Modifications du sommeil liées à l'âge : liens avec la cognition et les biomarqueurs du vieillissement et de la maladie d'Alzheimer en neuroimagerie

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Modifications du sommeil liées à l'âge : liens avec la cognition et les biomarqueurs du vieillissement et de la maladie d'Alzheimer en neuroimagerie

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Liste des abréviations

Aβ : Peptide β-amyloïde

AASM : *American Academy of Sleep Medicine*

APOE : Apolipoprotéine E

APP : *Amyloid Precursor Protein*

DMN : *Default Mode Network* (réseau du mode par défaut)

DNF : Dégénérescences Neurofibrillaires

ECG : Electrocardiogramme

EEG : Electroencéphalogramme

EMG : Electromyogramme

EOG : Electrooculogramme

FDG : ^{18}F-Fluorodésoxyglucose

IAH : Index d'Apnées-Hypopnées

IMAP : Imagerie Multimodale de la Maladie d'Alzheimer à un stade Précoce

IRM : Imagerie par Résonance Magnétique

IWG : *International Working Group*

LCS : Liquide Cérébro-Spinal

MA : Maladie d'Alzheimer

MCI : *Mild Cognitive Impairment*

MMSE : *Mini Mental State Examination*

NIA-AA : *National Institute of Aging-Alzheimer's Association*

PIB : *Pittsburgh Compound-B*

PPC : Pression Positive Continue

PSG : Polysomnographie

PSQI : *Pittsburgh Sleep Quality Index*

SAOS : Syndrome d'Apnées Obstructives du Sommeil

SCD : *Subjective Cognitive Decline*

SL : Sommeil Lent

SLP : Sommeil Lent Profond (N3)

SP : Sommeil Paradoxal

SUVr : *Standardized Uptake Value ratio*

Tau : *Tubule Associated Unit*

- p-tau : phospho-tau
- t-tau : tau total

TEP : Tomographie par Emission de Positons

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1. INTRODUCTION GENERALE

Selon l'Organisation Mondiale de la Santé, la proportion de personnes âgées de plus de 60 ans va presque doubler à l'horizon 2050, et dépasser les 20% de la population totale. Ce vieillissement de la population s'accompagne d'une augmentation de la prévalence des pathologies liées à l'âge, notamment des démences. La forme de démence la plus fréquente est la maladie d'Alzheimer (MA), qui est une pathologie multifactorielle dont l'étiologie reste à ce jour mal comprise, et pour laquelle il n'existe aucun traitement curatif. Un axe majeur des recherches actuelles est d'identifier les différents facteurs pouvant influencer les mécanismes physiopathologiques de la MA, dans l'espoir de développer de nouvelles stratégies thérapeutiques visant à retarder l'apparition des symptômes, et/ou ralentir le déclin cognitif. Dans ce contexte, l'étude du sommeil fait l'objet d'un intérêt croissant. En effet, le sommeil joue un rôle majeur dans la cognition, et des études récentes menées sur modèle animal montrent qu'il serait lié aux processus physiopathologiques de la MA. Cependant, les études chez l'Homme sont encore peu nombreuses, d'autant plus lorsque l'on considère spécifiquement la population agée. Ainsi, l'objectif de cette thèse est de mieux caractériser les liens entre les modifications du sommeil liées à l'âge, les capacités cognitives, et les biomarqueurs du vieillissement et de la MA en neuroimagerie. Nous poserons tout d'abord le cadre théorique de ce travail de thèse, en décrivant dans une première partie l'état actuel des connaissances sur la MA, avec une emphase particulière sur ses altérations cérébrales associées, en comparaison du vieillissement normal. Ensuite, nous aborderons de manière détaillée le sommeil, ses modifications dans le vieillissement et la MA, et ses liens avec l'intégrité cognitive et cérébrale. Dans la partie expérimentale, nous présenterons les résultats des trois études menées dans le cadre de ce travail de thèse, que nous discuterons et remettrons en perspective dans une dernière partie.

2. CADRE THEORIQUE

2.1. MALADIE D'ALZHEIMER

2.1.1. GENERALITES

La maladie d'Alzheimer (MA) est une pathologie neurodégénérative caractérisée par un déclin cognitif progressif conduisant à une perte d'autonomie dans la vie quotidienne et à la démence. Elle représente la forme de démence la plus commune du sujet âgé, comptant pour 60 à 70% des cas selon l'Organisation Mondiale de la Santé (OMS). Les troubles mnésiques sont au centre du tableau clinique, survenant de façon précoce et évoluant progressivement. Ils affectent en premier lieu la mémoire épisodique, correspondant à la mémoire des événements personnellement vécus, situés dans leur contexte spatio-temporel d'acquisition. On observe également des troubles exécutifs ainsi qu'un syndrome aphaso-apraxo-agnosique, fréquemment accompagnés de symptômes neuropsychiatriques tels que l'apathie ou des symptômes anxio-dépressifs.

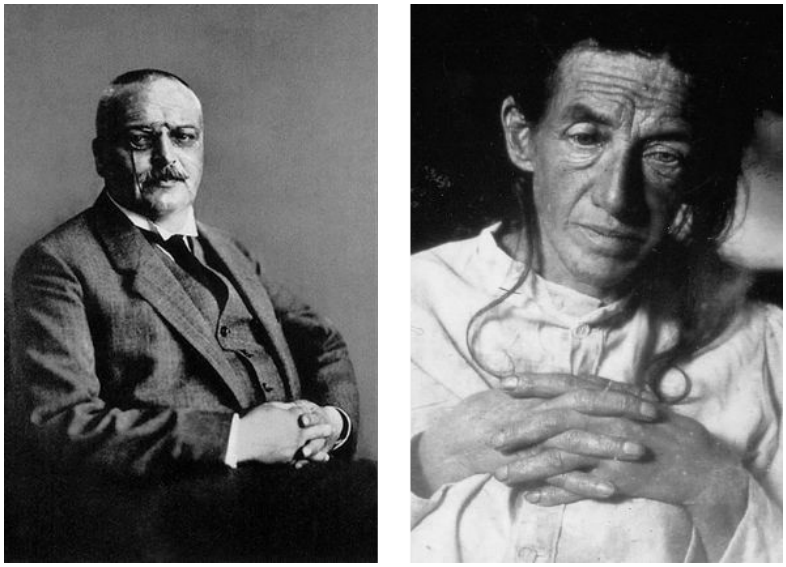


Figure 1: Portraits d'Aloïs Alzheimer *(gauche)* **et Auguste Deter** *(droite)*.

Si la description initiale par Aloïs Alzheimer en 1906 reposait sur le cas d'Auguste Deter, âgée de seulement 55 ans **(Figure 1)**, la MA est en réalité essentiellement une maladie du vieillissement. En effet, moins de 2% des cas de MA sont observés chez des patients âgés de moins de 65 ans (Winblad et al., 2016). L'OMS estime qu'à l'échelle mondiale, près de 50 millions de personnes sont atteintes de démence (dont 1 à 1,5 millions en France). On dénombrerait 10 millions de nouveaux cas par an dans le monde, dont environ 200 000 cas en France. L'âge est le principal facteur de risque de démence, et les projections à l'horizon 2050 prévoient une considérable augmentation de la proportion de personnes âgées de plus de 60 ans dans le monde **(Figure 2A)**. De plus, on s'attend à un triplement du nombre de personnes atteintes de démence avec plus de 131 millions de patients concernés à l'échelle mondiale **(Figure 2B)**.

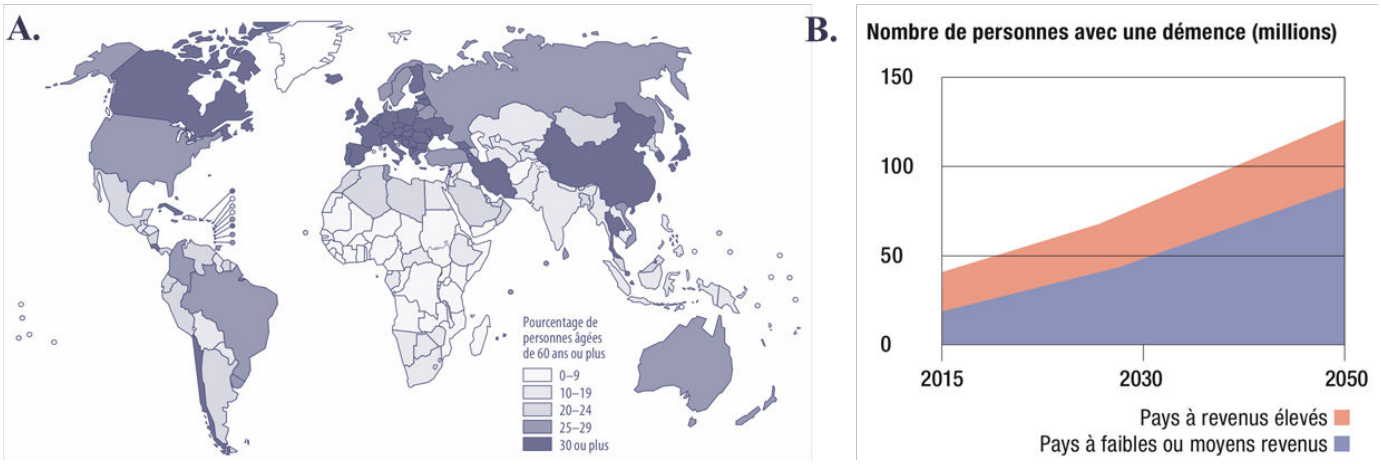


Figure 2: Projections démographiques et épidémiologiques à l'horizon 2050.

A) Proportion de personnes âgées de plus de 60 ans à l'horizon 2050.

D'après le rapport mondial sur le vieillissement (2016) (*Organisation Mondiale de la Santé, www.who.int).*

B) Nombre de personnes atteintes de démence dans le monde à l'horizon 2050.

D'après le World Alzheimer Report (2015) *(Alzheimer's Disease International, www.alz.co.uk).*

Si l'on commence à observer une légère diminution de l'incidence et de la prévalence de la démence dans les pays occidentaux, notamment en Europe et aux Etats-Unis (Grasset et al., 2016; Matthews et al., 2013), probablement grâce à une meilleure prise en charge de certains facteurs de risque cardiovasculaires, une forte augmentation de la prévalence est attendue dans les pays à revenus faibles à intermédiaires **(Figure 2B)**. Ainsi, la MA constitue un enjeu sociétal majeur à l'échelle mondiale.

2.1.2. PROCESSUS NEUROPATHOLOGIQUES

La physiopathologie de la MA se caractérise par des lésions positives, correspondant aux dépôts extracellulaires de peptide beta-amyloïde (Aβ) et aux dégénérescences neurofibrillaires (DNF) intracellulaires, et des lésions négatives que constituent les pertes neuronales et synaptiques (voir Duyckaerts et al., 2009 pour revue). Les lésions négatives ne sont que peu spécifiques de la MA, si bien que prises de manière isolée, elles n'entrent pas en compte dans le diagnostic de certitude de la MA.

2.1.2.1. Pathologie amyloïde

a. Peptide Aβ

Le peptide Aβ résulte du clivage enzymatique de la protéine transmembranaire APP (pour « *amyloid precursor protein* »). Le clivage de l'APP par l'enzyme α-sécrétase constitue la voie catabolique non amyloïdogénique, la plus fréquente. En revanche, la voie catabolique amyloïdogénique résulte du clivage successif de l'APP par deux enzymes : la β-sécrétase clive l'APP dans son domaine extracellulaire, créant le fragment membranaire C99, lui-même clivé par

l'enzyme γ-sécrétase (Duyckaerts et al., 2009). Ce double clivage conditionne la production du peptide Aβ, pouvant comporter 38 à 43 acides aminés, les isoformes principales étant l'Aβ40 (80 à 90% des formes existantes) et l'Aβ42 (5 à 10%). L'isoforme Aβ42 est de nature hydrophobe, et semble très encline à s'agréger en plaques extracellulaires **(Figure 3A)**. Les oligomères Aβ solubles préfibrillaires semblent quant à eux plus toxiques que les plaques elles-mêmes, et provoqueraient de nombreux dysfonctionnements cellulaires et synaptiques (voir Walsh and Selkoe, 2007 pour revue).

b. Topographie des lésions amyloïdes

La propagation des dépôts amyloïdes cérébraux suit une séquence hiérarchisée décrite par Braak et Braak en 1991, en trois stades successifs **(Figure 3B)**. Au stade A, les dépôts sont situés au niveau des aires néocorticales orbito-frontales, temporales et occipitales, puis s'étendent au reste du lobe frontal et au lobe pariétal au stade B (où la formation hippocampique peut également être concernée), avant de toucher l'ensemble des aires néocorticales au stade C (Braak and Braak, 1991).

En 2002, Thal et collaborateurs ont affiné cette séquence hiérarchique en proposant 5 stades d'accumulation (Thal et al., 2002) **(Figure 3C)**. Lors de la première phase, les dépôts Aβ sont situés au niveau du néocortex frontal, temporal, pariétal et occipital. Durant la phase 2, ils touchent la région temporale interne (le cortex entorhinal et le sous-champ CA1 de l'hippocampe) et l'insula, ainsi que l'amygdale et le cortex cingulaire pour 33 à 50% des individus. Au stade 3, les dépôts s'étendent aux noyaux sous-corticaux, atteignant notamment les noyaux caudés, le putamen, le thalamus, et l'hypothalamus. La 4ème phase marque la propagation des dépôts dans les noyaux du

tronc cérébral (substance noire, colliculi supérieurs et inférieurs, formation réticulée), avant d'atteindre le pont et le cervelet dans la 5ème et dernière phase.

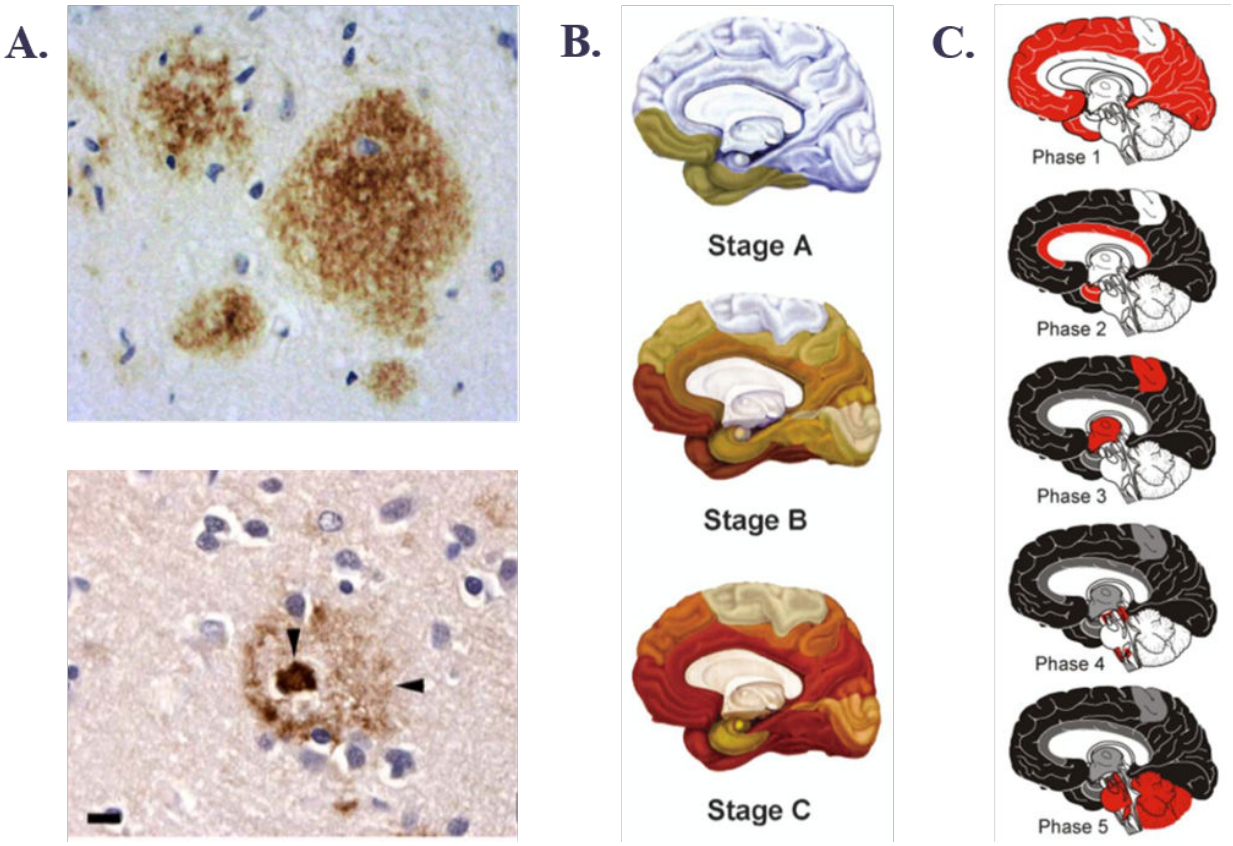


Figure 3: Pathologie amyloïde.

