seulement en termes de volume de substance grise mais aussi de métabolisme du glucose. Plus précisément, le groupe de méditants expérimentés avait un volume de substance grise et un métabolisme du glucose plus importants au niveau du cortex cingulaire antérieur et préfrontal ventromédian, de l'insula, de la jonction temporopariétale ainsi que du cortex cingulaire postérieur par rapport au groupe témoin. De manière intéressante, ces résultats se superposaient étroitement avec les régions dont le volume de substance grise et le métabolisme du glucose diminuaient le plus avec l'âge, mises en évidence dans cette même étude chez 186 sujets sains âgés de 20 à 87 ans.

Les régions cérébrales modifiées dans le cadre de la pratique de la méditation chez le sujet âgé sont similaires aux régions mises en évidence dans les études effectuées chez des sujets jeunes et d'âge intermédiaire. L'ensemble de ces résultats suggère que la pratique de la méditation pourrait aider à préserver la structure et le métabolisme cérébral du déclin progressif lié à l'âge, en conduisant éventuellement à une réserve cérébrale et cognitive plus élevée. Cette réserve

pourrait permettre de diminuer le risque de développer une démence, comme la maladie d'Alzheimer par exemple, ou de retarder sa survenue [1].

Modifications de l'activité et de la connectivité fonctionnelle des réseaux cérébraux liées à la pratique de la méditation

Les études en IRM fonctionnelle ont, quant à elles, permis d'appréhender l'activité cérébrale mise en jeu lorsque des sujets sont dans un état méditatif. Par exemple, durant la méditation par attention focalisée, basée sur un support tel que la respiration, il est décrit différentes activations cérébrales en fonction de l'état mental des méditants [31]. Ainsi, (1) lors du vagabondage de l'esprit, il est observé une activation des régions appartenant au RMD comme le cortex cingulaire postérieur, le précuneus, le cortex pariétal et temporal latéral, ainsi que le cortex préfrontal médian ; (2) lors de la prise de conscience de la distraction, s'active le réseau de saillance, comprenant l'insula et le cortex cingulaire antérieur ; (3) puis la réorientation de l'attention sollicite l'activation du cortex préfrontal dorsolatéral et pariétal inférieur, faisant partie du réseau frontopariétal ; (4) enfin, lors du maintien de la concentration sur une période prolongée, le cortex préfrontal dorsolatéral reste actif [31].

Une méta-analyse réunissant 25 études d'imagerie fonctionnelle a mis en évidence que différentes formes de méditation sont associées à l'activation de plusieurs régions cérébrales communes telles que l'insula, le cortex préfrontal, cingulaire antérieur et moyen, prémoteur et l'aire motrice supplémentaire [32]. Cependant, chaque type de méditation semble recruter ou désengager des régions spécifiques à la pratique en elle-même. Par exemple, la méditation de pleine conscience s'accompagne, en plus d'une activation des régions précédemment citées, d'une désactivation du thalamus, interprétée comme une diminution du filtrage sélectif de certains signaux sensoriels dont le rôle est imputé à cette région. Cette hypothèse semble cohérente avec l'exercice mental demandé par cette pratique, à savoir être ouvert et réceptif aux stimuli sensoriels en l'absence de jugement, sans utilisation de filtre [32]. L'amygdale serait également moins activée lors de la présentation de stimuli émotionnels négatifs, à la suite d'un entraînement de méditation de pleine conscience ou chez des méditants expérimentés [33].

Les activations cérébrales relatives aux états méditatifs sont donc souvent accompagnées par un désengagement de certaines régions cérébrales. En effet, il a été observé une diminution de l'activité au sein du RMD chez les méditants expérimentés comparés à des sujets témoins, interprétée comme étant le reflet d'une réduction des processus mentaux tels que le vagabondage de l'esprit et les traitements de référence à soi [34]. Par ailleurs, il a été montré dans cette même étude une augmentation de la connectivité fonctionnelle chez les méditants expérimentés entre une région du RMD (cortex cingulaire postérieur), et des régions impliquées dans le contrôle cognitif, la détection de conflit et la mémoire de travail (cortex cingulaire antérieur et préfrontal dorsolatéral). Cette connectivité fonctionnelle plus importante entre ces régions est interprétée comme un contrôle cognitif plus élevé sur le fonctionnement du RMD chez les méditants expérimentés. Nous pouvons supposer qu'une activité plus mesurée du RMD liée à une diminution des processus mentaux en référence à soi et du vagabondage de l'esprit, ainsi qu'un meilleur contrôle cognitif sur son fonctionnement pourraient avoir un effet protecteur sur les structures de ce réseau, connu pour être particulièrement vulnérable aux effets de l'âge [30].

Les modifications cérébrales anatomiques et fonctionnelles, associées à la pratique de la méditation, semblent surtout concerner des régions frontales, limbiques et l'insula, c'est-à-dire des régions particulièrement sensibles au vieillissement. Cet entraînement mental pourrait ainsi préserver ces structures des effets de l'âge, et de ce fait participer au maintien des performances cognitives et éventuellement réduire les risques de développer une maladie neurodégénérative, ou retarder sa survenue.

Limites et perspectives

La méditation semble avoir un effet positif sur les différentes sphères qui déclinent avec l'avancée en âge. Elle agit sur de nombreux aspects à la fois émotionnels, cognitifs, anatomiques et fonctionnels, de façon directe ou indirecte. Elle influe également sur d'autres paramètres du vieillissement qui n'ont pas été développés ici, tels que l'inflammation, le stress oxydatif, les facteurs de risques cardiovasculaires ou encore les télomérases (enzymes qui protègent les extrémités des chromosomes, appelées télomères, de leur altération avec l'âge) [10, 23].

Cependant, les différentes études ne permettent pas d'établir de liens de cause à effet directs de la méditation sur la cognition, le sommeil ou encore le cerveau. En effet, la méditation pourrait faire partie d'un système complexe comprenant les émotions, la cognition et le sommeil, qui s'influenceraient mutuellement. Par exemple, les émotions négatives telles que les symptômes anxieux ou dépressifs ont un impact négatif sur la structure du cerveau et sur la cognition [5, 7] ; leur diminution *via* un entraînement de méditation pourrait induire les améliorations cognitives observées dans les différentes études. Cependant, Moynihan *et al*. [35] ont montré une amélioration des fonctions exécutives après une intervention de MBSR, sans modification des scores d'anxiété ou de dépression, ce qui semble suggérer un potentiel effet à la fois direct et indirect de la méditation sur la cognition. Le même raisonnement peut être fait avec le sommeil, qui, lorsqu'il est altéré comme c'est le cas dans le vieillissement, entraîne une diminution des capacités cognitives et une augmentation des symptômes dépressifs [4, 36]. L'effet de la méditation sur la cognition pourrait donc être médié par l'amélioration du sommeil ou d'autres paramètres émotionnels. Il serait donc intéressant de mesurer ces différents paramètres dans

le cadre d'une étude portant sur un échantillon suffisant de participants pour pouvoir évaluer, par exemple *via* des analyses de médiation, les relations de cause à effet qu'ils entretiennent.

Dans les différentes études longitudinales, il a été noté une forte adhésion des sujets, ainsi qu'une bonne faisabilité des diverses interventions de méditation, même chez des patients ou des sujets présentant des déficits cognitifs [22, 25]. Ce type d'intervention non pharmacologique multidomaine et sans risque semble donc particulièrement adapté. Il pourrait être mis en place pour promouvoir un vieillissement en bonne santé mais aussi pour prévenir le déclin cognitif et les maladies neurodégénératives (ou d'autres pathologies liées à l'âge), aussi bien chez des populations âgées saines que chez des sujets à risque, ou encore chez des patients présentant un déclin cognitif (avec des adaptations du programme selon les déficits). Ce type d'intervention présente l'avantage de permettre aux personnes concernées d'être actives dans leur prise en charge.