A) Dépôts amyloïdes observés en microscopie après marquage immunohistochimique.
D'après Small *et al.*, 2008 *(haut)* et Duyckaerts *et al.*, 2009 *(bas)*.

B) Evolution topographique des dépôts amyloïdes selon les 3 stades de Braak.
D'après Braak & Braak, 1991.

C) Evolution topographique des dépôts amyloïdes selon les 5 phases de Thal.
D'après Thal *et al.*, 2002.

2.1.2.2. Pathologie tau

a. Protéine Tau

La protéine Tau (pour *tubule-associated unit*) appartient à la famille des protéines associées aux microtubules (MAP, pour *microtubule-associated proteins*). En conditions physiologiques, elle joue un rôle de stabilisation des microtubules au travers d'un jeu de phosphorylations, et est donc essentielle au trafic intracellulaire (Billingsley and Kincaid, 1997). En conditions pathologiques, la protéine tau est transloquée dans le compartiment somato-dendritique, où elle subit un niveau anormal de phosphorylation. Cela provoque sa dissociation des microtubules puis son agrégation en paires de filaments au niveau intracellulaire, conduisant à une désorganisation du transport vésiculaire intraneuronal puis à la mort cellulaire (Ballatore et al., 2007). Les agrégats de protéine Tau sont présents au niveau du corps cellulaire du neurone (dégénérescences neurofibrillaires, ou « DNF »), dans les dendrites (fibres tortueuses, ou « *neuropil threads* »), et au niveau axonal (couronne des plaques dendritiques) (Duyckaerts et al., 2009).

b. Topographie des DNF

Les DNF présentent également une séquence de progression stéréotypée, tout d'abord découpée en 6 stades par Braak & Braak en 1991. Au stade I, les lésions sont présentes au niveau du cortex transentorhinal, du noyau basal de Meynert et du locus coeruleus, puis se propagent ensuite lors du stade II vers le cortex entorhinal ainsi que vers l'hippocampe, dans une moindre mesure. Ensuite, l'hippocampe, le thalamus et l'amygdale sont touchés au stade III. Lors des stades IV et V, les DNF atteignent le néocortex associatif de façon modérée puis sévère, puis touchent l'ensemble du cerveau au stade VI (Braak and Braak, 1991). Classiquement, les stades I et II sont regroupés pour constituer le *transentorhinal stage*, les stades III et IV forment le *limbic stage*, et les stades V et VI

forment l'*isocortical stage*. Cette séquence a par la suite été affinée en 10 stades (S1 à 10) (Delacourte et al., 1999). Ainsi, les DNF touchent d'abord le cortex transentorhinal (S1), puis le cortex entorhinal (S2) et l'hippocampe (S3). Ensuite, les DNF touchent le cortex temporal antérieur (S4), inférieur (S5), et moyen (S6). Au stade S7, les DNF atteignent le cortex cingulaire et les aires polymodales d'association (dont les régions temporales supérieures, pariétales inférieures, et frontales antérieures). Au stade S8, les aires unimodales (dont l'aire de Broca) sont touchées. Suivent ensuite les aires sensorielles ou motrices primaires (dont le cortex moteur et les aires occipitales) au stade S9. Enfin, au stade S10, les DNF sont présentes dans l'ensemble du néocortex. Les auteurs précisent que d'un point de vue clinique, les stades S1 et S2 sont asymptomatiques, puis les troubles cognitifs apparaissent entre les stades S3 et S6, avant l'apparition de la démence à partir du stade S7 pour la majorité des cas.

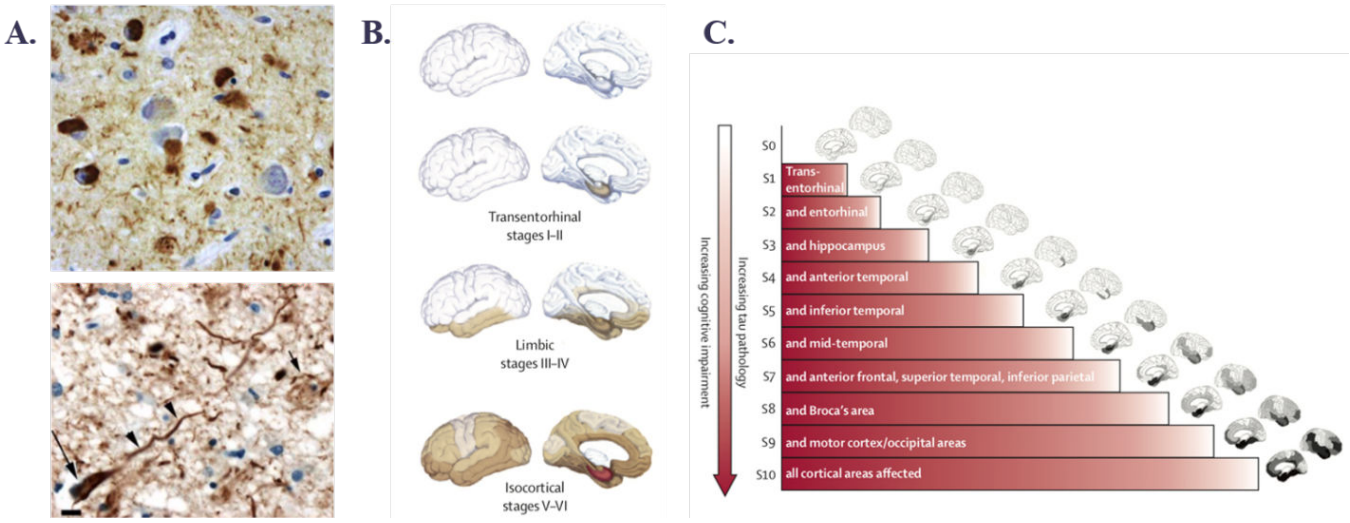


Figure 4: Pathologie tau.
A) Dégénérescences neurofibrillaires (DNF) observées en microscopie après marquage immunohistochimique. D'après Small et al., 2008 *(haut)* et Duyckaerts et al., 2009 *(bas)*.
B) Progression des DNF selon les 6 stades de Braak, d'après Braak & Braak, 1991.
C) Progression des DNF selon les 10 stades de Delacourte, d'après Delacourte et al., 1999.

2.1.2.3. Pertes neuronales et synaptiques

Les pertes neuronales et synaptiques dans la MA sont à l'origine de l'atrophie cérébrale, et ont principalement été documentées dans le lobe temporal interne, notamment au niveau du sous-champ CA1 de l'hippocampe, au début de la maladie (Scheff and Price, 2006; West et al., 1994). De plus, elles sont également observées au niveau du lobe temporal externe, des régions frontales et pariétales (Gómez-Isla et al., 1997; Grignon et al., 1998; Scheff and Price, 2006). Leur topographie correspond à celle des DNF, mais leur proportion est parfois plus importante que ces dernières dans une même région (Gómez-Isla et al., 1997), si bien qu'elles pourraient également être le résultat de l'apoptose induite par la toxicité de l'Aβ (Duyckaerts et al., 2009; McLean et al., 1999). Enfin, si certaines études sont en faveur de leur apparition précoce et de leur implication dans les symptômes cognitifs (Gómez-Isla et al., 1997), d'autres études les identifient comme un phénomène tardif survenant après l'apparition des symptômes (Grignon et al., 1998).

2.1.3. NEUROPSYCHOLOGIE

2.1.3.1. Effets de l'âge

L'avancée en âge s'accompagne d'une diminution progressive des performances cognitives (Craik and Salthouse, 2008; Harada et al., 2013). De façon générale, ces modifications concernent la vitesse de traitement, les capacités attentionnelles, les fonctions exécutives, la mémoire de travail (permettant le maintien temporaire et la manipulation d'informations) et la mémoire épisodique, correspondant à la mémoire des évènements vécus, situés dans leur contexte spatio-temporel d'acquisition (Tulving, 2004). En revanche, certains domaines cognitifs semblent bien résister aux effets de l'âge, comme la mémoire sémantique (mémoire des mots, des concepts et des

connaissances générales sur le monde) et la mémoire procédurale, correspondant aux habiletés perceptives, motrices et cognitives et aux savoir-faires.

2.1.3.2. Profil neuropsychologique des patients MA

Au-delà des effets du vieillissement normal, les patients atteints de MA présentent des troubles cognitifs spécifiques, comparés à des sujets sains de même âge. Comme décrit précédemment, les troubles mnésiques sont au centre du tableau clinique des patients atteints de MA (Eustache et al., 2006), et affectent en premier lieu la mémoire épisodique, pour les formes typiques, majoritaires. Ces déficits de mémoire épisodique concernent à la fois les processus d'encodage, de stockage et de récupération (Carlesimo and Oscar-Berman, 1992; Eustache et al., 2006; Salmon and Bondi, 2009), et sont dits « authentiques » puisque dans des tâches d'apprentissage de listes de mots, les performances ne sont que peu améliorées dans les conditions de rappel indicé ou de reconnaissance. En comparaison, dans le vieillissement normal, les troubles de mémoire épisodique sont dits « apparents » car ils sont plutôt la conséquence de difficultés de récupération, avec un bénéfice de l'indiçage (Isingrini and Taconnat, 2008).

Avec l'avancée dans la pathologie, les atteintes se propagent à la mémoire de travail (Belleville et al., 1996; Collette et al., 1999a; Huntley and Howard, 2010) et à la mémoire sémantique (Adlam et al., 2006; Aronoff et al., 2006; Henry et al., 2004; Hodges and Patterson, 1995). En revanche, le système de représentations perceptives, qui sous-tend notamment les effets d'amorçage, et la mémoire procédurale sont relativement préservés, du moins aux premiers stades de la maladie (Eustache et al., 2006; Park et al., 1998; Salmon and Bondi, 2009; van Halteren-van Tilborg et al., 2007). En parallèle, les patients MA présentent également des troubles attentionnels et exécutifs

(fonctions de haut niveau permettant de réaliser des tâches complexes et inhabituelles) (Perry and Hodges, 1999). On constate notamment des difficultés de flexibilité mentale, d'inhibition, et de planification, respectivement mesurées grâce au Trail Making Test, test de Stroop et à la tour de Londres (Amieva et al., 2004; Collette et al., 1999b; Franceschi et al., 2007).

Enfin, divers symptômes neuropsychiatriques sont fréquemment observés, augmentant avec l'avancée de la pathologie. Les symptômes les plus prévalents sont l'apathie, l'anxiété, et la dépression, mais on peut également retrouver des symptômes d'agitation et d'hallucination à des stades plus tardifs (Geda et al., 2013; Lanctôt et al., 2017; Zhao et al., 2016). De plus, une anosognosie vis-à-vis des troubles cognitifs est fréquemment observée (Salmon et al., 2005).

2.1.4. CRITERES DIAGNOSTIQUES CLINIQUES

2.1.4.1. Critères de Maladie d'Alzheimer

Les critères les plus utilisés en pratique clinique sont ceux 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). Ces critères probabilistes proposent trois degrés de certitude du diagnostic : possible, probable et certain. Les critères de *MA probable* reposent sur la présence d'un syndrome démentiel (c'est-à-dire une perte d'autonomie dans la vie quotidienne) déclaré entre 40 et 90 ans, impliquant des déficits dans au moins deux domaines cognitifs et un déclin progressif des performances mnésiques, en l'absence de toute autre pathologie cérébrale ou systémique pouvant expliquer les déficits observés. Ce diagnostic peut être appuyé par la détérioration de fonctions cognitives spécifiques, telles que le

langage (aphasie), les capacités motrices (apraxie), perceptives (agnosie), ou des antécédents familiaux de MA. En revanche, le diagnostic de certitude (ou *MA certaine*) n'est pas possible du vivant du patient, puisqu'il n'est établi qu'après une autopsie confirmant la présence de lésions neuropathologiques caractéristiques. Ces critères diagnostiques de démence de type Alzheimer sont très proches de ceux proposés dans le DSM IV. Les critères de McKhann se basent principalement sur l'évaluation clinique et neuropsychologique du patient, et reposent sur la présence d'un syndrome démentiel. Or, il est désormais bien démontré que la pathologie commence à se développer plusieurs décennies avant l'apparition de la démence (voir la section 2.2 Neuroimagerie du vieillissement normal et pathologique), et l'installation des déficits cognitifs est donc insidieuse et progressive. De nombreuses recherches se sont donc employées à étudier et poser un cadre autour des stades pré-démentiels de la MA, afin de pouvoir diagnostiquer la pathologie dès les premiers symptômes cognitifs mais avant le stade de démence.

2.1.4.2. Concept et critères de Mild Cognitive Impairment

Dans ce contexte, le concept de *Mild Cognitive Impairment* (MCI, ou Trouble Cognitif Léger) a été proposé afin de caractériser des patients particulièrement à risque d'évoluer vers une maladie d'Alzheimer, présentant une plainte mnésique associée à des déficits cognitifs objectifs de nature mnésique, avec toutefois une autonomie préservée en vie quotidienne. Les critères initiaux de MCI ont été proposés par Petersen en 1999 (Petersen et al., 1999), et stipulent que le patient doit présenter :

- Une plainte de mémoire, préférentiellement corroborée par un informant.
- Une altération de la mémoire, documentée en fonction des valeurs de référence aux tests neuropsychologiques.

- Une relative préservation des domaines non-mnésiques.
- Une préservation des activités de la vie quotidienne.
- Une absence de syndrome démentiel.

La population de patients MCI ainsi définie restant hétérogène, ces critères initiaux ont été révisés et affinés, afin d'introduire les concepts de MCI amnésique (aMCI, où la mémoire est préférentiellement altérée) et non-amnésique (naMCI, où d'autres domaines cognitifs sont déficitaires), en précisant le nombre de fonctions cognitives atteintes (*single versus multi-domain*) (**Figure 5A** ; Petersen, 2004). Cette nouvelle classification permet de distinguer des patients possédant des étiologies sous-jacentes présumées différentes, et qui évolueront vers des pathologies différentes **(Figure 5B)**. Ainsi, une présentation de type aMCI aurait plus de risque d'évoluer vers une MA (Mitchell and Shiri-Feshki, 2009; Nordlund et al., 2010; Petersen et al., 2009).

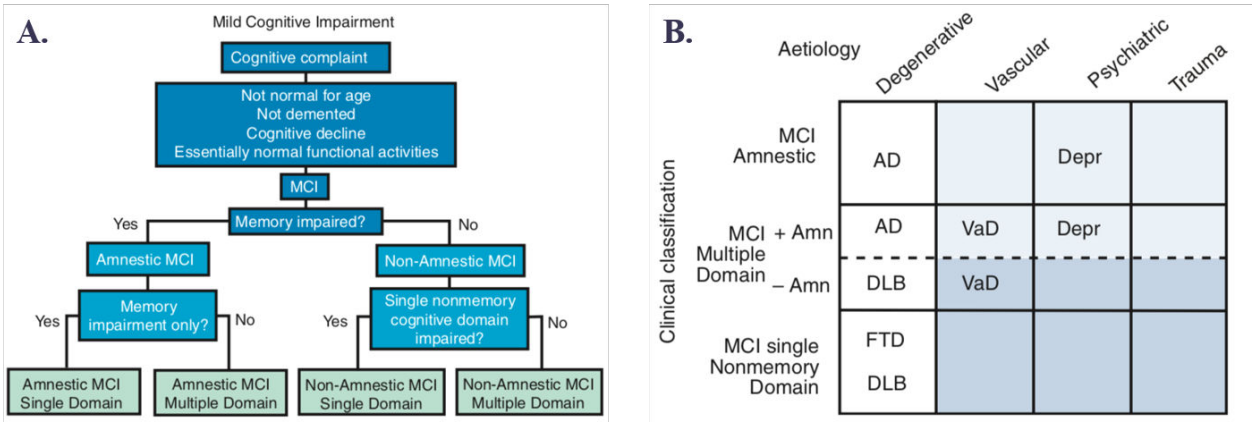


Figure 5: Critères de classification des patients MCI.
Organigramme de classification (A) et étiologie sous-jacente préférentielle (B) des différents sous-types de patients MCI. *D'après Petersen et al., 2004.*
Abréviations : AD : Alzheimer's Disease (Maladie d'Alzheimer), Depr : Depression (Dépression), DLB : Dementia with Lewy Bodies (Démence à Corps de Lewy), MCI : Mild Cognitive Impairment, VaD : Vascular Dementia (Démence Vasculaire).

La prévalence du MCI est estimée entre 12 et 18% chez les plus de 60 ans, avec un ratio de deux aMCI pour un naMCI (Di Carlo et al., 2007; Langa and Levine, 2014; Petersen, 2016). Le taux annuel de conversion des patients MCI vers une MA est de 5 à 20% (Langa and Levine, 2014; Manly et al., 2008; Petersen et al., 2009), et il est à noter que beaucoup de patients restent stables et ne progresseront pas vers une MA, même après 10 ans de suivi, voire effectueront une réversion vers des performances dans les normes (Mitchell and Shiri-Feshki, 2009).

2.1.4.3. Concept et critères de Subjective Cognitive Decline

Plus récemment, le concept de *Subjective Cognitive Decline* (SCD) a été proposé par la Subjective Cognitive Decline Initiative (SCD-I) (Jessen et al., 2014) **(Figure 6)**.

Le SCD correspond à un stade pré-MCI caractérisé par :

- La perception d'un déclin des capacités cognitives en comparaison d'un statut antérieur, sans relation avec un événement aigu.
- Des performances dans les normes pour l'âge, le sexe, et le niveau d'éducation aux tests neuropsychologiques standards, utilisés pour diagnostiquer un MCI ou une MA au stade prodromal.

Les critères d'exclusion sont la présence d'un MCI, d'une MA au stade prodromal, ou d'une démence, ou le fait que la plainte puisse être expliquée par une pathologie psychiatrique ou neurologique (autre qu'une MA), une autre pathologie, la prise de médicaments ou de toute substance psychoactive.

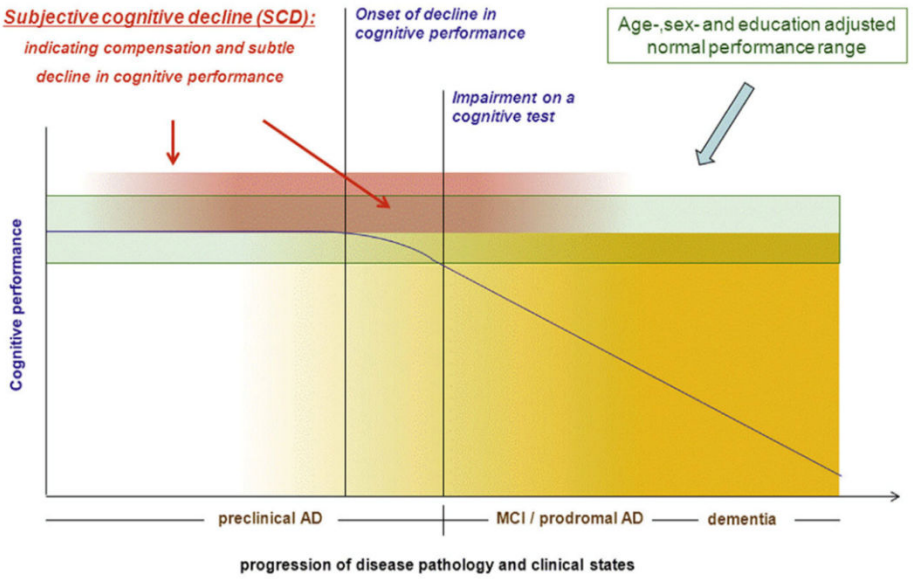


Figure 6: Décours du déclin cognitif.
Le stade de SCD est conceptualisé comme un stade préclinique caractérisé par des efforts cognitifs compensatoires et un déclin cognitif subtil, précédant le stade de MCI. *D'après Jessen et al., (2014).*

Il est à noter que dans ces critères généraux, la plainte cognitive peut toucher toutes les sphères de la cognition, et n'est pas nécessairement restreinte à la mémoire épisodique. Ainsi, des critères « *SCD plus* » ont été proposés afin d'identifier des individus plus susceptibles d'entrer dans le cadre d'une MA au stade préclinique (Jessen et al., 2014). En plus des critères généraux, les éléments augmentant la susceptibilité du stade préclinique de la MA incluent :

- Un sentiment de déclin des performances mnésiques.
- Une apparition de la plainte dans les 5 dernières années.
- Une apparition de la plainte après l'âge de 60 ans.
- Une inquiétude associée à la présence du déclin cognitif subjectif.
- Le sentiment de présenter des performances inférieures aux individus de même âge.

Et si possible :

- Que le déclin cognitif subjectif soit corroboré par un proche.
- Que l'individu soit porteur de l'allèle ε4 du gène de l'APOE.
- Confirmé par la présence d'un biomarqueur de la pathologie (définissant le stade préclinique de la MA).

2.1.5. INTEGRATION DES BIOMARQUEURS : VERS UNE DEFINITION BIOLOGIQUE DE LA MA

Les principales limites des premiers critères de McKhann établis en 1984 résidaient dans le fait qu'ils reposent sur la présence d'un syndrome démentiel, conditionnant un diagnostic à un stade très tardif de la maladie et sans prise en compte de la neuropathologie sous-jacente. Toutefois, il est maintenant clairement établi que la neuropathologie progresse plusieurs décennies avant la déclaration de la démence. Ainsi, à la lumière de la compréhension croissante des mécanismes de la pathologie, et de l'accessibilité croissante des techniques d'imagerie en pratique clinique, l'ensemble des critères reposant uniquement sur les symptômes cognitifs ont subi des révisions, laissant une place grandissante à l'intégration des biomarqueurs de la pathologie.

Ainsi, trois catégories de biomarqueurs sont couramment considérées dans le cadre de la MA :

- Les biomarqueurs de la pathologie amyloïde mesurés dans le liquide cérébro-spinal (LCS) (niveaux d'Aβ42 ou ratio Aβ42/Aβ40) ou en Tomographie par Emission de Positons (TEP).
- Les biomarqueurs de la pathologie tau, correspondant au niveau de phospho-tau (p-tau) dans le LCS, ou au marquage tau mesuré en TEP.

- Les biomarqueurs de neurodégénérescence, que sont l'atrophie mesurée en IRM, l'hypométabolisme mesuré en TEP couplée au ^{18}F-Fluorodésoxyglucose (TEP-FDG), ou le niveau de tau total (t-tau) dans le LCS.

En 2011, le National Institute of Aging-Alzheimer's Association (NIA-AA) a publié une série de nouveaux critères diagnostiques permettant de distinguer la phase préclinique (Sperling et al., 2011), le stade de MCI (Albert *et al.*, 2011, avec une introduction de la notion de MCI dû à une maladie d'Alzheimer, ou « *MCI due to AD* ») et de démence (McKhann *et al.*, 2011, avec la notion de « *dementia due to AD* »), intégrant les biomarqueurs de la pathologie amyloïde (mesurés en TEP ou dans le LCS) et de la neurodégénérescence (t-tau dans le LCS, hypométabolisme temporo-pariétal, atrophie du lobe temporal médian), cette fois-ci nécessairement de façon concomitante (voir le **Tableau 1** ci-dessous). Il est à noter que plusieurs critères ont été successivement proposés pour la recherche par L'*International Working Group* (IWG), intégrant les biomarqueurs dès 2007 (Dubois et al., 2007), avec des révisions successives, notamment afin d'élargir ces critères aux formes atypiques de MA (Dubois et al., 2010, 2014, 2016), que nous ne détaillerons pas ici.

Maladie d'Alzheimer au stade préclinique (« Preclinical AD ») *Sperling et al., 2011*	• **Stade 1 :** Amyloïdose asymptomatique • **Stade 2 :** Amyloïdose + Neurodégénerescence • **Stade 3 :** Amyloïdose + Neurodégénerescence + Déclin Cognitif Subtil
MCI dû à la MA (« MCI due to AD ») *Albert et al., 2011*	• **Probabilité intermédiaire :** positivité à l'amyloïde et lésions neuronales non testées, ou positivité à l'amyloïde non testée mais lésions neuronales présentes. • **Probabilité élevée :** positivité à l'amyloïde et lésions neuronales.
Démence Alzheimer probable (« Probable AD dementia ») *McKhann et al., 2011*	**Critères généraux de démence, et caractéristiques additionnelles décrites ci-dessous remplies :** • Début insidieux • Evidence claire d'une dégradation • Déficits initiaux et principaux: o Profil amnésique : le plus commun. o Présentations non amnésiques : langage, visuospatiale, exécutive. **Appuyé par:** • Un déclin cognitif documenté. • La présence de mutations génétiques causales de la MA (APP, PSEN1 ou 2). **Certitude augmentée en cas de présence de neuropathologie caractéristique de la MA** (dépôts amyloïdes et lésions ou dégénérescence neuronale).

Tableau 1: Tableau récapitulatif des critères diagnostiques de 2011 du NIA-AA.

D'après Sperling *et al.*, 2011, Albert *et al.*, 2011, et McKhann *et al.*, 2011.

Les dernières recommandations pour la recherche, proposées par le NIA-AA en 2018 (Jack et al., 2018a), représentent un important changement de paradigme, puisque selon ces critères, les différents stades du continuum Alzheimer sont définis uniquement par la pathologie sous-jacente, et ne reposent plus sur les symptômes cognitifs. Ainsi, en accord avec l'hypothèse dominante de la

cascade amyloïde (Hardy and Selkoe, 2002), la présence avérée de biomarqueurs de la pathologie amyloïde place un individu au sein du continuum Alzheimer, et la présence conjointe de marqueurs amyloïde et tau caractérise la maladie d'Alzheimer **(Tableau 2)**. Les biomarqueurs de neurodégénérescence ainsi que les symptômes cognitifs ne sont désormais utilisés que pour évaluer la sévérité des atteintes. Il est à noter que cette définition « biologique » de la MA est actuellement débattue dans la communauté scientifique (Jagust et al., 2019; Louie, 2019; McCleery et al., 2019; Sweeney et al., 2019).

AT(N) profiles	**Biomarker category**	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

Tableau 2: Définition des profils selon les biomarqueurs A/T/N.
Abréviations : A, amyloïde ; T, tau ; N, neurodégenerescence. *D'après Jack et al., 2018.*

2.2. NEUROIMAGERIE DU VIEILLISSEMENT NORMAL ET PATHOLOGIQUE

2.2.1. MODIFICATIONS STRUCTURALES : SUBSTANCE GRISE

2.2.1.1. Sujets âgés cognitivement sains

L'Imagerie par Résonance Magnétique (IRM) est une technique d'imagerie non invasive permettant notamment de visualiser *in vivo* le volume ou la densité de la substance grise, et de mesurer l'atrophie cérébrale consécutive aux pertes neuronales et synaptiques. Chez les sujets âgés cognitivement sains, on observe un élargissement ventriculaire et une diminution du volume de substance grise cérébrale avec l'âge (Raz et al., 2005). Cette perte de volume suit un gradient antéro-postérieur, et est donc maximale au niveau des aires frontales (Kalpouzos et al., 2009; Lockhart and DeCarli, 2014; Raz et al., 1997, 2005; Resnick et al., 2003; Salat et al., 2004). Bien qu'affectés dans une moindre mesure, cette atrophie concerne également les lobes pariétaux, temporaux et occipitaux, ainsi que le thalamus et l'hippocampe antérieur, notamment le subiculum (de Flores et al., 2015b; Fjell et al., 2009; La Joie et al., 2010; Lockhart and DeCarli, 2014; Raz et al., 2005; Resnick et al., 2003; Salat et al., 2004).

2.2.1.2. Dans la MA et aux stades pré-démentiels

Comparés à des sujets sains de même âge, l'une des caractéristiques majeures des patients atteints de MA est une importante atrophie hippocampique (Apostolova et al., 2012; Chetelat and Baron,

2003; Colliot et al., 2008). Cette atrophie semble concerner préférentiellement le sous-champ CA1 de l'hippocampe de façon précoce, dès le stade de MCI (Apostolova et al., 2010; Chételat et al., 2008b; Frisoni et al., 2008; La Joie et al., 2013). A l'image de la progression des DNF, l'atrophie se propage avec l'avancée de la démence aux autres sous-champs hippocampiques, ainsi qu'au cortex temporo-pariétal, incluant le gyrus cingulaire postérieur et le précuneus, puis atteint les aires primaires unimodales à un stade avancé (Baron *et al.*, 2001; Apostolova *et al.*, 2007; Dickerson *et al.*, 2009; Schroeter *et al.*, 2009 ; voir également pour revues Apostolova and Thompson, 2008 et Pini *et al.*, 2016) **(Figure 7)**. D'autres régions, telles que les aires frontales, occipitales et le cervelet, semblent quant à elles relativement préservées aux stades de démence légère à modérée (Apostolova and Thompson, 2008; Pini et al., 2016).

Certaines de ces modifications structurales néocorticales sont déjà détectables au stade de MCI, puisque ces patients présentent, outre une atrophie hippocampique clairement mesurable, des atteintes significatives au niveau du néocortex temporo-pariétal et du cortex cingulaire postérieur (Chételat et al., 2002; Whitwell et al., 2007), en particulier chez les patients MCI convertissant vers une MA (« *MCI converters* ») (Chételat et al., 2005; Karas et al., 2008; Whitwell et al., 2008). En revanche, l'atrophie du lobe temporal interne semble rester le meilleur prédicteur structural de la conversion vers la MA (Ferreira et al., 2011). L'atrophie cérébrale apparaît très liée aux troubles cognitifs des patients. En effet, les déficits de mémoire épisodique sont corrélés à l'atrophie hippocampique, à la fois au stade de MCI (Chetelat et al., 2003; Fjell et al., 2008; Grundman et al., 2003) et de démence (Pantel et al., 2004).