Cependant, comme nous l'avons vu, si ces premières études rapportent des résultats encourageants quant à l'impact positif de la méditation dans le vieillissement, elles présentent également un certain nombre de limites. Ainsi, la plupart des études sur le sujet sont transversales, et lorsqu'elles sont longitudinales, elles ne présentent pas de groupe témoin actif et/ou passif, et sont rarement randomisées, c'est-à-dire qu'elles laissent le choix du groupe aux participants [10]. Les résultats peuvent donc être biaisés par exemple par des différences individuelles présentes avant l'intervention et éventuellement liées au choix du groupe d'intervention. Les études portent également souvent sur des effectifs limités (*i.e.* inférieurs au seuil de 33 sujets par groupe considéré comme nécessaire pour détecter des effets larges à moyens de l'intervention selon une revue sur des études utilisant le MBSR) [22]. Un autre paramètre qui rend les résultats difficiles à généraliser est la diversité des pratiques de méditation utilisées dans les différentes études, et une absence de standardisation des procédures. Pour finir, les mesures recueillies dans le cadre de ces études évaluent les performances à des tests neuropsychologiques mais pourraient ne pas toujours refléter le fonctionnement de la personne dans la vie quotidienne. Il serait donc pertinent d'ajouter des mesures plus écologiques, qui permettraient de mettre en lien les meilleures performances cognitives avec le fonctionnement quotidien, qui influe sur la qualité de vie. Les résultats encourageants des premières études doivent donc être confirmés, au moyen d'études randomisées contrôlées et portant sur des échantillons homogènes et suffisamment larges, avec un éventail de mesures complémentaires permettant de mieux comprendre les mécanismes sous-jacents.

Le projet de recherche européen Medit-ageing a été conçu dans cette perspective. Medit-ageing est un projet de grande envergure financé par la commission européenne et visant à mieux comprendre les déterminants de la santé mentale et du bien-être dans le vieillissement. Il comprend deux essais cliniques randomisés contrôlés sponsorisés par l'Inserm qui testeront notamment l'impact d'un entraînement à la méditation chez des personnes de plus de 60 ans.

Le premier essai clinique inclura 137 sujets cognitivement sains âgés de plus de 65 ans, et évaluera les effets d'une intervention de méditation ou d'apprentissage de l'anglais (contrôle actif) sur 18 mois, comparé à un groupe témoin passif. Les participants de cette étude bénéficieront de multiples examens complémentaires avant et après l'intervention, incluant des mesures comportementales, du sommeil, de marqueurs sanguins et de neuro-imagerie, permettant ainsi de comprendre de manière plus intégrée les mécanismes et les interactions entre ces différents facteurs. Un groupe de 30 méditants expérimentés âgés de plus de 65 ans effectuera les mêmes examens dans le cadre de ce projet, permettant ainsi d'identifier les modifications de ces mêmes mesures associées à la pratique régulière et à long terme de la méditation. Enfin, dans le second essai clinique, 160 patients présentant une plainte cognitive subjective (SCD) seront randomisés dans deux groupes effectuant un programme de huit semaines, soit de MBSR, soit de cours d'éducation à la santé. Des mesures comportementales cognitives, de mode de vie et de bien-être, ainsi que des mesures sanguines seront également réalisées avant et après l'intervention, ainsi que quatre mois après la fin de l'intervention. Ce projet devrait permettre d'avoir une vue générale des effets de la méditation dans le vieillissement, chez des participants sans déficits cognitifs et des patients présentant une plainte cognitive subjective, sur un éventail de mesures comportementales et biologiques, après une intervention relativement courte (standardisée de huit semaines), ou plus longue (18 mois, spécialement adaptée aux seniors). Il s'intéressera aux mécanismes sous-jacents en évaluant plus spécifiquement le rôle des processus attentionnels et de régulation émotionnelle. Ce projet devrait donc apporter une contribution significative, à notre connaissance, des effets de la méditation sur le vieillissement et, à notre compréhension, des mécanismes qui les sous-tendent.

Conclusion

L'étude de la méditation dans le cadre du vieillissement est un domaine de recherche récent mais prometteur, qui nécessite d'être approfondi. Les études actuelles rapportent des résultats encourageants à la fois sur le bien-être et les facteurs psychoaffectifs, sur la cognition, ainsi que sur la structure et le fonctionnement cérébral, et particulièrement dans des domaines et des régions cérébrales fragilisés dans le vieillissement normal. Ce type de programme non pharmacologique ciblant plusieurs facteurs de risques (dits « multidomaines ») permet également aux personnes de se sentir actives dans leur prise en charge. Il pourrait donc être pertinent de l'inclure dans un programme de prévention de maladies liées au vieillissement en particulier, de maintien ou d'amélioration de la santé des personnes âgées en général, éventuellement en complément

d'autres modalités telles que le régime alimentaire ou encore l'activité physique. Dans ce cadre, le programme de recherche européen Medit-ageing a été développé en tenant compte des recommandations soulevées par la littérature, afin d'approfondir notre compréhension des effets de la méditation sur le vieillissement et des mécanismes qui les sous-tendent. ■

Liens d'intérêt

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Inès Moulinet et Edelweiss Touron déclarent ne pas avoir de lien d'intérêt en rapport avec cet article.

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6.4. Collaboration à des études publiées dans des revues internationales

6.4.1. André et al., JAMA Neurology, 2020

Research

JAMA Neurology | Original Investigation

Association of Sleep-Disordered Breathing With Alzheimer Disease Biomarkers in Community-Dwelling Older Adults
A Secondary Analysis of a Randomized Clinical Trial

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IMPORTANCE Increasing evidence suggests that sleep-disordered breathing (SDB) increases the risk of developing Alzheimer clinical syndrome. However, the brain mechanisms underlying the link between SDB and Alzheimer disease are still unclear.

OBJECTIVE To determine which brain changes are associated with the presence of SDB in older individuals who are cognitively unimpaired, including changes in amyloid deposition, gray matter volume, perfusion, and glucose metabolism.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional study was conducted using data from the Age-Well randomized clinical trial of the Medit-Ageing European project, acquired between 2016 and 2018 at Cyceron Center in Caen, France. Community-dwelling older adults were assessed for eligibility and were enrolled in the Age-Well clinical trial if they did not meet medical or cognitive exclusion criteria and were willing to participate. Participants who completed a detailed neuropsychological assessment, polysomnography, a magnetic resonance imaging, and florbetapir and fluorodeoxyglucose positron emission tomography scans were included in the analyses.

MAIN OUTCOMES AND MEASURES Based on an apnea-hypopnea index cutoff of 15 events per hour, participants were classified as having SDB or not. Voxelwise between-group comparisons were performed for each neuroimaging modality, and secondary analyses aimed at identifying which SDB parameter (sleep fragmentation, hypoxia severity, or frequency of respiratory disturbances) best explained the observed brain changes and assessing whether SDB severity and/or SDB-associated brain changes are associated with cognitive and behavioral changes.

RESULTS Of 157 participants initially assessed, 137 were enrolled in the Age-Well clinical trial, and 127 were analyzed in this study. The mean (SD) age of the 127 participants was 69.1 (3.9) years, and 80 (63.0%) were women. Participants with SDB showed greater amyloid burden (t_{114} = 4.51; familywise error–corrected P = .04; Cohen d, 0.83), gray matter volume (t_{119} = 4.12; familywise error–corrected P = .04; Cohen d, 0.75), perfusion (t_{116} = 4.62; familywise error–corrected P = .001; Cohen d, 0.86), and metabolism (t_{79} = 4.63; familywise error–corrected P = .001; Cohen d, 1.04), overlapping mainly over the posterior cingulate cortex and precuneus. No association was found with cognition, self-reported cognitive and sleep difficulties, or excessive daytime sleepiness symptoms.

CONCLUSIONS AND RELEVANCE The SDB-associated brain changes in older adults who are cognitively unimpaired include greater amyloid deposition and neuronal activity in Alzheimer disease–sensitive brain regions, notably the posterior cingulate cortex and precuneus. These results support the need to screen and treat for SDB, especially in asymptomatic older populations, to reduce Alzheimer disease risk.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02977819

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Supplemental content

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Sleep-disordered breathing (SDB) is a respiratory disorder characterized by recurrent upper airway collapse during sleep, associated with intermittent hypoxia and sleep fragmentation.[1,2] It affects 30% to 80% of older adults who are cognitively unimpaired, depending on the SDB definition criteria.[3,4] Patients with a clinical diagnosis of Alzheimer disease (AD) are even more likely to suffer from SDB,[5] and untreated SDB is associated with cognitive decline and conversion to the Alzheimer clinical syndrome at a younger age.[6-8]

To clarify the mechanisms underlying the association between SDB and dementia risk, growing efforts have been deployed to better characterize the brain changes associated with SDB. Yet, previous studies have provided heterogeneous results, showing both SDB-associated decreases[9-11] and increases[12,13] in gray matter (GM) volume or cortical thickness in various brain areas including frontal, temporal, and parietal regions. Similarly, both decreased perfusion[14-16] and increased perfusion[15,17] have been reported in patients with SDB compared with control participants. Finally, SDB has been associated with increased amyloid and tau levels in the blood and cerebrospinal fluid, both cross sectionally and longitudinally.[18-21] However, cross-sectional positron emission tomography (PET) studies have reported inconsistent results, some showing greater amyloid burden in association with SDB,[22,23] while others do not report significant associations.[21,24] These discrepancies may be explained by the characteristics of patients with SDB (eg, recruited from sleep clinics vs from the community, differences in age and disease duration), the scoring criteria of respiratory events, sample sizes, and/or the lack of controls for possibly biasing covariates.

To our knowledge, no previous study has used a multimodal neuroimaging approach to highlight early brain changes associated with the presence of untreated SDB within a large sample of older participants who are cognitively unimpaired and are recruited from the community, with no or few sleep symptoms. Therefore, our main objective was to provide a comprehensive picture of structural, functional, and molecular brain changes associated with untreated SDB in aging, to provide substantial advances in the understanding of early brain mechanisms underlying the associations between SDB and AD. Secondary objectives aimed at identifying which aspect of SDB severity (ie, sleep fragmentation, hypoxia severity, or frequency of respiratory events) is most associated to brain changes. Lastly, we investigated the associations between SDB severity and/or SDB-associated brain changes and cognitive performance, self-reported cognitive and sleep difficulties, or symptoms of sleepiness.

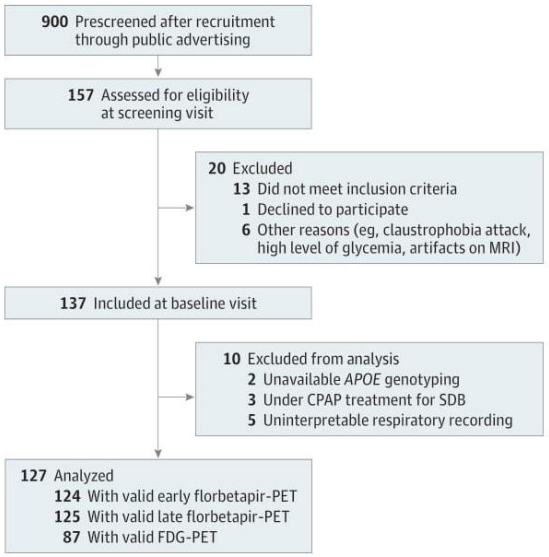
Key Points

Question Which brain changes are associated with sleep-disordered breathing in aging?

Findings In this cross-sectional study of 127 community-dwelling older individuals who were cognitively unimpaired, the presence of sleep-disordered breathing was associated with greater amyloid burden, gray matter volume, metabolism, and perfusion in the posterior cingulate cortex and precuneus. There was no association with cognitive performance, self-reported cognitive or sleep difficulties, or excessive daytime sleepiness.

Meaning Sleep-disordered breathing–associated changes include amyloid deposition in brain regions typically involved in Alzheimer disease, which might explain why sleep-disordered breathing is associated with an increased risk for developing Alzheimer clinical syndrome at a younger age.

Figure 1. Flow Diagram of the Inclusion Process



APOE indicates apolipoprotein E; CPAP, continuous positive airway pressure; FDG, ^{18}F-fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography; SDB, sleep-disordered breathing.

Methods

Participants

We included 127 older adults who were cognitively unimpaired from the baseline visit of the Age-Well randomized clinical trial of the Medit-Ageing European Project[25] (flow diagram in **Figure 1**), sponsored by the French National Institute of Health and Medical Research (INSERM). Participants were recruited from the general population, older than 65 years, native French speakers, retired for at least 1 year, educated for at least 7 years, and able to perform within the normal range on standardized cognitive tests. The main exclusion criteria were safety concerns associated with magnetic resonance image (MRI) or PET scanning, evidence of a major neurological or psychiatric disorder (including alcohol or drug abuse), history of cerebrovascular disease, presence of a chronic disease or acute unstable illness, and current or recent medication usage that may interfere with cognitive functioning.

Participants meeting inclusion criteria performed a detailed cognitive assessment, a polysomnography, structural MRI, fluorine 18-labeled (^{18}F) florbetapir PET and ^{18}F-fluorodeoxyglucose (FDG) PET scans, and apolipoprotein E ε4 (*APOE4*) genotyping within a maximum period of 3 months. All participants gave their written informed consent prior to the examinations, and the Age-Well randomized clinical trial was

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approved by the ethics committee (Comité de Protection des Personnes Nord-Ouest III, Caen, France; trial registration number: EudraCT: 2016-002441-36; IDRCB: 2016-A01767-44; ClinicalTrials.gov Identifier: NCT02977819).

Cognitive and Behavioral Assessment

The detailed neuropsychological evaluation encompassed global cognitive functioning, processing speed, attention, working memory, executive functions, and episodic memory.[25] For each cognitive domain, a composite score was computed (eAppendix in the Supplement). In addition, self-reported cognitive difficulties were assessed using the Cognitive Difficulties Scale.[26] Moreover, self-reported sleep quality was assessed using the Pittsburgh Sleep Quality Index,[27] and excessive daytime sleepiness symptoms were measured using the Epworth Sleepiness Scale.[28]

Neuroimaging Examinations

All participants underwent high-resolution T1-weighted anatomical imaging to measure GM volume and a florbetapir-PET scan with a 10-minute early acquisition that began immediately after the intravenous injection and reflected brain perfusion and a 10-minute late acquisition (beginning 50 minutes after injection) that reflected amyloid burden. A subset of participants (n = 87) also underwent an FDG-PET scan to measure brain glucose metabolism. All participants were scanned at Cyceron Center (Caen, France) on the same MRI scanner (Philips Achieva 3.0T) and PET scanner (Discovery RX VCT 64 PET-CT; General Electric Healthcare). The detailed acquisition and preprocessing procedures[25] are available in the eAppendix in the Supplement. The PET analyses were performed on images corrected for partial volume effects (PVE) using the 3-compartmental voxelwise Müller-Gartner method.[29]

SDB Characterization

Participants underwent polysomnography using a portable home device (Siesta; Compumedics). Acquisition parameters are described in the eAppendix in the Supplement. Sixty-eight percent of the participants (86 of 127 individuals) underwent 2 polysomnography recordings, including a habituation night, which was not included in the analyses. The remaining 39 participants only had 1 polysomnography recording. Recordings were visually scored in 30-second epochs following the recommended standard criteria of the American Academy of Sleep Medicine.[1] Sleep apnea was defined by a 90% or greater drop of nasal pressure for at least 10 seconds, whereas sleep hypopnea was characterized by a 30% or greater drop of nasal pressure for a minimum of 10 seconds, associated with an arousal or a 3% or greater oxygen desaturation.