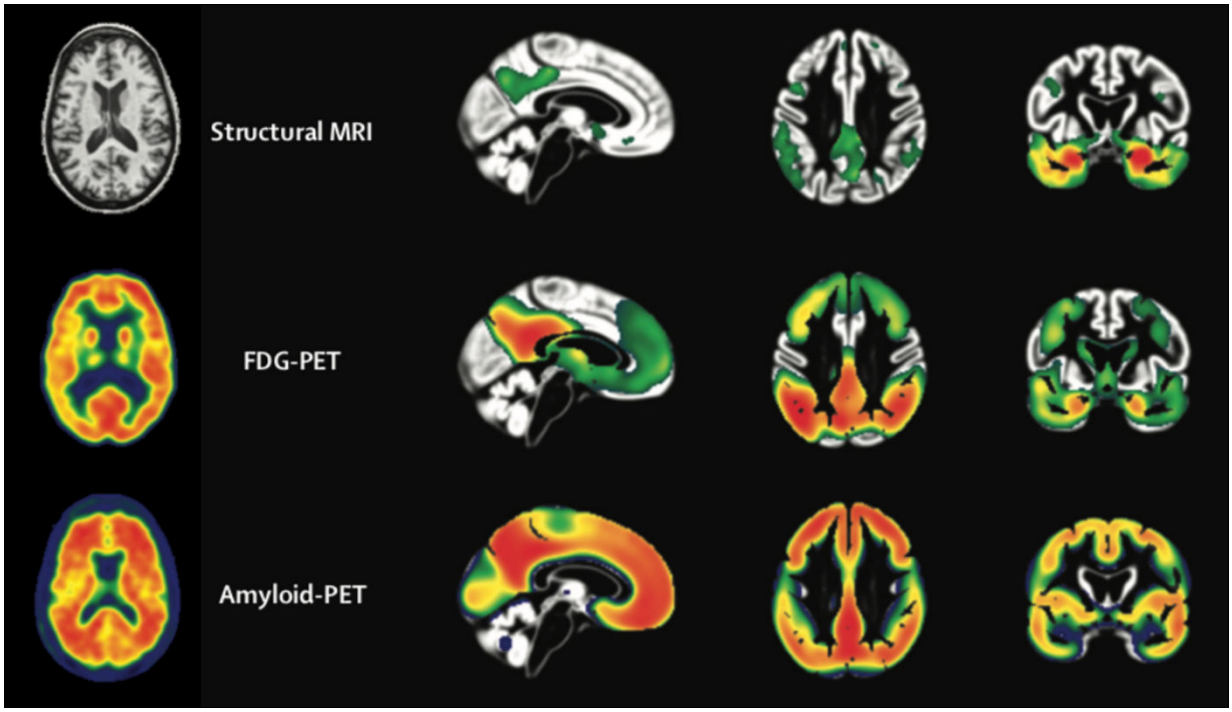


Figure 7: Profil typique de maladie d'Alzheimer en neuroimagerie.
Profils typiques d'atrophie en IRM, d'hypométabolisme en TEP-FDG, et de dépôts amyloïdes (mesurés en TEP) chez des patients atteints de maladie d'Alzheimer. Les couleurs allant du vert au rouge indiquent des niveaux croissants d'atrophie, hypométabolisme et charge amyloïde.
D'après Teipel et al., 2015.

2.2.2. MODIFICATIONS FONCTIONNELLES : METABOLISME CEREBRAL DU GLUCOSE

2.2.2.1. Sujets âgés cognitivement sains

La Tomographie par Émission de Positons (TEP) est une technique d'imagerie reposant sur l'injection en intraveineuse d'un radiotraceur émetteur de positons. L'injection du ^{18}F-Fluoro-deoxy-glucose (FDG) permet de visualiser *in vivo* le métabolisme cérébral du glucose au repos. Les études menées chez les sujets âgés cognitivement sains révèlent une diminution globale du

métabolisme cérébral du glucose avec l'âge (Tumeh et al., 2007). Les régions antérieures, notamment les cortex préfrontal, orbitofrontal et cingulaire antérieur, présentent un hypométabolisme plus marqué (Willis *et al.*, 2002; Kalpouzos *et al.*, 2009; Hsieh *et al.*, 2012; Yoshizawa *et al.*, 2014, et voir Tumeh *et al.*, 2007 et Berti *et al.*, 2014 pour revue). L'hypométabolisme touche également d'autres régions, telles que l'insula, le cortex temporal et pariétal (Berti et al., 2014; Kalpouzos et al., 2009). Au contraire, le cortex occipital, cingulaire postérieur, le précunéus, le cervelet, le thalamus, l'hippocampe et les ganglions de la base semblent préservés jusqu'à un âge très avancé (Berti et al., 2014; Kalpouzos et al., 2009; Willis et al., 2002).

2.2.2.2. Dans la MA et aux stades pré-démentiels

Comparativement aux sujets sains de même âge, les patients atteints de MA présentent un profil d'hypométabolisme au niveau des régions temporo-pariétales, notamment du précunéus et du cortex cingulaire postérieur (Chételat et al., 2008a; Choo et al., 2007; Ishii et al., 2005; Langbaum et al., 2009; Minoshima et al., 1997), déjà présent de façon précoce au stade de MCI (Arnáiz et al., 2001; Chételat et al., 2003; Langbaum et al., 2009; Nestor et al., 2003; Schroeter et al., 2009) **(Figure 7)**. De plus, une étude rapporte la présence de l'hypométabolisme temporo-pariétal de manière encore plus précoce, chez les patients SCD, présentant une plainte mnésique malgré des performances objectives préservées (Scheef et al., 2012). Ce profil d'hypométabolisme temporo-pariétal s'aggrave et s'étend vers les zones frontales avec la progression de la démence, tandis que l'on observe une relative préservation du métabolisme des ganglions de la base, du thalamus, du cervelet et du cortex sensorimoteur primaire (Alexander et al., 2002; Choo et al., 2007; Mielke et al., 1994; Nestor et al., 2003). L'hypométabolisme temporo-pariétal et frontal corrèle avec les déficits cognitifs des patients (Chetelat et al., 2003; Furst et al., 2012; Herholz et al., 2002) et est

prédicteur du déclin cognitif (Chételat et al., 2003; Drzezga et al., 2003; Fouquet et al., 2009; Landau et al., 2011). Ainsi, compte tenu de la valeur prédictive de l'hypométabolisme temporo-pariétal, il a été considéré comme un biomarqueur de la MA dans les critères révisés de McKhann (McKhann et al., 2011), dès les stades de MCI (Albert et al., 2011) et précliniques (Sperling et al., 2011).

2.2.3. IMAGERIE DES PLAQUES AMYLOÏDES

Plusieurs radiotraceurs couplés à la technique de TEP permettent de mesurer *in vivo* les dépôts amyloïdes cérébraux. Parmi eux, les plus fréquemment utilisés sont le PIB (*Pittsburgh Compound-B*, marqué au ^{11}C), et les traceurs marqués au ^{18}F tels que le Florbetaben, le Flutemetamol et le Florbetapir (Klunk *et al.*, 2004; Rowe *et al.*, 2008; Choi *et al.*, 2009; Koole *et al.*, 2009 ; voir Villemagne, 2016 pour revue). En pratique clinique, ces images TEP peuvent être interprétées visuellement afin de déterminer si un patient est amyloïde positif (Aβ+) ou négatif (Aβ-). Dans le cadre de la recherche, des méthodes quantitatives plus fines sont employées. En effet, il est possible d'extraire l'intensité du signal dans des régions d'intérêt afin d'obtenir des valeurs de *Standardized Uptake Value ratio* (SUVr) ou de *Distribution Volume Ratio* (DVR), ou encore d'effectuer des analyses voxel à voxel sur l'ensemble du cerveau.

En accord avec la topographie des lésions en neuropathologie, les études en neuroimagerie montrent que les patients MA présentent une forte accumulation de dépôts amyloïdes au niveau du néocortex frontal, temporal, pariétal, cingulaire, ainsi que dans le striatum, tandis que les niveaux d'amyloïde dans le cortex sensori-moteur, le lobe temporal interne et le thalamus sont relativement

similaires à des sujets sains (Kemppainen et al., 2006; Klunk et al., 2004; Rowe et al., 2007, 2008; Villemagne, 2016) **(Figure 7)**. Dans une récente méta-analyse (Ossenkoppele et al., 2015), la prévalence de la positivité à l'amyloïde chez les patients présentant un diagnostic clinique de MA a été estimée à environ 88%, indiquant que certains patients possèdent un marquage de type Aβ-.

De plus, il est maintenant bien établi que la pathologie amyloïde débute plusieurs décennies avant les premiers symptômes cognitifs, comme en témoigne le marquage amyloïde chez les patients aux stades pré-démentiels de la pathologie, et même chez les sujets âgés cognitivement sains. Globalement, environ 50 à 70% des patients diagnostiqués comme MCI présentent un marquage de type Aβ+ (Forsberg et al., 2008; Jansen et al., 2015; Okello et al., 2009; Wolk et al., 2009), cette proportion atteignant plus de 80% chez les patients MCI amnésiques multidomaines (Wolk et al., 2009). Chez les patients MCI, la topographie des dépôts amyloïdes apparaît comme un intermédiaire entre les sujets âgés cognitivement sains et les patients atteints de démence, avec une partie des patients présentant un marquage Aβ- similaire aux contrôles, et l'autre partie un marquage Aβ+ similaire aux patients MA (Forsberg et al., 2008; Price et al., 2005; Rowe et al., 2007). Les patients MCI « converteurs » présentent également un pattern de dépôts amyloides similaire à celui observé au stade de démence (Forsberg et al., 2008; Koivunen et al., 2011). De plus, 10 à 44% des sujets âgés cognitivement sains, et 12 à 43% des patients SCD présentent un marquage de type Aβ+, selon une méta-analyse récente (Jansen et al., 2015). Dans ces populations, le marquage est principalement important dans les régions préfrontales et cingulaires postérieures (Rowe et al., 2007; Villemagne, 2016; Villemagne et al., 2008).

En revanche, si la pathologie amyloïde est l'un des deux processus neuropathologiques sous-tendant la MA, les liens avec la sévérité des déficits cognitifs sont peu évidents au stade de démence (Rowe *et al.*, 2007; Furst *et al.*, 2012, pour revue voir Villemagne and Chételat, 2016), ce qui pourrait justement s'expliquer par le fait que l'accumulation des dépôts se produit en amont et atteindrait un plateau avant l'apparition des premiers symptômes. Cette hypothèse est renforcée par les études montrant qu'aux stades pré-démentiels, la présence d'un marquage de type Aβ+ favorise la conversion vers un MCI ou une démence (Forsberg et al., 2008; Okello et al., 2009; Villemagne et al., 2008, 2011; Villemagne and Chételat, 2016; Wolk et al., 2009).

2.2.4. IMAGERIE DES DNF

De manière très récente, des radiotraceurs TEP ont également été mis au point afin de mesurer *in vivo* la pathologie tau, parmi lesquels le T807 (ou AV1451), le T808 et le THK 5351 sont les plus utilisés (Chien et al., 2013; Harada et al., 2016; Leuzy et al., 2019; Lockhart et al., 2016).

Les premières études révèlent que la topographie de la pathologie tau est conforme aux stades de Braak, et que la rétention du marquage augmente graduellement des sujets âgés cognitivement sains aux patients MCI puis atteints de démence. En effet, on observe un faible marquage tau chez les sujets cognitivement sains au niveau des structures temporales médiales, incluant le cortex entorhinal, parahippocampique et l'hippocampe (Hall et al., 2017; Lockhart et al., 2016; Ossenkoppele et al., 2016; Schöll et al., 2016), et le marquage augmente et s'étend au cortex temporal inférieur et latéral ainsi qu'au gyrus cingulaire postérieur chez les sujets Aβ+ (Jack et al., 2018b; Lowe et al., 2018; Schöll et al., 2016) **(Figure 8)**. Aux stades de MCI et de démence, le

marquage tau est plus étendu au niveau des régions temporales (dont l'hippocampe), pariétales et orbitofrontales (Chiotis et al., 2016; Cho et al., 2016b, 2016a; Hall et al., 2017; Lockhart et al., 2016; Ossenkoppele et al., 2016) **(Figure 8)**. La pathologie tau mesurée en TEP est étroitement associée aux mesures des niveaux de tau total et phosphorylé dans le LCS (Gordon et al., 2016), ainsi qu'au statut cognitif des patients et aux performances mnésiques (Cho et al., 2016b; Ossenkoppele et al., 2016; Schöll et al., 2016).

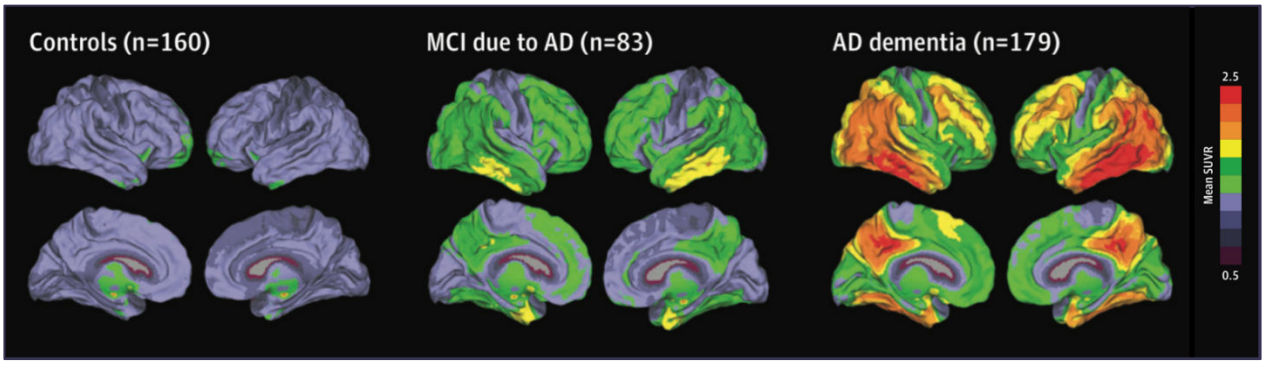


Figure 8: Imagerie Tau.
Profils de rétention du ^{18}F-Flortaucipir chez les contrôles cognitivement sains *(gauche)*, patients MCI *(centre)*, et atteints de démence Alzheimer *(droite)*.
D'après Ossenkoppele et al., 2018.

Cependant, la mise au point de radiotraceurs mesurant de façon sensible et spécifique la pathologie tau est difficile, et reste à l'heure actuelle un challenge (pour revues, voir Villemagne *et al.*, 2015 et Leuzy *et al.*, 2019). En effet, le caractère intracellulaire de la pathologie tau nécessite un radioligand liposoluble passant à la fois la barrière hémato-encéphalique et la membrane cellulaire des neurones, fixant les différentes isoformes de tau, tout en présentant une absence d'affinité pour la substance blanche et les dépôts amyloïdes extracellulaires. Il est important de souligner que les

traceurs actuels présentent toujours des fixations non spécifiques, notamment sur les mono-amine oxydases.

2.3. FACTEURS DE RISQUE ET DE PROTECTION DU DECLIN COGNITIF

Plusieurs facteurs de risque et de protection du déclin cognitif ont été identifiés (pour revues, voir Baumgart *et al.*, 2015 et Winblad *et al.*, 2016) **(Figure 9)**. Ce champ de recherche représente actuellement un enjeu majeur, puisqu'une meilleure compréhension de ces facteurs de risque et de protection permettrait, d'une part, d'identifier les sujets à risque de développer une MA, et d'autre part, d'agir sur les facteurs de risque modifiables, afin de retarder l'apparition ou l'évolution de la pathologie. En effet, Barnes et Yaffe (2011) ont estimé que la moitié des cas de démence dans le monde seraient potentiellement attribuables à des facteurs de risque modifiables (Barnes and Yaffe, 2011).

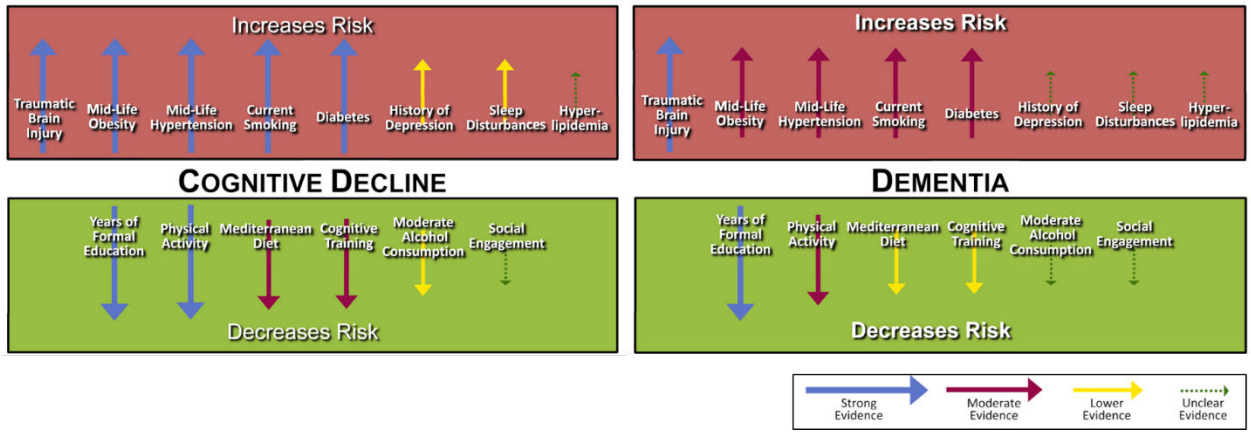


Figure 9: Principaux facteurs de risque et de protection du déclin cognitif et de la démence. Résumé de l'état actuel des connaissances sur les principaux facteurs de risque et de protection du déclin cognitif *(gauche)* et de la démence *(droite)*, d'après *Baumgart et al., 2015*. Les flèches indiquent la force relative de l'état actuel des connaissances pour chaque facteur de risque ou de protection.