Based on the apnea-hypopnea index (AHI) value (ie, the sum of apnea and hypopnea events per hour of sleep), participants were classified into 2 groups with a cutoff value of 15, independent of clinical symptoms, in accordance with the recommendations of the third edition of the International Classification of Sleep Disorders.[30] Thus, we obtained a group without SDB (AHI <15 events per hour; n = 31) and a group with SDB (AHI ≥15 events per hour; n = 96).[6,20,31,32] The subsample of 87 participants who also had an FDG-PET scan was composed of 69 participants with SDB and 18 participants without SDB, who did not differ from the main sample regarding the proportion of participants with vs without SDB ($\chi^2_1 = 0.26$; $P = .61$) or demographic, sleep, and cognitive variables (data not shown).

Lastly, to address secondary objectives, we computed 2 composite scores reflecting sleep fragmentation and hypoxia severity. This composite score approach, also used in a previous study,[12] was preferred to a single-item approach, to minimize the issue of multiple statistical testing. The sleep fragmentation composite score corresponded to the mean of the *z* scores of the respiratory arousal index, the number of shifts to non-rapid eye movement sleep stage 1 per hour, and the number of nocturnal awakenings per hour. The hypoxia composite score corresponded to the mean of the *z* scores of the oxygen desaturation index, the proportion of total sleep time with oxygen desaturation of 90% or less, and the minimal oxygen saturation.

Statistical Analyses

Between-Group Differences

Between-group differences for demographical, behavioral, sleep, and cognitive variables were assessed using *t* tests for continuous variables and χ^2 statistics for categorical variables, with statistical significance set to $P < .05$. Voxelwise group differences in amyloid burden, GM volume, perfusion, and glucose metabolism were explored using analyses of covariance in SPM12 (Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology), controlling for age, sex, education, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), sleep medication use, and *APOE4* status. Voxelwise analyses were performed using MRI and PVE-corrected PET data and considered significant at a voxel-level threshold of $P < .005$ and a cluster-level threshold of $P < .05$, corrected for familywise errors (FWE).

Stepwise Regression Analyses

As a second step, we aimed at further assessing which aspect of SDB severity (ie, the frequency of respiratory disturbances, associated sleep fragmentation, and/or hypoxia severity) was more specifically involved in the SDB-associated brain changes highlighted in the previous analysis. For this purpose, amyloid burden, GM volume, perfusion, and glucose metabolism signal values were extracted from the significant clusters obtained in the voxelwise group comparisons. Then, stepwise regression analyses were performed on the whole sample of participants, with 9 measures entered in the model as independent variables (ie, the AHI value, sleep fragmentation composite score, hypoxia composite score, age, sex, education, BMI, sleep medication use, and *APOE4* status), while dependent variables were neuroimaging signal values, each modality being tested separately.

Partial Correlation Analyses

Finally, partial correlations were performed on the whole sample of participants to assess potential associations between (1) the

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Table 1. Participant Characteristics and Between-Group Differences

Characteristic	Mean (SD)		*P* value for between-group differences[a]
	Without SDB (n = 31)	With SDB (n = 96)	
Demographic			
Age, y	69.19 (3.53)	69.00 (3.98)	.81
Female, No. (%)	24 (77.4)	56 (58.3)	.06
Education, y	13.45 (2.94)	12.90 (3.12)	.38
Geriatric Depression Scale score	1.55 (1.89)	1.21 (1.70)	.35
State-Trait Inventory form B total score	36.13 (7.35)	34.05 (6.88)	.15
BMI	24.77 (5.07)	26.73 (3.92)	.03
Current sleep medication use, No. (%)[b]	2 (6.45)	10 (10.42)	.51
Florbetapir standard uptake value ratio[c]	0.91 (0.13)	0.99 (0.23)	.07
Amyloid positive, %	10	25	.08
Carrying *APOE4*, No. (%)	9 (29.03)	26 (27.08)	.83
Sleep			
Pittsburgh Sleep Quality Index score	4.39 (2.67)	5.17 (3.16)	.22
Epworth Sleepiness Scale score	4.77 (3.04)	5.22 (3.45)	.52
Total sleep time, min	358.63 (59.13)	362.81 (67.62)	.76
Sleep efficiency, %	76.39 (10.24)	77.36 (9.89)	.64
Sleep onset latency, min	18.73 (12.41)	21.12 (12.49)	.35
Apnea-hypopnea index events, No. per h	9.63 (3.91)	30.54 (13.26)	<.001
Fragmentation composite score	−0.68 (0.41)	0.22 (0.81)	<.001
Respiratory arousals index, No. per h	7.15 (3.34)	25.28 (11.30)	<.001
Shifts to non-rapid eye movement sleep stage 1, No. per h	5.81 (2.08)	8.39 (3.53)	.001
Awakenings, No. per h	3.29 (1.12)	4.11 (1.72)	.02
Hypoxia composite score[d]	−0.44 (0.39)	0.15 (0.85)	<.001
Oxygen desaturation ≥3% index, No. per h	5.50 (3.96)	16.50 (11.21)	<.001
Total sleep time with oxygen saturation ≤90%, %	0.50 (1.08)	2.88 (9.69)	.18
Minimal oxygen saturation, %	88.27 (3.82)	85.89 (5.05)	.02
Cognition scores			
Mini-Mental State Examination	28.81 (1.08)	29.06 (1.04)	.24
Mattis Dementia Rating Scale	140.61 (2.89)	141.17 (2.64)	.32
Processing speed composite	0.05 (0.85)	−0.02 (0.70)	.66
Attention composite	−0.04 (0.66)	0.04 (0.63)	.58
Executive functioning composite	0.12 (0.70)	−0.04 (0.67)	.26
Working memory composite	0.04 (1.03)	−0.03 (0.85)	.72
Episodic memory composite	0.16 (0.81)	−0.05 (0.69)	.17
Cognitive Difficulties Scale	33.84 (14.27)	34.18 (15.59)	.91

Abbreviations: *APOE*, apolipoprotein E; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); SDB, sleep-disordered breathing.

[a] Between-group differences were assessed using *t* tests for continuous variables and χ^2 statistics for categorical variables. Statistical significance was set to $P < .05$.

[b] Use of sleep medication on a regular basis (>1/week), excluding phytotherapy and homeopathy.

[c] Thirty control participants with valid florbetapir–positron emission tomography scan. The threshold for amyloid positivity was defined as more than 0.99 and corresponded to the 99.9th percentile of the neocortical standard uptake value ratio distribution among 45 healthy young individuals younger than 40 years.

[d] Thirty participants without SDB and 88 participants with SDB with valid oxygen saturation data.

3 measures of SDB severity and (2) SDB-associated brain changes with cognitive and behavioral variables. These analyses were controlled for age, sex, education, BMI, sleep medication use, and *APOE4* status, and considered significant at a $P < .05$ threshold, after applying a Bonferroni correction for multiple comparisons. Thus, the threshold for significance was set to $P \leq$ (0.05/number of comparisons).

Results

Participants' Characteristics

Participants' characteristics, including demographical and behavioral variables, neuropsychological scores, and sleep parameters, as well as corresponding between-group differences, are provided in **Table 1**. Participants with vs without SDB did not differ in age, sex, education, depression and anxiety scores, current use of sleep medication, and the proportion of individuals carrying *APOE4*. As expected, participants with SDB had significantly higher BMI values ($t_{125} = 2.25$; mean difference, 1.96 [95% CI, 0.23-3.69]; $P = .03$), AHI values ($t_{125} = 8.64$; mean difference, 20.91 [95% CI, 16.12-25.70]; $P < .001$), levels of sleep fragmentation ($t_{125} = 5.96$; mean difference, 0.90 [95% CI, 0.60-1.20]; $P < .001$), and hypoxia ($t_{116} = 3.68$; mean difference, 0.59 [95% CI, 0.27-0.91]; $P < .001$). Interestingly, no between-group difference was observed for subjective sleep quality, daytime sleepiness symptoms, objectively measured total sleep time, sleep efficiency, and sleep onset latency on the polysomnography night. Moreover, cognitive performance

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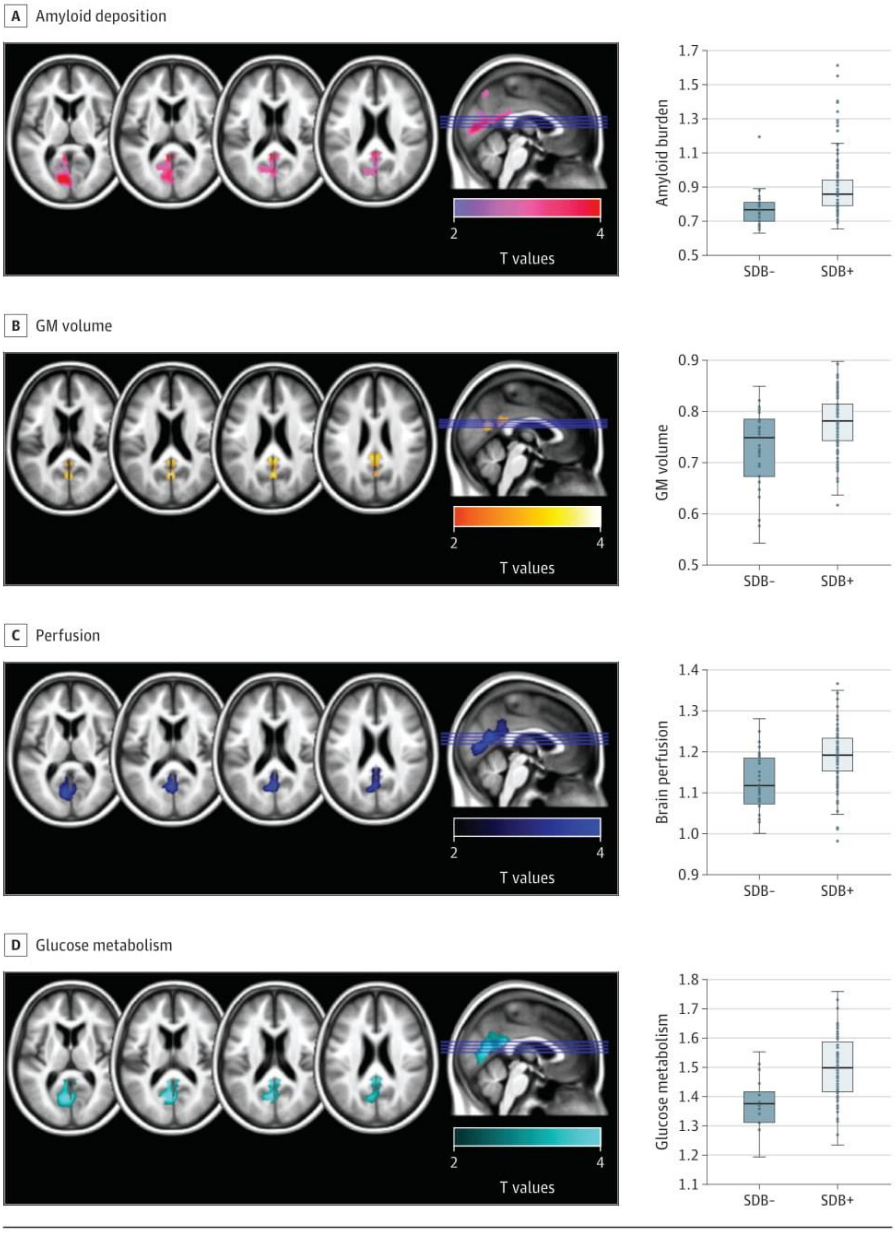
Figure 2. Neuroimaging Pattern of the Significant Differences Between Participants With vs Without Sleep-Disordered Breathing in Amyloid Deposition, Gray Matter Volume, Perfusion, and Glucose Metabolism



Results of the voxelwise analyses of covariance exhibiting between-group differences in amyloid deposition (A), gray matter (GM) volume (B), perfusion (C), and glucose metabolism (D), using magnetic resonance imaging and partial volume effects–corrected positron emission tomography data. Analyses were adjusted for age, sex, education, body mass index, sleep medication use, and *APOE4* status. Results were obtained at a $P < .005$ (uncorrected) threshold, and only clusters surviving a familywise error–cluster-level correction are reported. *APOE* indicates apolipoprotein E; SDB−, negative for sleep-disordered breathing; SDB+, positive for sleep-disordered breathing.

and self-reported cognitive difficulties were comparable between the 2 groups.

Brain Changes Associated With the Presence of SDB

Results of between-group comparisons for MRI and PVE-corrected PET data are presented in **Figure 2**. Cluster peak statistics and coordinates are detailed in eTable 1 in the Supplement.

Participants with SDB presented greater amyloid burden in the left precuneus, posterior cingulate, calcarine, and cuneus regions (Figure 2A; $t_{117} = 4.51$; FWE-corrected $P = .04$; Cohen d, 0.83), compared with participants without SDB. They also showed greater GM volume in the precuneus and posterior cingulate cortex, bilaterally (Figure 2B; $t_{119} = 4.12$; FWE-corrected $P = .04$; Cohen d, 0.75), and greater perfusion in parietooccipital regions, including the precuneus, posterior cingulate, calcarine, and lingual areas (Figure 2C; $t_{116} = 4.62$; FWE-corrected $P = .001$; Cohen d, 0.86). Finally, participants with SDB presented greater glucose metabolism in the precuneus, posterior cingulate, and lingual areas, bilaterally (Figure 2D; $t_{79} = 4.63$; FWE-corrected $P = .001$; Cohen d, 1.04). Additionally, we compared brain changes between participants with moderate SDB (ie, 15≤ AHI values <30) vs severe SDB (AHI values ≥30) and found no significant differences at the

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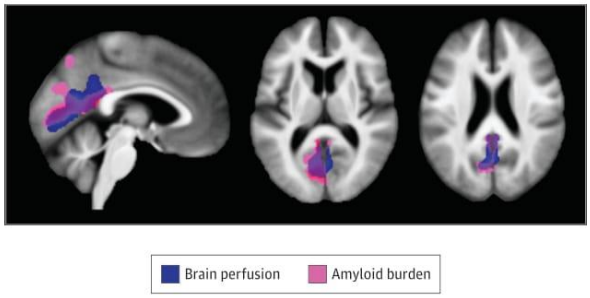
Figure 3. Overlap of Sleep-Disordered Breathing–Associated Brain Changes Across Neuroimaging Modalities



Representation of the overlap between sleep-disordered breathing–associated patterns of greater perfusion (blue) and amyloid deposition (pink), obtained at a $P < .005$ (uncorrected) threshold combined with a familywise error–cluster-level correction.

$P < .005$ level, combined with an FWE cluster-level correction (data not shown). This suggests that brain changes associated with SDB are detectable from the moderate stage and are not exacerbated in participants with severe SDB.