2.3.1. FACTEURS DE RISQUE

Plusieurs facteurs de risque favorisant le développement d'une MA ont été mis en évidence, parmi lesquels nous pouvons opposer les facteurs de risque « non modifiables », liés à l'âge, au sexe, ou d'origine génétique, aux facteurs de risque « modifiables », plutôt liés au style de vie (Baumgart et al., 2015; Winblad et al., 2016) **(Figure 9)**.

Parmi les facteurs de risque dits « non modifiables », l'avancée en âge reste le facteur de risque principal des démences en général (Winblad et al., 2016). De plus, on observe un effet du sexe, puisque l'incidence de la MA semble plus élevée chez les hommes de moins de 80 ans, tandis que la tendance s'inverse passé cet âge (Fratiglioni et al., 1997; Letenneur et al., 1999; Mielke et al., 2014; Ruitenberg et al., 2001). Enfin, plusieurs études suggèrent une susceptibilité génétique à la

MA, puisque le risque de développer cette pathologie est plus important lorsque le patient présente des antécédants familiaux (Mayeux et al., 1991) et/ou est porteur de l'allèle ε4 du gène codant pour l'Apolipoprotéine E (APOE) (touchant 15% de la population générale) (Farrer et al., 1997; Genin et al., 2011). Parmi les autres facteurs de risque génétiques identifiés plus récemment, on retrouve des gènes impliqués dans la production ou la clairance de l'amyloïde, ou dans le système immunitaire, tels que SORL1, TREM2, PLD3 et PICALM (Cruchaga et al., 2014; Guerreiro et al., 2013; Lambert et al., 2013, 2015; Vardarajan et al., 2015; Winblad et al., 2016).

Les facteurs de risque « modifiables » les plus mis en cause sont d'origine cardio-vasculaire, tels que le diabète, l'obésité, l'hypertension artérielle et l'hypercholestérolémie (Anstey et al., 2008; Biessels et al., 2006; Kivipelto et al., 2001; Kloppenborg et al., 2008; Profenno et al., 2010; Stewart et al., 2007). D'autres facteurs de risque sont d'origine psycho-affective, incluant la dépression et l'anxiété (Barnes et al., 2012; Diniz et al., 2013), ou liés au style de vie, comme le tabagisme (Anstey et al., 2007; Beydoun et al., 2014; Chen, 2012), la consommation excessive d'alcool (Schwarzinger et al., 2018; Topiwala et al., 2017) et un mode de vie sédentaire (Beydoun et al., 2014; Blondell et al., 2014; Lautenschlager et al., 2008).

2.3.2. FACTEURS DE PROTECTION

Parmi les facteurs conférant une protection contre le déclin cognitif et le risque de démence **(Figure 9)**, certains sont d'origine génétique et sont donc non modifiables, comme par exemple être porteur de l'allèle ε2 du gène de l'APOE (Corder et al., 1994; Farrer et al., 1997), tandis que d'autres sont plutôt liés au style de vie. Ces facteurs protecteurs liés au style de vie incluent un niveau

d'éducation et un engagement cognitif et social élevés au cours de la vie (Beydoun et al., 2014; Fratiglioni et al., 2004; Meng and D'Arcy, 2012; Scarmeas et al., 2001; Stern et al., 1994; Valenzuela and Sachdev, 2009), l'adhérence à un régime alimentaire de type méditerranéen (Barberger-Gateau et al., 2007; Morris et al., 2015; Scarmeas et al., 2009), une activité physique régulière et importante (Beydoun et al., 2014; Blondell et al., 2014; Lautenschlager et al., 2008; Rovio et al., 2005; Scarmeas et al., 2009).

2.3.3. LA PLACE DU SOMMEIL

Dans ce contexte d'identification des facteurs de risque pouvant augmenter le risque de développer une démence, les troubles du sommeil font l'objet d'un intérêt croissant. En effet, leur prévalence augmente avec l'âge, et ils sont liés aux performances cognitives et au déclin cognitif. De plus, des études récentes montrent que la qualité du sommeil serait étroitement liée aux mécanismes physiopathologiques de la MA. Ainsi, la partie suivante de cette thèse s'intéressera à décrire les modifications du sommeil liées à l'âge et rencontrées dans la MA et ses stades pré-démentiels, ainsi que leurs liens avec la cognition et l'intégrité cérébrale.

2.4. SOMMEIL DANS LE VIEILLISSEMENT NORMAL ET PATHOLOGIQUE

2.4.1. CARACTERISATION ET PHYSIOLOGIE DU SOMMEIL

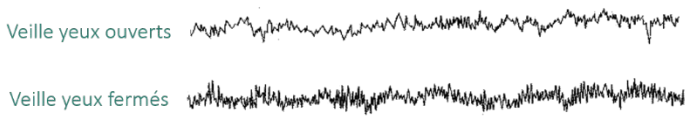
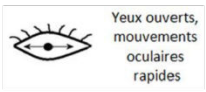
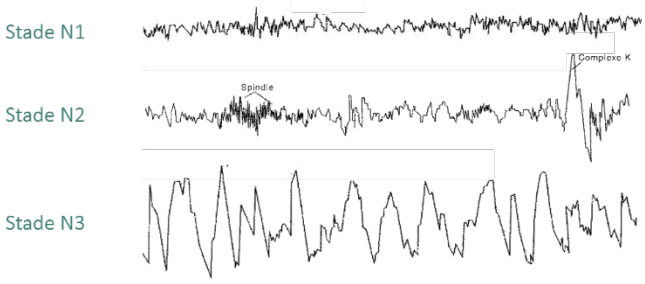
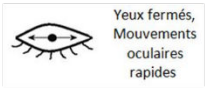
2.4.1.1. Définition

Le sommeil occupe environ un tiers de notre vie, et est un état physiologique caractérisé par une perte temporaire et réversible de conscience et de réactivité aux stimuli extérieurs. L'avènement de la technique d'électroencéphalographie, mise au point dans les années 1920 par le neurophysiologiste allemand Hans Berger, a permis une caractérisation et une compréhension croissantes de ce comportement particulier. Grâce à des électrodes placées à la surface du scalp, cette technique permet de mesurer et d'enregistrer de manière non invasive la nature du signal électrique résultant des potentiels d'action émis de façon synchrone par des millions de neurones. Ainsi, l'examen de référence du sommeil, la polysomnographie (PSG), comprenant l'enregistrement des activités cérébrale (électroencéphalogramme, ou EEG), cardiaque (électrocardiogramme, ou ECG), oculaire (électrooculogramme, ou EOG), musculaire (électromyogramme, ou EMG) et respiratoire, a permis de révéler que le sommeil n'est pas un comportement unitaire, mais est composé d'une succession de stades distincts, résumés dans le **Tableau 3** ci-dessous, et que nous allons décrire plus amplement ci-après (Arnulf, 2007; Dauvilliers and Billiard, 2004; Petit et al., 2004).

2.4.1.2. Électrophysiologie et bases neurales des états de veille et de sommeil

a. Éveil

L'activité électroencéphalographique de veille est rapide et désynchronisée, et se caractérise par deux types de rythmes cérébraux dont la présence dépend de l'ouverture et de la fermeture des yeux. L'état de veille yeux ouverts est caractérisé par le *rythme bêta*, d'une amplitude de 10-30 µV et d'une fréquence rapide de 14-40 Hz. En état de veille calme (yeux fermés), le rythme bêta laisse place au rythme plus lent *alpha*, d'une amplitude de 20-40 µV et d'une fréquence de 8-12 Hz. De plus, lors de l'état de veille, le tonus musculaire est soutenu et l'on observe la présence de mouvements oculaires rapides.

Etat	EEG	EOG	EMG
Veille			++
Sommeil lent (NREM)			+
Sommeil paradoxal (REM)			Aboli

<u>Tableau 3:</u> Principales caractéristiques physiologiques des états de veille et de sommeil.
Adapté de *Rauchs et al. (2011)* et *Dauvilliers & Billiard (2004)*.
<u>Abréviations</u> : EEG, électroencéphalogramme ; EMG, électromyogramme ; EOG, électrooculogramme ; NREM : non rapid eye movement ; REM : rapid eye movement.

b. Sommeil lent

Le sommeil lent (SL, ou NREM pour « *non-rapid eye movement* ») est subdivisé en 3 stades de profondeur croissante, d'après la classification de l'*American Academy of Sleep Medicine* (AASM) (Berry et al., 2017; Iber et al., 2007). Les stades N1 et N2 constituent le sommeil lent léger, tandis que le stade N3 compose le sommeil lent profond (SLP).

Le **stade N1** correspond à une phase de transition entre les états de veille au repos et de sommeil lent, représentant moins de 5% de la durée totale de sommeil. Durant cette phase d'endormissement, le rythme alpha postérieur est remplacé par une activité *thêta* (4-8 Hz), ainsi que par l'apparition de « pointes vertex » correspondant à des déflexions négatives d'amplitude maximale au sommet du scalp. De plus, on observe la présence de mouvements oculaires lents et pendulaires, ainsi qu'une activité musculaire présente mais toutefois inférieure à celle observée à l'état de veille.

Le **stade N2** de sommeil lent représente environ 50 à 60% de la durée totale de sommeil. Il se caractérise par une activité de fond thêta sur laquelle apparaissent des grapho-éléments caractéristiques, tels que les *fuseaux de sommeil* (ou « *sleep spindles* ») et les *complexes K*, une faible activité musculaire et une abolition des mouvements oculaires. Les fuseaux de sommeil correspondent à des trains d'ondes thalamo-corticales rapides (ou rythme *sigma* de 11-16 Hz) d'une durée allant de 0,5 à 2 secondes, majoritairement observés sur les dérivations centrales et frontales. Les études en neuroimagerie fonctionnelle (en TEP ou IRM fonctionnelle) confirment que l'apparition des fuseaux de sommeil est associée à une activation des thalami, de l'insula, des aires frontales (cortex cingulaire antérieur, gyrus frontal supérieur et médian), des aires temporales et de

l'hippocampe (Caporro et al., 2012; Dang-Vu, 2012; Schabus et al., 2007). Les *complexes K* correspondent à des ondes lentes biphasiques de grande amplitude (>75 µV) et basse fréquence (<4Hz), d'une durée de 0,5 à 3 secondes, majoritairement observés sur les dérivations frontales et centrales. Ils sont associés à des activations au niveau du thalamus, des régions frontales et pariétales (Caporro et al., 2012; Dang-Vu, 2012).

Enfin, le **stade N3** correspond au sommeil lent profond (SLP, ou « *slow wave sleep* ») et occupe environ 15 à 20% du temps total de sommeil. Durant ce stade, le tonus musculaire est faible, et les mouvements oculaires sont absents. Il est caractérisé par une activité encéphalographique très synchronisée composée d'ondes lentes *delta*, de grande amplitude (>75 µV) et basse fréquence (1,5-4 Hz). Les ondes lentes caractéristiques du N3 prennent leur origine au niveau du néocortex frontal, cingulaire et de l'insula (Dang-Vu et al., 2005, 2008; Massimini et al., 2004; Murphy et al., 2009) puis se propagent le plus souvent vers les régions néocorticales postérieures, incluant le cortex cingulaire postérieur et le précuneus.

En sommeil lent, le métabolisme et la perfusion cérébrale diminuent de près de 40% par rapport à l'état d'éveil, de façon particulièrement marquée dans les régions frontales, pariétales (incluant le précunéus et le cortex cingulaire postérieur), l'insula, les ganglions de la base et le thalamus (Braun et al., 1997; Maquet, 2000; Maquet et al., 1990). Toutefois, des études couplant EEG et IRM fonctionnelle, présentant une meilleure résolution temporelle que la TEP, ont révélé des augmentations régionales et transitoires de l'activité cérébrale lors de la génération des ondes lentes (Dang-Vu et al., 2008) ou des fuseaux de sommeil (Schabus et al., 2007).

c. Sommeil paradoxal

Enfin, le sommeil paradoxal (SP, ou REM pour « *rapid eye movement* ») représente 20 à 25% du temps total de sommeil, et se caractérise par une activité cérébrale désynchronisée de faible amplitude et de fréquences rapides mixtes majoritairement de type thêta, alpha ou beta, complétée par la présence d'*ondes en dents de scie.* Le SP est également caractérisé par la présence de mouvements oculaires rapides et une abolition totale du tonus musculaire, transitoirement interrompue par de brèves décharges musculaires dénommées « *twitches* ». Le débit sanguin cérébral au cours du SP est comparable à l'éveil, avec une augmentation de la perfusion dans les aires limbiques (incluant l'hippocampe, l'amygdale et le thalamus), le tegmentum pontique, le cortex cingulaire antérieur, l'insula et les aires temporales, tandis que les zones pariétales (incluant le cortex cingulaire postérieur et le précunéus) sont plutôt hypoperfusées (Braun et al., 1997; Maquet, 2000; Maquet et al., 1996).

2.4.1.3. Organisation générale d'une nuit de sommeil

Une nuit de sommeil chez l'adulte s'organise en 4 à 6 cycles consécutifs de sommeil, d'une durée moyenne de 90 à 100 minutes chacun. Chaque cycle est composé de la succession des différents stades de SL (N1 à 3) décrits ci-dessus, puis l'individu repasse généralement en N2 avant d'entamer un épisode de SP **(Figure 11)** (Arnulf, 2007; Dauvilliers and Billiard, 2004). La composition des cycles de sommeil évolue avec l'avancée dans la nuit : la durée du SLP est maximale en début de nuit et diminue progressivement à mesure que les cycles se succèdent et que la pression de sommeil s'atténue. A l'inverse, la durée des épisodes de SP augmente au cours de la nuit, et atteint son maximum en fin de nuit.

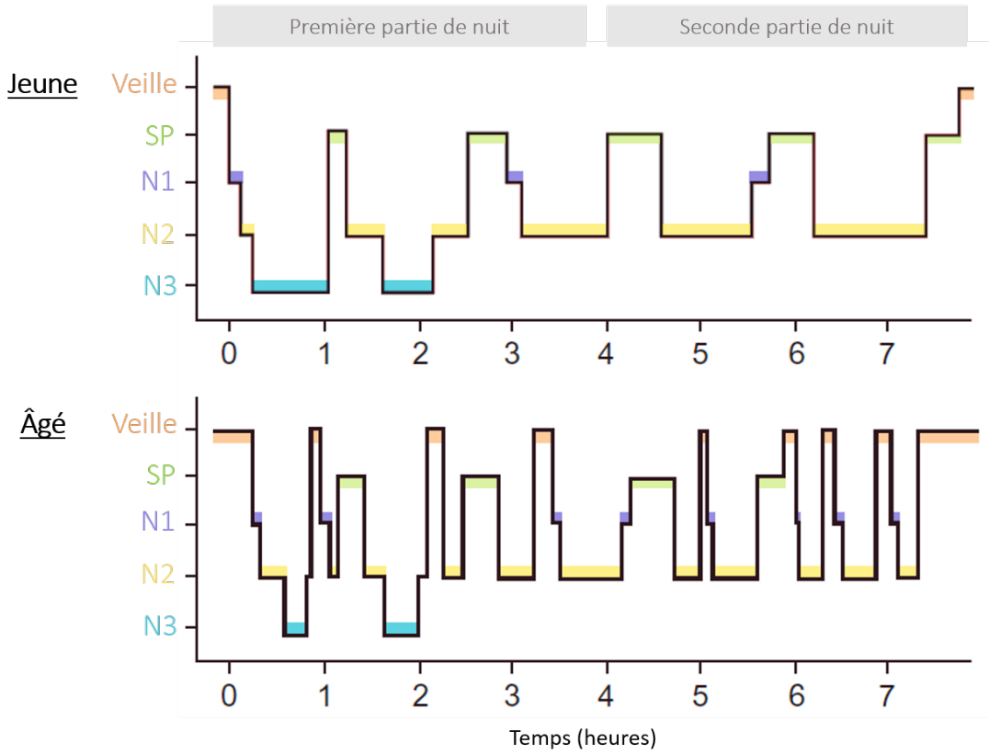


Figure 10: Hypnogrammes typiques d'un sujet jeune sain et d'un sujet âgé sain.
Adapté de Pace-Schott & Spencer (2011). La première partie de nuit est particulièrement enrichie en sommeil lent profond (N3), tandis que le SP est particulièrement abondant en seconde moitié de nuit. Les sujets âgés présentent un sommeil fragmenté et plus léger comparativement aux sujets jeunes.