Interestingly, there was an overlap between brain changes observed in all 4 neuroimaging modalities over the posterior cingulate cortex, the precuneus, and the cuneus (**Figure 3**). Perfusion, metabolism, and GM volume signal values extracted from significant clusters showed strong intercorrelations (brain perfusion and glucose metabolism: Pearson *r*, 0.70 [95% CI, 0.58-0.80]; $P < .001$; brain perfusion and GM volume: Pearson *r*, 0.59 [95% CI, 0.46-0.69]; $P < .001$; metabolism and GM volume: Pearson *r*, 0.40 [95% CI, 0.21-0.56]; $P < .001$), and amyloid deposition was significantly correlated with GM volume (Pearson *r*, 0.21 [95% CI, 0.03-0.37]; $P = .02$) and perfusion (Pearson *r*, 0.34 [95% CI, 0.18-0.49]; $P < .001$; eTable 2 in the Supplement).

Lastly, for the sake of completeness, region of interest–based complementary analyses were performed. The signal was extracted from PVE-corrected and uncorrected FDG, early and late florbetapir PET images, in regions of interest from the Automated Anatomical Labeling Atlas[33] overlapping with the significant clusters obtained in the voxelwise analyses. The results are summarized in eTable 3 in the Supplement and are consistent overall with the findings from the voxelwise analyses. Only results obtained with PVE-uncorrected amyloid PET images were less significant, with between-group comparisons being significant for 3 regions of interest when using uncorrected PET images (right cuneus, F, 4.21; $P = .04$; partial η^2, 0.04; left precuneus, F, 4.03; $P = .05$, partial η^2, 0.03; left lingual, F, 4.26; $P = .04$; partial η^2, 0.04), compared with 9 regions of interest with corrected PET images (eTable3 in the Supplement), which likely reflect the between-group differences in GM volume highlighted in the main analyses.

Links Between SDB-Associated Brain Changes and Measures of SDB Severity

Forward stepwise regressions were then performed to determine which aspect of SDB severity is the most closely associated with SDB-associated brain changes (**Table 2**). The factors most strongly associated with amyloid burden were the hypoxia composite score, explaining 8% of the variance (unstandardized β, 0.06 [95% CI, 0.02-0.10]; $P = .002$), followed by *APOE4* status, explaining 4% of the variance (unstandardized β, 0.07 [95% CI, 0.001-0.14]; $P = .05$). No other variable entered the model. The AHI value was the only variable associated with GM volume, explaining 4% of the variance (unstandardized β, 0.01; $P = .04$). No variable was significantly associated with brain perfusion or metabolism.

To ensure that these findings were not biased by a possible circularity issue, we replicated stepwise regression analyses with neuroimaging values that were independent from the previous between-group comparison. For this purpose, amyloid deposition was more globally measured through the global neocortical standardized uptake value ratio, and GM volume was extracted from the composite regions of interest of posterior regions of the Automated Anatomical Labeling Atlas described above (eTable 4 in the Supplement). Briefly, results were similar for amyloid burden, with hypoxia severity being the variable most strongly associated with the global neocortical amyloid standardized uptake value ratio (unstandardized β, 0.06 [95% CI, 0.01-0.11]; $P = .01$), followed by *APOE4* status (unstandardized β, 0.09 [95% CI, 0.01-0.17]; $P = .04$). Moreover, the AHI value remained the SDB-associated variable most strongly associated with GM volume, although it was preceded by the BMI, sex, and age.

Links With Cognition, Self-reported Cognitive Difficulties, and Sleep Difficulties

Lastly, we aimed at exploring the cognitive and behavioral correlates of SDB severity and associated brain changes. No association survived the Bonferroni correction for multiple comparisons (eTable 5 in the Supplement). Neither measures of SDB severity nor measures of SDB-associated brain changes were associated with cognitive performance, self-reported cognitive and sleep difficulties, or symptoms of sleepiness.

Discussion

The main goal of the present study was to provide a comprehensive overview of brain changes associated with untreated SDB in community-dwelling older participants who had few self-reported sleep difficulties. Our results show that participants with SDB presented greater amyloid burden, GM volume, metabolism, and perfusion in parietooccipital regions, including the precuneus and posterior cingulate cortex. Interestingly, greater amyloid burden was robustly associated with the severity of hypoxia. Neither SDB severity nor SDB-associated brain changes were associated with cognitive performance, self-reported cognitive and sleep difficulties, and symptoms of sleepiness.

The association between SDB and greater amyloid deposition is in line with previous studies showing that SDB is associated with lower serum and cerebrospinal fluid amyloid levels.[18,20] Furthermore, these results characterize the regional pattern of amyloid deposition in individuals with SDB who are cognitively unimpaired, extending the findings of

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Table 2. Results of Forward Stepwise Regressions Showing the Variables Most Strongly Associated With SDB-Associated Brain Changes

Factor	Unstandardized coefficient (95% CI)	Standardized coefficient	R^2	*P* value
Amyloid burden				
Step 1				
Intercept	0.88 (0.85-0.91)	NA	NA	<.001
Hypoxia composite	0.06 (0.02-0.10)	0.28	0.08	.002
Step 2				
Intercept	0.86 (0.82-0.90)	NA	NA	<.001
Hypoxia composite	0.06 (0.02-0.10)	0.26	NA	.004
APOE4 status	0.07 (0.001-0.14)	0.18	0.11	.05
Full model	NA	NA	0.16	.02
Gray matter volume				
Step 1				
Intercept	0.77 (0.76-0.78)	NA	NA	<.001
Apnea-hypopnea index	0.01 (5.718×10^{-4}-0.02)	0.19	0.04	.04
Full model	NA	NA	0.11	.20

Abbreviations: *APOE4*, apolipoprotein E; NA, not applicable.

Yun and colleagues[23] to a larger sample of older individuals. The association between amyloid deposition and hypoxia severity is also consistent with animal studies, showing that hypoxia promotes the cleavage of the amyloid precursor protein by the β-secretase and γ-secretase, leading to increased β-amyloid levels.[34-36] Moreover, it may partly explain why this specific aspect of SDB, rather than the AHI value or sleep fragmentation, is significantly associated with cognitive decline and conversion to Alzheimer clinical syndrome in older adults.[6,37]

Interestingly, participants with SDB also presented greater GM volume, perfusion, and metabolism, in line with the findings of several other studies.[12,15,17,38,39] Nevertheless, other groups have also reported GM atrophy, hypoperfusion, and hypometabolism in participants with SDB.[9-11,14,16] Discrepancies across studies may be attributable, at least in part, to methodological differences, because most studies have been performed on smaller samples of young and middle-aged participants with severe SDB (AHI >30 events per hour). Alternatively, it is possible that studies including participants with less severe SDB (ie, from the moderate stage, corresponding to an AHI >15 events per hour) and few symptoms, as in the present study and in others,[12,15] may be more able to capture earlier brain changes associated with the presence of SDB.

Importantly, to the best of our knowledge, our results show in vivo for the first time that greater amyloid burden colocalizes with greater GM volume, perfusion, and metabolism in older participants with SDB who are cognitively unimpaired.[38,40-42] We believe that these overlapping patterns reinforce the likelihood of common underlying mechanisms. Indeed, it has been demonstrated that higher neuronal activity is associated with increased β-amyloid production.[43-46] In addition, several studies[47] have shown that neuroinflammatory processes play a central role in AD progression and are associated with higher levels of amyloid deposition. Thus, SDB-associated neuroinflammatory processes and associated neuronal hyperactivity are likely to promote amyloid deposition in the same area. Furthermore, greater GM volume, perfusion, and metabolism colocalizing with amyloid deposition may precede the development of neuronal injury, such as hypometabolism and atrophy.[48,49] Alternatively, greater GM volume, perfusion, and metabolism could also reflect higher brain reserve,[50] helping to cope with amyloid pathology and maintain cognitive performance.