2.4.2. MODIFICATIONS DU SOMMEIL DANS LE VIEILLISSEMENT NORMAL ET PATHOLOGIQUE

2.4.2.1. Sujets âgés cognitivement sains

Le vieillissement s'accompagne d'un déclin progressif de la qualité et de la quantité de sommeil. Environ 50% des personnes âgées se plaignent de leur sommeil, les femmes présentant souvent la plainte la plus importante (Foley et al., 1995). La plainte de sommeil se concentre sur la sensation d'un sommeil non réparateur, la survenue fréquente de réveils nocturnes, d'importantes difficultés d'endormissement et des symptômes de somnolence diurne (Foley et al., 1995; Mander et al., 2017). Les modifications objectives du sommeil surviennent au niveau circadien, macrostructural et microstructural (pour revue, voir Mander *et al.*, 2017).

A l'échelle circadienne, les principales modifications consistent en une avance de phase, des réveils matinaux précoces, une fragmentation et une diminution de l'amplitude du rythme, avec notamment des réveils matinaux précoces et une augmentation de la fréquence des siestes (Buysse et al., 2005; Kondratova and Kondratov, 2012; Musiek et al., 2018). A l'échelle macroscopique, l'avancée en âge s'accompagne de difficultés d'endormissement, reflétées par une augmentation de la latence d'endormissement, d'une diminution de la durée de sommeil, d'une augmentation du nombre et de la durée des réveils nocturnes, résultant en une augmentation de la fragmentation et une diminution de l'efficacité de sommeil (Ohayon *et al.*, 2004; Mander *et al.*, 2017, et voir la **Figure 10** ci-dessus). La quantité de SLP décroit de façon marquée avec l'âge, tandis qu'en parallèle, la proportion des stades de sommeil lent léger (N1 et N2) augmente, en particulier pour le stade N1 (Ohayon et al., 2004). Le sommeil paradoxal est également touché, mais de façon plus

tardive et discrète que le SLP (Floyd et al., 2007; Ohayon et al., 2004). Au niveau de la microstructure du sommeil, l'avancée en âge s'accompagne d'une accélération globale des rythmes oscillatoires en EEG. La puissance spectrale diminue dans les bandes de fréquence delta, theta et alpha en SL et SP (Dijk et al., 1989; Landolt et al., 1996; Landolt and Borbély, 2001), avec une atteinte particulièrement importante des rythmes en SL. En effet, le nombre, l'amplitude et la puissance spectrale des ondes delta du sommeil lent diminuent (Carrier et al., 2001, 2011; Landolt and Borbély, 2001; Latreille et al., 2019; Münch et al., 2004). De même, on observe une diminution du nombre, de la durée, de la densité, de l'amplitude et de la puissance spectrale des fuseaux de sommeil (Crowley et al., 2002; Martin et al., 2013) et des complexes K (Crowley et al., 2002).

2.4.2.2. Dans la MA et aux stades prédémentiels

a. Au stade de démence Alzheimer

On estime que 25 à 60% des patients atteints de MA souffrent de troubles du sommeil (Guarnieri et al., 2012; Moran et al., 2005; Peter-Derex et al., 2015; Petit et al., 2004). Certaines modifications du sommeil dans la maladie d'Alzheimer sont une aggravation des modifications observées chez les sujets âgés sains. On observe ainsi une augmentation du nombre et de la durée des éveils nocturnes, entrainant une fragmentation du sommeil accompagnée d'une diminution de son efficacité, et une somnolence diurne excessive (Bonanni et al., 2005; Liguori et al., 2014; Peter-Derex et al., 2015). Les patients atteints de MA présentent une réduction importante de la quantité de sommeil lent profond en lien avec la sévérité de la démence, et une augmentation de la quantité de sommeil lent léger (Benca et al., 1992; Maestri et al., 2015; Peter-Derex et al., 2015; Prinz et al., 1982). D'autres troubles sont en revanche plus spécifiques de la pathologie. Ainsi, l'atteinte du

sommeil paradoxal est un élément caractéristique de la MA, qui semble toutefois survenir à un stade relativement avancé de la démence. Elle se traduit par un allongement de la latence d'apparition, une réduction de la durée moyenne des épisodes et une fragmentation de ce stade de sommeil (Bliwise et al., 1989; Maestri et al., 2015; Montplaisir et al., 1995). D'un point de vue de la microstructure du sommeil, les patients MA présentent une dimiution du nombre, de l'amplitude ou de la densité des fuseaux de sommeil et des complexes K (De Gennaro et al., 2017). Les analyses spectrales révèlent une accélération globale des rythmes du SLP chez les patients atteints de MA, avec notamment une diminution de la génération des rythmes delta du SLP comparativement aux sujets âgés sains de même âge et un ralentissement des rythmes en SP (Hassainia et al., 1997; Petit et al., 1993, 2004). Ainsi, l'augmentation du ratio *(delta+theta)/(alpha+beta)* en SP semble être un marqueur sensible afin de discriminer les patients MA des contrôles (Hassainia et al., 1997).

Enfin, 25 à 50% des patients présentent une altération générale des rythmes circadiens, incluant une avance de phase et une réduction de l'amplitude du rythme circadien (Leng et al., 2019; Motohashi et al., 2000; Weldemichael and Grossberg, 2010), et un phénomène d'agitation vespérale (ou « *sundowning »)*, se caractérisant par une tendance à s'agiter et à déambuler à la tombée du jour, avec des signes d'anxiété, des troubles émotionnels, une pensée et un discours désorganisés (Khachiyants et al., 2011).

b. Aux stades pré-démentiels de la maladie d'Alzheimer

Les altérations du sommeil décrites ci-dessus semblent survenir précocement dans la pathologie. En effet, 14 à 59% des patients MCI se plaignent de leur sommeil (Beaulieu-Bonneau and Hudon, 2009), et présentent des scores plus importants à l'Index de Qualité de Sommeil de Pittsburgh

(PSQI, Buysse *et al.*, 1989) reflétant des difficultés auto-rapportées de sommeil (McKinnon et al., 2014; Yu et al., 2017).

Les études mesurant le sommeil chez les patients MCI grâce à des méthodes plus objectives sont peu nombreuses, et certaines ne mettent pas en évidence de différences entre les sujets contrôles et les patients (Basta et al., 2019; Kim et al., 2011; Reda et al., 2017; Wams et al., 2017; Westerberg et al., 2010). Parmi les études montrant des différences, des anomalies du SL et du SP ont été rapportées chez les patients MCI, comparativement aux sujets âgés cognitivement sains. En effet, les patients MCI présenteraient une diminution de la quantité de SL et une augmentation de sa fragmentation (Hita-Yañez et al., 2012; Naismith et al., 2014; Reda et al., 2017; Sanchez-Espinosa et al., 2014), ainsi qu'une altération des fuseaux de sommeil rapides et une diminution de la puissance spectrale des ondes delta et theta (Gorgoni et al., 2016; Hita-Yañez et al., 2012; Reda et al., 2017; Westerberg et al., 2012). Les altérations du SP, plus spécifiques de la MA, semblent également retrouvées à un stade précoce. Plusieurs études raportent une diminution de sa durée, une augmentation de sa latence d'apparition, une diminution de la puissance spectrale des ondes theta, et un ralentissement global des rythmes en SP (Brayet et al., 2016; Hita-Yañez et al., 2012; Maestri et al., 2015; Naismith et al., 2014; Sanchez-Espinosa et al., 2014). De façon intéressante, la diminution de proportion du SP semble accentuée chez les patients MCI porteurs de l'allèle epsilon4 du gène de l'APOE (Hita-Yañez et al., 2012), et les patients MCI qui convertiront vers une MA (Carnicelli et al., 2019).

Toutefois, la plupart de ces études n'ont pas été réalisées sur de grands échantillons de patients bien caractérisés d'un point de vue étiologique. En effet, les études incluent pour la plupart tous types de patients MCI (i.e., sans distinction du MCI amnésique *versus* non amnésique, ou single

versus multi-domain), sans information relative à la neuropathologie sous-jacente. Ainsi, la nature hétérogène de la présentation et la progression clinique de ces patients est probablement l'une des raisons pouvant expliquer l'hétérogénéité ou l'absence de résultats des études explorant la qualité de leur sommeil.

2.4.2.3. Focus sur le syndrome d'apnées obstructives du sommeil

Le syndrome d'apnées obstructives du sommeil (SAOS) est un trouble du sommeil caractérisé par la survenue de pauses respiratoires (ou *apnées*) et de réductions du débit respiratoire (ou *hypopnées*), suite à une obstruction complète ou partielle des voies aériennes supérieures au cours du sommeil. Ces évènements respiratoires engendrent des épisodes d'hypoxémie et d'hypoxie intermittentes, ainsi que des micro-réveils consécutifs à la reprise respiratoire (pour revue, voir Malhotra and White, 2002 et Lim and Pack, 2017). Selon les critères recommandés par l'American Academy of Sleep Medicine (AASM) parus en 2017 (Berry et al., 2017), une apnée se définit par une diminution supérieure ou égale à 90% du flux respiratoire d'au moins 10 secondes, tandis qu'une hypopnée se définit par une réduction du flux respiratoire d'au moins 30% pour une durée minimale de 10 secondes, accompagnée d'un micro-réveil ou d'une désaturation en oxygène supérieure ou égale à 3% **(Figure 11)**. L'index d'apnées et hypopnées par heure (IAH, correspondant à la somme des apnées et hypopnées divisées par le temps total de sommeil) est communément utilisé afin d'établir la sévérité du SAOS. Classiquement, un IAH compris entre 5 et 15 constitue un SAOS léger, puis modéré entre 15 et 30, et sévère lorsque l'IAH est supérieur à 30. Les principaux facteurs de risque du SAOS incluent l'avancée en âge, le surpoids et l'obésité, être de sexe masculin et l'hypertension artérielle (Lim and Pack, 2017).

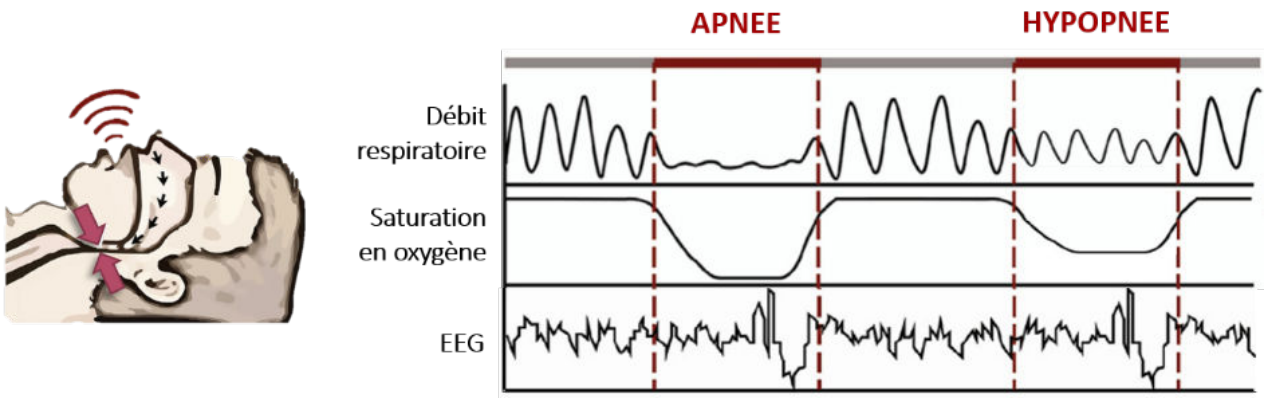


Figure 11: Représentation schématique d'une apnée et d'une hypopnée.
Figure adaptée de Gaspar *et al.*, 2017.

Le diagnostic du SAOS s'effectue par le biais d'une polysomnographie ou d'une polygraphie ventilatoire, mais cette pathologie est largement sous-diagnostiquée. Sa prévalence augmente très fortement avec l'âge, puisque l'on estime qu'entre 30 et 80% des sujets âgés cognitivement sains souffrent d'un SAOS (Ancoli-Israel et al., 1981; Senaratna et al., 2017), selon les critères diagnostiques utilisés et les populations étudiées. De plus, il a été montré que le SAOS est une comorbidité fréquente chez les patients atteints de MA, qui auraient cinq fois plus de chances de souffrir de SAOS comparativement aux sujets cognitivement sains (Emamian et al., 2016). Enfin, le génotype APOE4 serait un facteur de risque de développer un SAOS (Kadotani et al., 2001).

2.4.3. SOMMEIL, COGNITION ET DECLIN COGNITIF

Le sommeil joue un rôle essentiel dans de nombreuses fonctions physiologiques, telles que la thermorégulation, la réparation tissulaire, l'immunité, et le métabolisme énergétique (pour revues, voir Barone and Krieger, 2015 et Krueger *et al.*, 2016). De plus, des centaines d'études ont montré

que le sommeil est indispensable au bon fonctionnement cognitif et émotionnel. En effet, chez le sujet jeune, un certain nombre de fonctions cognitives sont sensibles au manque de sommeil, qu'il soit expérimental par le biais d'études de privation, ou lié à des troubles du sommeil (pour revues, voir Waters and Bucks, 2011 et Krause *et al.*, 2017, et la **section 2.4.3.1** ci-dessous). En revanche, les associations entre les modifications du sommeil liées à l'âge et les performances cognitives dans le vieillissement, ou les déficits cognitifs des patients atteints de MA, sont quant à elles plus controversées (voir les **sections 2.4.3.2** et **2.4.3.3** ci-dessous).

2.4.3.1. Privation de sommeil et performances cognitives chez les sujets jeunes.

a. Processus attentionnels

Les capacités attentionnelles et de vigilance sont parmi les processus les plus vulnérables aux problèmes de sommeil (Lowe et al., 2017). En effet, suite à une privation de sommeil on observe une augmentation des temps de réaction à des tâches telles que le *Psychomotor Vigilance Test* (PVT) (Blatter et al., 2006; Doran et al., 2001; Goel et al., 2014; Lo et al., 2012; Van Dongen et al., 2003), dans laquelle les participants doivent appuyer sur un bouton lorsqu'une lumière apparaît. Cette altération des performances semble « dose-dépendante », augmentant avec le temps passé éveillé et l'accumulation de la pression de sommeil (Belenky et al., 2003; Van Dongen et al., 2003). Les études en imagerie fonctionnelle d'activation montrent que chez les sujets privés de sommeil, les déficits attentionnels semblent sous-tendus par des anomalies d'activation au sein des réseaux attentionnels thalamo-corticaux, incluant des régions telles que le cortex pariétal, préfrontal dorsolatéral et le thalamus (Chee et al., 2010; Krause et al., 2017; Ma et al., 2015; Tomasi et al., 2009).

b. Fonctions exécutives et mémoire de travail

Les différentes composantes des fonctions exécutives, très dépendantes du lobe frontal, sont également sensibles à la privation de sommeil. Les performances en mémoire de travail semblent diminuer suite à une privation ou une restriction de sommeil (Drummond et al., 2012; Lowe et al., 2017; Turner et al., 2007), bien que les résultats soient hétérogènes, surtout pour les études utilisant des tâches complexes telles que le n-back (Lo et al., 2012; Lowe et al., 2017; Rupp et al., 2012). De plus, on observe également une diminution des performances de flexibilité mentale mesurées notamment grâce au Trail Making Test (Lowe et al., 2017; Stenuit and Kerkhofs, 2008; Van Dongen et al., 2003), et d'inhibition mesurée grâce aux tâches de Go-No Go (Demos et al., 2016; Drummond et al., 2006; Lowe et al., 2017; Stenuit and Kerkhofs, 2008). Si les effets négatifs de la privation de sommeil sur les performances en mémoire de travail semblent impliquer les régions composant les réseaux attentionnels (i.e., cortex préfrontal dorsolatéral, pariétal et thalamus) (Chee and Choo, 2004; Chee and Chuah, 2007; Krause et al., 2017; Lythe et al., 2012), les déficits d'inhibition aux tâches de Go-No Go semblent être plutôt sous-tendus par des activations anormales au niveau des cortex préfrontaux et cingulaire antérieur (Drummond et al., 2006).

c. Mémoire épisodique

Il est bien établi que le sommeil joue un rôle majeur dans la consolidation de souvenirs en mémoire à long terme, correspondant au processus de transformation d'une trace mnésique labile en une trace stable, résistante aux interférences (pour revues, voir Rauchs *et al.*, 2005; Diekelmann and Born, 2010; Harand *et al.*, 2012). Pour la mémoire épisodique, ce processus complexe semble particulièrement bénéficier du sommeil lent (Plihal and Born, 1997), impliqué dans la consolidation des aspects temporels du souvenir, tandis que le SP jouerait un rôle complémentaire, et serait plutôt

bénéfique à la consolidation des aspects spatiaux et émotionnels du souvenir épisodique (Baran et al., 2012; Gujar et al., 2011; Nishida et al., 2009; Rauchs et al., 2004; Wagner et al., 2001).