In our study, SDB-associated brain changes were not associated with cognitive performance, self-reported cognitive and sleep difficulties, or symptoms of excessive daytime sleepiness. We believe that this finding indicates that greater amyloid deposition, GM volume, perfusion, and metabolism may represent early and asymptomatic brain changes associated with SDB. Studies exploring the associations between SDB and cognitive performance using cross-sectional designs have provided mixed results,[7,51-53] but longitudinal studies showed that SDB is associated with conversion to Alzheimer clinical syndrome and cognitive decline over time.[6-8] Therefore, older adults with SDB may exhibit silent brain changes, including increased amyloid deposition, which may propagate with time and explain why they are more at risk of developing Alzheimer clinical syndrome. The main strengths of the present study are, first, the multimodal assessment of bain integrity, which allowed us to reveal the overlap of brain changes, and second, the detailed cognitive assessment, on a large sample of older individuals who are cognitively unimpaired.

Limitations

However, the cross-sectional design of the analyses does not allow for the assessment of the causal associations between SDB and brain changes. Longitudinal studies are needed to investigate whether these early SDB-associated brain changes will progress to neurodegeneration and cognitive deficits.

Conclusions

Taken together, community-dwelling older individuals with untreated SDB presented greater amyloid deposition, GM volume, perfusion, and metabolism mainly over the posterior

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cingulate, cuneus, and precuneus areas, which are typically altered in AD. However, no association with cognitive performance, self-reported cognitive or sleep difficulties, or sleepiness symptoms was observed. Early neuroinflammatory and neuronal hyperactivity processes promoting amyloid deposition could represent the underlying mechanisms increasing the susceptibility to AD at an asymptomatic stage of SDB. Our findings highlight the need to treat sleep disorders in the older population, even in the absence of cognitive or behavioral manifestations.

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6.5. *Curriculum vitae* de la doctorante

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Doctorante en Sciences de la Vie et de la Santé

Unité INSERM - UNICAEN - EFS U1237
PhIND "*Physiopathology and Imaging of Neurological Disorders*"
Équipe C "*Multimodal neuroimaging and Lifestyle in Ageing and Alzheimer Disease*"

FORMATION UNIVERSITAIRE

2017-2019 **Doctorat en Sciences de la Vie et de la Santé. Unité INSERM – UNICAEN – EFS U1237 Caen, France**, Université de Caen-Normandie

« Vers une meilleure compréhension et une prise en charge des facteurs psychoaffectifs (anxiété et dépression) dans le vieillissement normal et la maladie d'Alzheimer : Liens avec les facteurs de vie et la neuroimagerie multimodale, et impact d'un programme de méditation.»

Supervision : Dr Gaëlle CHETELAT (DR – HDR) et co-encadrement du Dr Géraldine POISNEL (IR)

Financement : INSERM, CDD 3 ans à temps plein (2017-2020)

2015-2017 **Master Sciences Biomédicales, Spécialité Neurosciences et Sciences des comportements, Parcours Neurosciences,** Université de Caen-Normandie – Mention Bien

- **Stage de Recherche de Master 2 (Septembre 2016 – Juin 2017) : INSERM-UNICAEN-EFS U1237, Caen, France :** *« Corrélats cérébraux de l'anxiété dans le vieillissement normal et pathologique : Etude multimodale »* dans le cadre du protocole IMAP+, sous la direction du Dr Gaëlle CHETELAT et l'assistance du Dr Robin DE FLORES
- **Stage de Recherche de Master 1 (Avril – Mai 2016) : Unité Inserm-EPHE-UNICAEN 1077, Caen, France :** *« Corrélats cérébraux de l'anxiété dans le vieillissement normal, en IRM »* dans le cadre du protocole IMAP+, sous la direction du Dr Gaëlle CHETELAT et l'assistance de Robin DE FLORES

2012-2015 **Licence de Biologie, Parcours Sciences du Vivant puis Neurosciences**, Université de Caen Normandie - Mention Assez Bien

Formations complémentaires :

2019 **Statistiques :** Notions fondamentales et traitement des petits échantillons – INSERM

2019 **Statistiques :** Analyses de données avec le logiciel R - INSERM

PRODUCTIONS SCIENTIFIQUES

Articles scientifiques

- Moulinet I*, Touron E*, Chételat G. La méditation dans le vieillissement : impact sur le bien-être, la cognition et le cerveau de la personne âgée. *Revue de Neuropsychologie* 2018 ; 10 (4) : 304-12 doi:10.1684/nrp.2018.0478
- Moulinet I*, Kuhn E*, Perrotin A, La Joie R, Tomadesso C, Desgranges B, Vivien D, Poisnel G, Chételat G. Cross-sectional and longitudinal characterization of SCD patients recruited from the community versus from a memory clinic: subjective cognitive decline, psychoaffective factors, cognitive performances and atrophy progression over time. *Alzheimer's Research & Therapy* 2019. doi.org/10.1186/s13195-019-0514-z
- Moulinet I, Landeau B, Touron E, De la Sayette V, Desgranges B, Vivien D, Marchant N, Poisnel G, Chételat G. Sex-specificities in anxiety and depressive symptoms across the lifespan and their links with multimodal neuroimaging: Anxiety is related to neurodegeneration in women (*Soumis*).
- Moulinet I, Touron E, Mézenge F, Dautricourt S, De la Sayette V, Vivien D, Marchant N, Poisnel G, Chételat G. Relationships of depressive symptoms to brain markers of neurodegeneration and amyloid deposition across the Alzheimer's continuum (*En préparation*).

Articles en co-auteure

- André C, Rehel S, Kuhn E, Landeau B, Moulinet I, Touron E, Ourry V, Le Du G, Mézenge F, Tomadesso C, de Flores R, Bejanin A, Sherif S, Delcroix N, Manrique A, Abbas A, Marchant N, Lutz A, Klimecki O, Collette F, Arenaza-Urquijo E, Poisnel G, Vivien D, Bertran F, de la Sayette V, Chételat G, Rauchs G and the Medit-Ageing Research Group. Association of Sleep-Disordered Breathing With Alzheimer Disease Biomarkers in Community-Dwelling Older Adults: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Neurology* 2020 ; e200311. doi:10.1001/jamaneurol.2020.0311
- Ourry V, Gonneaud J, Landeau B, Moulinet I, Touron E, Dautricourt S, Le Du G, Mézenge F, André C, Bejanin A, Sherif S, Marchant N, Paly L, Poisnel G, Vivien D, Chocat A, Quillard A, Ferrand-Derouge E, De la Sayette V, Rauchs G, Arenaza-Urquijo E, Chételat G, and the Medit-Ageing Research Group.Association of quality of life with structural, functional and molecular brain imaging in community-dwelling older adults (*Soumis*).
- Whitfield T, Barnhofer T, Acabchuk R, Cohen A, Lee M, Schlosser M, Arenaza-Urquijo E M, Böttcher A, Coll-Padros N, Collette F, Chételat G, Dautricourt S, Demnitz-King H, Klimecki O, Meiberth D, Moulinet I, Müller T, Parsons E, Sannemann L, Schild A-K, Touron E, Wirth M, Walker Z, Moitra E, Lutz A, Lazar S, Vago D, Marchant N. The effect of mindfulness-based programs on cognitive function in adults: a systematic review and meta-analysis (*Soumis*).