D'un point de vue mécanistique, des réactivations neuronales au sein de l'hippocampe (Peigneux et al., 2004; Wilson and McNaughton, 1994) surviendraient en étroite synchronie avec l'apparition des fuseaux de sommeil, des ondes lentes et des sharp-waves ripples hippocampiques (Gais et al., 2002; Girardeau et al., 2009; Huber et al., 2004). Ces différents événements permettraient un dialogue entre l'hippocampe et le néocortex (ou « *dialogue hippocampo-néocortical* »), favorisant ainsi la réorganisation et le stockage à long terme des traces mnésiques au sein des aires néocorticales (Buzsáki, 1996; Maingret et al., 2016), notamment le cortex préfrontal ventro-médian (Takashima et al., 2006). A l'échelle cellulaire, l'hypothèse de l'*homéostasie synaptique* (Tononi and Cirelli, 2003, 2006) propose que le sommeil joue un rôle essentiel dans le contrôle et le maintien de la plasticité synaptique. Ainsi, à l'éveil, les apprentissages s'effectuent grâce à un phénomène de potentialisation des connexions synaptiques. Au cours du sommeil, on observerait un recalibrage synaptique afin de normaliser le nombre et la puissance des synapses, en vue de permettre de nouveaux apprentissages et d'éviter une saturation (Huber et al., 2004; Vyazovskiy et al., 2008). Ce recalibrage s'effectuerait principalement au cours du SLP. Le modèle du dialogue hippocampo-néocortical et la théorie de l'homéostasie synaptique ne sont pas mutuellement exclusifs, et opèreraient en parallèle dans des régions cérébrales distinctes (Mascetti et al., 2013). Le processus de consolidation des souvenirs en mémoire à long terme serait lui aussi perturbé suite à une privation de sommeil (Drummond et al., 2000; Lowe et al., 2017; Stenuit and Kerkhofs, 2008).

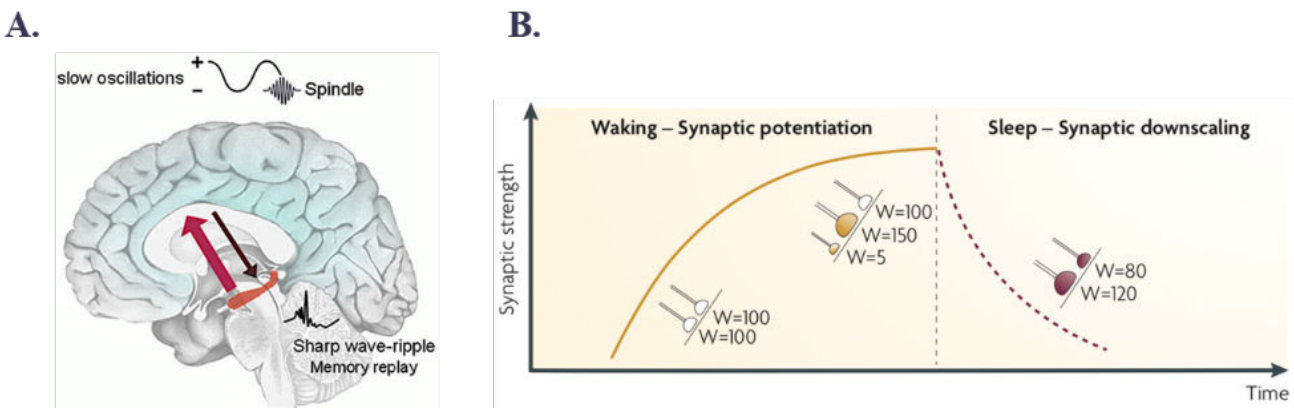


Figure 12: Mécanismes sous-tendant la consolidation mnésique dépendante du sommeil.
A) Dialogue hippocampo-néocortical.
Ce modèle, proposé par Buzsaki en 1996, stipule que lors du SLP, l'hippocampe se réactive grâce aux ondes lentes, aux fuseaux de sommeil et aux *sharp wave ripples* hippocampiques, afin de transférer les traces mnésiques de l'hippocampe vers les aires de stockage néocorticales, principalement situées au niveau du cortex préfrontal ventromédian.
B) Théorie de l'homéostasie synaptique.
Selon cette théorie, proposée par Tononi & Cirelli en 2003, un recalibrage synaptique s'effectue lors du sommeil, permettant de normaliser le nombre et la force des synapses afin de réaliser de futurs apprentissages.
Les figures sont adaptées de Harand et al. 2012 (gauche) et Diekelman & Born 2010 (droite).

2.4.3.2. Liens entre sommeil et cognition chez les sujets âgés cognitivement sains

Comme abordé précédemment, il est bien démontré que le sommeil joue un rôle crucial pour un bon fonctionnement cognitif, notamment au niveau attentionnel, exécutif et mnésique chez les sujets jeunes (Diekelmann and Born, 2010; Lowe et al., 2017). Cependant, l'effet bénéfique du sommeil sur la cognition dans le vieillissement est plus débattu (pour revue, voir Scullin and Bliwise, 2015 et Scullin, 2017, et se référer au tableau en **Annexe 6.1** pour une synthèse des études explorant les liens entre sommeil et cognition chez les sujets âgés cognitivement sains).

a. Etudes transversales

Un large éventail de paramètres de sommeil, mesurés de façon subjective au moyen de questionnaires ou de façon plus objective par actimétrie ou polysomnographie, sont associés à un meilleur fonctionnement cognitif global. Ainsi, une augmentation de la latence d'endormissement, une diminution de l'efficacité de sommeil, une augmentation de la durée des réveils nocturnes, une courte (<6h) ou longue (>8h) durée de sommeil, les altérations circadiennes, et les symptômes de somnolence diurne excessive ont été associés à un moins bon fonctionnement cognitif global (Blackwell et al., 2006; Cochrane et al., 2012; Lo et al., 2016; Ohayon and Vecchierini, 2002; Tworoger et al., 2006). Les études en PSG montrent, quant à elles, qu'un moins bon fonctionnement cognitif global est associé à une proportion plus importante de sommeil lent léger (stade N1), et une réduction de la proportion de SP (Blackwell et al., 2011).

Les études mesurant plus finement le fonctionnement cognitif montrent que plusieurs paramètres de sommeil sont associés à une diminution de la vitesse de traitement, des performances attentionnelles, exécutives, de mémoire de travail, et de mémoire déclarative, tels qu'une augmentation de la latence d'endormissement (Cavuoto et al., 2016; Luik et al., 2015; Schmutte et al., 2007), une diminution de l'efficacité de sommeil (Lambiase et al., 2014; Miyata et al., 2013), une augmentation du nombre et de la durée des éveils nocturnes (Cavuoto et al., 2016; Spira et al., 2017; Wilckens et al., 2014), une courte ou longue durée de sommeil (Lo et al., 2016), les symptômes de somnolence diurne excessive (Ramos et al., 2016; Tsapanou et al., 2016) et les altérations circadiennes (Luik et al., 2015; Oosterman et al., 2009). Les études menées en PSG montrent que les modifications des rythmes oscillatoires caractéristiques du sommeil lent, tels que les fuseaux de sommeil (Lafortune et al., 2014; Mander et al., 2014; Seeck-Hirschner et al., 2012)

et les ondes lentes (Anderson and Horne, 2003; Lafortune et al., 2014; Mander et al., 2013, 2015), sont surtout associés à une diminution des performances exécutives et de mémoire épisodique. Enfin, les patients souffrant de SAOS non traité semblent présenter de moins bonnes performances attentionnelles, exécutives, de mémoire de travail et de mémoire épisodique, comparativement à des sujets contrôles (Bucks et al., 2013; Olaithe et al., 2018; Stranks and Crowe, 2016). Les individus porteurs de l'allèle e4 du gène de l'APOE souffrant de SAOS seraient d'ailleurs ceux présentant les déficits mnésiques les plus importants (Kadotani et al., 2001).

Toutefois, les associations synthétisées ci-dessus varient de façon non négligeable dans la littérature, selon le type de mesures du sommeil considérées (i.e., auto-rapportées *versus* plus objectives) ou les populations considérées, certaines études n'ayant pas exclus les participants souffrant de troubles du sommeil ou présentant des symptômes dépressifs. De façon importante, de nombreuses études n'ont pas rapporté d'effet bénéfique du sommeil sur la cognition chez les personnes âgées (pour revue, voir Scullin and Bliwise, 2015).

b. Liens avec le déclin cognitif et la conversion vers le MCI ou la MA.

Les études longitudinales révèlent qu'une mauvaise qualité de sommeil auto-rapportée (Bubu et al., 2017; Shi et al., 2018), une augmentation de la latence d'endormissement et une diminution de l'efficacité de sommeil (Diem et al., 2016; Yaffe et al., 2007), une courte ou longue durée de sommeil (Liang et al., 2018; Virta et al., 2013), un sommeil fragmenté (Lim et al., 2013), les altérations circadiennes (Tranah et al., 2011) ou encore les symptomes de somnolence diurne excessive (Foley et al., 2001; Gabelle et al., 2017; Jaussent et al., 2012; Merlino et al., 2010; Nakakubo et al., 2018) sont associés au déclin cognitif et au risque de conversion vers le MCI ou

la MA. En effet, les individus présentant une fragmentation plus importante du sommeil auraient 1,5 fois plus de risque de développer une MA (Lim et al., 2013), ainsi qu'un déclin plus marqué des performances exécutives (Blackwell et al., 2014). A l'inverse, un sommeil plus consolidé diminuerait l'incidence de la démence (Lim et al., 2013). Les études récentes en PSG montrent que l'augmentation de la proportion de stade N1 (Song et al., 2015), la diminution de la puissance spectrale des ondes delta, theta et sigma en SL (Taillard et al., 2019), la diminution de la proportion de SP et l'augmentation de sa latence d'apparition (Pase et al., 2017; Song et al., 2015) prédisent le risque de MCI ou de démence.

De plus, l'augmentation de la latence d'endormissement, de la fragmentation du sommeil, des symptômes de somnolence diurne excessive, de la proportion de stade N1, ainsi que la diminution de l'efficacité de sommeil sont associés au déclin des performances exécutives (Blackwell et al., 2014; Ramos et al., 2016; Yaffe et al., 2007). Enfin, la présence d'un SAOS semble associée au déclin cognitif et au risque de développer un MCI ou une démence à un âge moins avancé (Leng et al., 2017; Osorio et al., 2015; Yaffe et al., 2011). Cette association semble particulièrement retrouvée chez les sujets présentant un AHI et un index de désaturation élevés, correspondant aux apnéiques sévères, et porteurs de l'allèle e4 du gène de l'APOE (Spira et al., 2008). De façon intéressante, Osorio et collaborateurs (2015) ont montré que les patients MCI et MA souffrant de SAOS non traité auraient des déficits mnésiques plus précoces, mais que le traitement du SAOS par pression positive continue (PPC) permettrait de contrer cet effet (Osorio et al., 2015).

2.4.3.3. Liens avec les déficits cognitifs des patients MCI et MA.

A ce jour, seul un faible nombre d'études a exploré les liens entre les altérations du sommeil des patients MCI et MA et leurs déficits cognitifs. Cependant, il a été rapporté qu'au stade de démence, un score plus faible au *Mini Mental State Examination* (MMSE) est associé aux symptômes de somnolence diurne excessive (Bonanni et al., 2005), à une réduction du nombre de fuseaux de sommeil (Gorgoni et al., 2016) et de la densité des complexes K (Reda et al., 2017). De plus, la sévérité des troubles de mémoire épisodique chez les patients MA a été associée à une réduction du nombre de fuseaux de sommeil rapides (Rauchs et al., 2008), une diminution de la fréquence moyenne de l'activité theta (Hot et al., 2011), et à une somnolence diurne excessive (Bonanni et al., 2005). Les scores de mémoire autobiographique ont quant à eux été corrélés avec la proportion de sommeil lent profond (Rauchs et al., 2013). Enfin, une étude a montré que potentialiser le sommeil paradoxal grâce à un traitement par donépézil à un stade léger à modéré de la démence permettait de diminuer les scores à l'échelle de l'ADAS-Cog, c'est-à-dire améliorer la cognition (Mizuno et al., 2004). Au stade de MCI, la sévérité des déficits mnésiques a été associée à une moins bonne qualité de sommeil auto-rapportée (Westerberg et al., 2010), une augmentation de la variabilité du sommeil mesuré de façon objective par actimétrie (Westerberg et al., 2010), et une diminution de la puissance spectrale des oscillations delta et theta en SL (Westerberg et al., 2012). Enfin, à la fois au stade de MCI et de démence, une étude récente rapporte qu'une augmentation de la durée de sommeil est associée à une diminution de la vitesse de traitement et des performances attentionnelles (Basta et al., 2019).

2.4.4. SOMMEIL ET INTEGRITE CEREBRALE

Les résultats des études explorant les liens entre la qualité du sommeil et l'intégrité cérébrale, au niveau structural, fonctionnel et des biomarqueurs de la MA sont résumés dans un tableau en **Annexe 6.2**.

2.4.4.1. Sommeil et substance grise

Les études transversales révèlent que de nombreux paramètres de sommeil sont associés à une diminution du volume de substance grise au niveau des régions frontales, dont une mauvaise qualité globale de sommeil auto-rapportée (Sexton et al., 2014), les réveils matinaux précoces (Stoffers et al., 2012), une somnolence diurne excessive (Killgore et al., 2012), une augmentation de la fragmentation du sommeil mesurée par actimétrie (Lim et al., 2016) et une diminution de l'activité à ondes lentes au cours du SLP (Dube et al., 2015; Latreille et al., 2019; Mander et al., 2013). De manière intéresssante, l'étude de Mander et collaborateurs (2013) démontre que l'atrophie du cortex préfrontal médian est associée à une altération du sommeil lent profond, sous-tendant une altération des processus de consolidation mnésique dépendants du sommeil. Par ailleurs, l'atrophie des régions temporo-pariétales (incluant l'hippocampe) a été associée à une moins bonne qualité de sommeil auto-rapportée (Alperin et al., 2019; Liu et al., 2018). De plus, la diminution du volume de substance grise dans l'insula a été associée à une augmentation du nombre de réveils nocturnes auto-rapportés (Branger et al., 2016) et une altération du sommeil lent profond (Dube et al., 2015). Enfin, les études réalisées auprès de patients apnéiques ne sont pas consensuelles, révélant aussi bien des diminutions (Huang et al., 2019; Shi et al., 2017; Tahmasian et al., 2016; Weng et al., 2014) que des augmentations de volume de substance grise (Baril et al., 2017; Cross et al., 2018;

Rosenzweig et al., 2013) au sein des régions temporales médiales, fronto-cingulaires et pariéto-occipitales.