Dans le cadre du groupe de recherche Medit-Ageing

- Poisnel G, Arenaza-Urquijo E, Collette F, Klimecki OM, Marchant NL5, Wirth M, de La Sayette V, Rauchs G, Salmon E, Vuilleumier P, Frison E, Maillard A, Vivien D, Lutz A, Chételat G; Medit-Ageing Research Group (2018). The Age-Well randomized controlled trial of the Medit-Ageing European project: Effect of meditation or foreign language training on brain and mental health in older adults. *Alzheimer's & Dementia,* 4: 714–723 doi: 10.1016/j.trci.2018.10.011
- Lutz A, Klimecki OM, Collette F, Poisnel G, Arenaza-Urquijo E, Marchant NL, De La Sayette V, Rauchs G, Salmon E, Vuilleumier P, Frison E, Vivien D, Chételat G; Medit-Ageing Research Group (2018). The Age-Well observational study on expert meditators in the Medit-Ageing European project. *Alzheimer's & Dementia,* 4:756-764. doi: 10.1016/j.trci.2018.11.002

Communications orales

- **14ème Réunion Francophone sur la Maladie d'Alzheimer et Syndromes Apparentés, (11-14 Juin 2018, Lille, France) présenté par Elizabeth Kuhn** : Plainte mnésique de la personne âgée: lien avec la plainte de l'aidant, les performances cognitives et les facteurs psychoaffectifs. Moulinet I*, Kuhn E*, Perrotin A, La Joie R, Tomadesso C, Desgranges B, Vivien D, Poisnel G, Chételat G.

Communications affichées

- **Alzheimer's Imaging Consortium 2019 (AIC), (12-13 Juillet 2019, Los Angeles, USA):** Cross-sectional and longitudinal characterization of SCD patients recruited from the community versus from a memory clinic: subjective cognitive decline, psychoaffective factors, cognitive performances and atrophy progression over time. Moulinet I*, Kuhn E*, Perrotin A, La Joie R, Tomadesso C, Desgranges B, Vivien D, Poisnel G, Chételat G.
- **Alzheimer's Association International Conference 2019 (AAIC), (14-18 Juillet 2019, Los Angeles, USA):** Cross-sectional and longitudinal characterization of SCD patients recruited from the community versus from a memory clinic: subjective cognitive decline, psychoaffective factors, cognitive performances and atrophy progression over time. Moulinet I*, Kuhn E*, Perrotin A, La Joie R, Tomadesso C, Desgranges B, Vivien D, Poisnel G, Chételat G.
- **Le Congrès du Sommeil, 9ème édition, (23-25 Novembre 2017, Marseille, France) :** Impact de la durée de sommeil lent profond sur la charge amyloïde, la structure et la perfusion cérébrale au cours du vieillissement. André C, Mary A, Rehel S, Tomadesso C, Kuhn E, Moulinet I, Mézenge F, Bertran F, Chételat G*, Rauchs G*.

ACTIVITES D'ENCADREMENT ET D'ENSEIGNEMENT

- Encadrement de stages de recherche :
  - 3 étudiants de niveau Master 1 en neurosciences.
  - 1 étudiante de niveau Master 2 en neurosciences.
- Présentations régulières des travaux de recherche à des étudiants de niveau licence ou master, et des étudiants en ortophonie en stage d'observation dans le laboratoire.
- 2019 : 16h de TP de Reproduction et Développement à des L2, à l'Université de Caen.

FINANCEMENTS ET PRIX

Financements obtenus

- **Bourse de thèse** (100 k€) financée par l'INSERM (1er septembre 2017 – 1er septembre 2020).

Prix et distinctions obtenus

- **Prix de la meilleure communication catégorie « Recherche Clinique »** décerné par le Comité Scientifique de la Réunion Francophone sur la Maladie d'Alzheimer et Syndromes apparentés – Présenté par E.Kuhn (RFMASA 2018 - Lille)

Titre - Vers une meilleure compréhension des facteurs psychoaffectifs (anxiété et dépression) dans le vieillissement normal et pathologique : liens avec la cognition et la neuroimagerie multimodale.

Résumé : Les symptômes psychoaffectifs anxieux et dépressifs infra-cliniques sont fréquents chez les personnes âgées et sont associés à un risque accru de développer une démence et de progresser d'un stade prédémentiel à un stade démentiel. Cependant, ils pourraient également être des symptômes associés à une démence, et pourraient constituer une manifestation clinique de la pathologie sous-jacente. L'objectif de cette thèse était de contribuer à une meilleure compréhension des liens entre symptômes anxieux et dépressifs et les modifications cognitives et cérébrales structurales, fonctionnelles et moléculaires typiques de la maladie d'Alzheimer (MA), à la fois dans le vieillissement normal et au cours de cette pathologie. Nos résultats montrent que des symptômes anxieux élevés sont associés à un volume de substance grise plus bas chez les sujets âgés cognitivement sains, et ce uniquement chez les femmes. Cette même association est présente chez les sujets *Subjective Cognitive Decline* (SCD) recrutés dans la population générale, et montre une vulnérabilité accrue aux maladies neurodégénératives liées à l'âge, telles que les démences. Chez les SCD ayant consulté pour leur déclin cognitif subjectif, des symptômes dépressifs élevés sont associés à une charge amyloïde plus importante dans le cerveau, et donc à un risque accru de développer une MA, tandis que chez les sujets *Mild Cognitive Impairment* (MCI) et MA amyloïde positifs, ils sont liés à une meilleure cognition et conscience de ses propres troubles. Les symptômes psychoaffectifs semblent donc avoir un rôle évolutif au cours du passage du vieillissement normal au vieillissement pathologique, d'abord manifestation d'une vulnérabilité cérébrale, puis manifestation d'une pathologie sous-jacente et d'un risque de développement de MA, ils sont au contraire un marqueur de préservation chez les patients présentant un déclin cognitif (MCI et MA).

Title - Towards a better understanding of psychoaffective factors (anxiety and depression) in normal and pathological aging: links with cognition and multimodal imaging

Abstract : Subclinical psychoaffective symptoms of anxiety and depression are common in the elderly and are associated with an increased risk of developing dementia and progressing from a pre-dementia stage to a dementia stage. However, they could also be symptoms associated with dementia and could be a clinical manifestation of the underlying pathology. The aim of this thesis was to contribute towards a better understanding of the links between anxiety and depressive symptoms and Alzheimer's disease (AD) hallmarks, including cognitive, structural, functional and molecular modifications, both in normal aging and during the course of this pathology. Our results show that higher anxiety symptoms are associated with lower grey matter volume in cognitively healthy elderly subjects, but only in women. This same association is present in all Subjective Cognitive Decline (SCD) participants recruited from the general population, and shows an increased vulnerability to age-related neurodegenerative diseases such as dementia. In Subjective Cognitive Decline (SCD) subjects, high depressive symptoms are associated with greater amyloid load in the brain, and thus an increased risk of developing AD, while in amyloid-positive Mild Cognitive Impairment (MCI) and AD subjects, they are related to better cognition and awareness of their cognitive deficits. Psychoaffective symptoms thus seem to have an evolving role during the transition from normal aging to pathological aging; they first manifest a brain vulnerability, then an underlying pathology and a risk of developing AD, and then are a marker of preservation in patients with cognitive decline (MCI and AD).

Mots Clés : Facteurs psychoaffectifs, symptômes anxieux, symptômes dépressifs, Vieillissement, Maladie d'Alzheimer, Neuroimagerie, Cognition, Protéine amyloïde bêta, Imagerie par Résonance Magnétique, Tomographie par Emission de Positons

Discipline : Sciences de La vie et de la Santé.

Laboratoire : Unité INSERM-Université de Caen Normandie U1237 PhIND "Physiopathology and Imaging of Neurological Disorders", Institute Blood and Brain @ Caen-Normandie (BB@C), GIP CYCERON, Bd Henri Becquerel, BP 5229, 14074 Caen Cedex.