Les études longitudinales sont moins nombreuses, et réalisées grâce à des mesures subjectives de sommeil, mais révèlent qu'une mauvaise qualité globale de sommeil est associée à une augmentation du taux d'atrophie des régions frontales, temporales et pariétales (Sexton et al., 2014). De plus, une faible ou une longue durée de sommeil auto-rapportée est associée à un taux d'atrophie frontale plus important (Spira et al., 2016). Enfin, les symptômes de somnolence diurne excessive sont associés à un taux d'atrophie plus important, essentiellement au niveau des régions temporales (Carvalho et al., 2017).

2.4.4.2. Sommeil, métabolisme et perfusion cérébrale

Peu d'études se sont intéressées aux liens entre la qualité du sommeil et le métabolisme ou la perfusion cérébrale, si bien que ces associations restent mal comprises. Ainsi, il a été montré que suite à une privation de sommeil, on observe une diminution du métabolisme cérébral au repos dans les régions frontales (Wu et al., 2006; Zhou et al., 2019) et temporales médiales (Zhou et al., 2019). De plus, chez les sujets d'âge moyen, une activité à ondes lentes préservée est associée à un métabolisme préfrontal au repos plus important (Wilckens et al., 2016). Il est à noter que chez les sujets âgés, Branger et collaborateurs n'ont rapporté aucun lien entre les paramètres de sommeil estimés de manière subjective sur les cinq dernières années et le métabolisme cérébral du glucose (Branger et al., 2016). Enfin, certaines études réalisées chez les individus souffrant de SAOS décrivent un profil d'hypoperfusion et d'hypométabolisme dans les zones temporales médiales, fronto-cingulaires et pariétales (incluant le précunéus et le cortex cingulaire postérieur) (Baril et

al., 2015; Innes et al., 2015; Kim et al., 2017; Nie et al., 2017; Shiota et al., 2014; Yaouhi et al., 2009), tandis que d'autres rapportent quant à elles une hyperperfusion des régions fronto-limbiques et de l'insula (Baril et al., 2015; Nie et al., 2017).

2.4.4.3. Sommeil et pathologie amyloïde

a. Régulation circadienne des niveaux de peptide amyloïde

Kang et collaborateurs (2009) ont démontré, sur modèle murin de MA, que les niveaux de peptide amyloïde présentent une fluctuation circadienne : ils augmentent pendant la phase d'éveil et diminuent lors du sommeil. L'amplitude de diminution des niveaux de peptide Aβ au cours du sommeil semble particulièrement dépendre de la quantité de sommeil lent profond (Kang et al., 2009; Roh et al., 2012). Suite à ces observations princeps chez l'animal, la fluctuation circadienne des niveaux de peptide amyloïde a été mise en évidence chez l'homme (Huang et al., 2012). Il a également été montré que suite à une nuit de privation de sommeil, les niveaux de peptide Aβ42 diminuent dans le LCS, traduisant une augmentation au niveau cérébral (Ooms et al., 2014). De plus, un effet de l'âge sur l'amplitude de la fluctuation circadienne des niveaux d'amyloïde a été mis en évidence, celle-ci diminuant de moitié chez les individus âgés Aβ- et de plus de 80% chez les individus Aβ+ (Huang et al., 2012; Lucey et al., 2017).

Deux mécanismes potentiels pourraient expliquer la diminution des niveaux de peptide Aβ au cours du sommeil, même si cette question n'est aujourd'hui pas tranchée et fait l'objet d'investigations. En effet, il a été proposé que l'une des fonctions majeures du sommeil serait de permettre l'élimination des métabolites toxiques accumulés au niveau cérébral pendant les périodes d'éveil.

Cette élimination se ferait grâce au « *système glymphatique* », un système de clairance périvasculaire permettant de drainer le liquide interstitiel du parenchyme cérébral (Tarasoff-Conway et al., 2015; Xie et al., 2013), qui semble particulièrement actif au cours du sommeil lent profond. En parallèle, l'augmentation des niveaux de peptide Aβ suite à une privation de sommeil pourrait résulter d'une augmentation de sa production, plutôt qu'un défaut de clairance. En effet, des études ont montré que la production de peptide Aβ est dépendante de l'activité neuronale (Bero et al., 2011; Cirrito et al., 2005). Ainsi, l'augmentation de la durée d'éveil en cas de privation ou de troubles du sommeil aurait pour conséquence une augmentation de l'activité neuronale, qui sous-tendrait une augmentation de la production de peptide Aβ.

b. Troubles du sommeil et dépôts amyloïdes chez l'Homme

Après la mise en évidence d'une fluctuation circadienne des niveaux de peptide Aβ, plusieurs études ont ensuite cherché à déterminer si les perturbations chroniques du sommeil sont associées à une augmentation des dépôts amyloïdes cérébraux chez l'Homme. Ainsi, une plus forte charge amyloïde, mesurée via une diminution des niveaux d'Aβ dans le LCS ou une augmentation du signal en TEP, a été associée à plusieurs paramètres de sommeil auto-rapportés, dont une mauvaise qualité globle de sommeil (Sprecher et al., 2017), une augmentation de la fréquence des siestes (Ju et al., 2013), une augmentation de la latence d'endormissement (Brown et al., 2016), et une courte durée de sommeil (Spira et al., 2013). De plus, ils ont également été associés à des paramètres de sommeil objectifs mesurés en actimétrie ou polysomnographie, incluant une moins bonne efficacité de sommeil (Ettore et al., 2019; Ju et al., 2013; Molano et al., 2017), une fragmentation du sommeil plus importante (Ettore et al., 2019; Lucey et al., 2019; Wilckens et al., 2018), une diminution du

sommeil lent profond et de l'activité à ondes lentes (Ju et al., 2017; Varga et al., 2016; Winer et al., 2019), et une augmentation de la latence d'apparition du SP (Lucey et al., 2019).

D'un point de vue régional, la charge amyloïde frontale est associée à une qualité et une quantité de sommeil ressenties comme insuffisantes et une somnolence diurne excessive (Sprecher et al., 2015), une augmentation de la latence d'endormissement auto-rapportée (Branger et al., 2016), et une altération du sommeil lent profond (Mander et al., 2015). De plus, la charge amyloïde pariétale, incluant le précunéus et le cortex cingulaire postérieur, est associée à une durée subjective de sommeil plus courte (Spira et al., 2013), et une qualité et une quantité de sommeil ressenties comme insuffisantes et une somnolence diurne excessive (Sprecher et al., 2015). Les études longitudinales montrent que les symptômes de somnolence diurne excessive sont liés à une accumulation de dépots amyloïdes plus importante au cours du temps (Spira et al., 2018), notamment au niveau du cortex cingulaire antérieur et postérieur et du précunéus (Carvalho et al., 2018).

Enfin, la sévérité du SAOS a également été associée, de manière transversale et longitudinale, à l'augmentation des niveaux de peptide amyloïde dans le LCS (Bu et al., 2015; Bubu et al., 2019; Liguori et al., 2017b; Sharma et al., 2018). A ce jour, une seule étude réalisé en TEP a montré que le SAOS est associé à une augmentation des dépôts amyloïdes au niveau du cortex cingulaire postérieur droit, en l'absence de modifications structurales de la substance grise (Yun et al., 2017). Cependant, cette étude a été réalisée sur un échantillon relativement restreint (n=19) de patients âgés de moins de 65 ans, et mérite d'être répliquée sur des échantillons plus importants de sujets âgés.

De façon intéressante, quelques études montrent que les liens entre sommeil et intégrité cérébrale ont des conséquences sur les performances cognitives. Ainsi, Mander et collaborateurs (2015) ont démontré que la charge amyloïde au sein du cortex préfrontal médian altérait la qualité des ondes lentes du sommeil lent profond, entraînant une perturbation des processus de consolidation mnésique dépendants du sommeil. De plus, deux études ont démontré qu'un sommeil de mauvaise qualité (Molano et al., 2017) et une augmentation du temps d'éveil au cours de la nuit (Wilckens et al., 2018) modéraient l'association entre l'augmentation de la charge amyloïde et la diminution des performances mnésiques.

2.4.4.4. Sommeil et pathologie tau

La pathologie tau, correspondant au deuxième processus neuropathologique caractérisant la MA, semble également associée aux altérations du sommeil, même si ces associations restent mal comprises du fait du peu d'études réalisées à ce jour. En revanche, l'émergence de l'imagerie TEP couplée aux radiotraceurs tau en fait un champ de recherche prometteur.

De manière générale, les études montrent qu'une mauvaise qualité subjective de sommeil et une somnolence diurne excessive sont associées à une augmentation des ratios t-tau et p-tau/Aβ42, reflétant des niveaux de pathologie plus importants (Sprecher et al., 2017). De plus, une augmentation des niveaux de p-tau dans le LCS est prédictive d'une moins bonne qualité subjective de sommeil chez les individus Aβ+ (Fjell et al., 2018). Plus spécifiquement, Ju et collaborateurs (2017) ont montré qu'une moins bonne efficacité du sommeil, mesurée par actimétrie sur 6 nuits consécutives, était associée à une augmentation des niveaux de tau dans le LCS. De manière intéressante, cette association semble principalement sous-tendue par une augmentation des

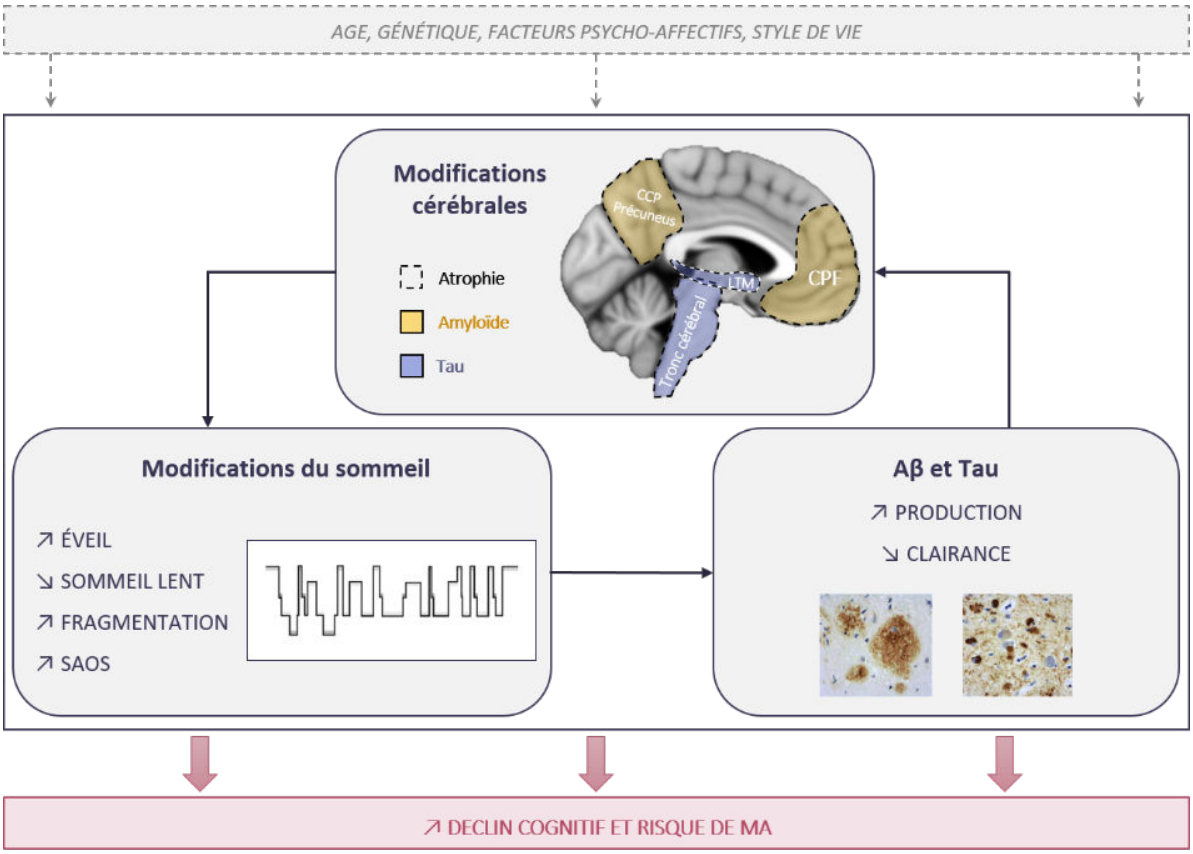
niveaux d'activité neuronale lors du sommeil chez les participants ayant une moins bonne efficacité de sommeil (Ju et al., 2017). De plus, une fragmentation du sommeil plus importante a été associée à des niveaux de DNF plus importants mesurés à l'autopsie (Lim et al., 2013). Les études en PSG montrent que les niveaux de tau sont associés aux altérations du sommeil lent profond (Lucey et al., 2019) et des fuseaux de sommeil (Kam et al., 2019). De manière intéressante, Winer et colaborateurs (2019) ont montré que le marquage tau au niveau des structures du lobe temporal médian est associé à une altération du couplage entre les fuseaux et les ondes lentes, connu pour sous-tendre les processus de consolidation mnésique dépendants du sommeil (Winer et al., 2019). Enfin, la présence d'un SAOS non traité a également été associée à une augmentation des niveaux de tau périphérique (Bu et al., 2015; Ju et al., 2016; Liguori et al., 2017b; Motamedi et al., 2018; Osorio et al., 2014). Les liens entre SAOS et accumulation de la pathologie tau, mesurée de façon longitudinale dans le LCS, sont moins clairs. En effet, une étude a montré une association positive entre SAOS et accumulation de la pathologie tau au cours du temps (Bubu et al., 2019), mais ce résultat n'est pas systématiquement retrouvé (Sharma et al., 2018).

2.4.5. SOMMEIL ET MA : UNE RELATION BIDIRECTIONNELLE ?

Si un nombre croissant d'études révèlent des associations entre divers aspects de la qualité du sommeil et l'intégrité cérébrale et cognitive, il convient de mentionner que les résultats obtenus restent hétérogènes. En effet, les études actuelles présentent une hétérogénéité importante au niveau des tailles d'échantillons, du contrôle statistique pour les comorbidités associées (y compris les troubles du sommeil tels que le SAOS), ou encore du type de mesure (i.e., subjective ou objective)

et du paramètre de sommeil considérés. La question de la direction et de la causalité de ces associations, à savoir si les troubles du sommeil sont plutôt une cause ou une conséquence des altérations cérébrales, reste également une importante source de débats, même si l'hypothèse dominante actuellement plaide en faveur d'une relation bidirectionnelle entre les altérations cérébrales et du sommeil. Un schéma récapitulatif des hypothèses actuelles concernant la modélisation de ces associations est proposé en **Figure 13** ci-après.

En effet, les modifications cérébrales liées à l'âge et au développement de la pathologie (i.e., l'atrophie, l'hypométabolisme, la charge amyloïde cérébrale et la pathologie tau) sont observées au sein de régions connues pour être impliquées dans la génération et le maintien du sommeil, telles que les régions frontales, temporales médianes ou du tronc cérébral (Dang-Vu et al., 2008; Massimini et al., 2004; Murphy et al., 2009; Schabus et al., 2007). Ainsi, ces modifications cérébrales pourraient entraîner l'apparition de troubles du sommeil, sous-tendant eux-mêmes des déficits cognitifs. Plusieurs études expérimentales étayent cette hypothèse (Cavuoto et al., 2016; Wilckens et al., 2014). En effet, il a notamment été montré que l'atrophie (Mander et al., 2013) et la présence de dépôts amyloïdes (Mander et al., 2015) au niveau du cortex préfrontal médian sous-tendait une altération des ondes lentes du SLP, qui était associée à une altération des processus de consolidation en mémoire épisodique, et à une diminution des performances de rappel après une nuit de sommeil. Enfin, Wilckens et collaborateurs (2018) ont montré que l'augmentation du temps passé éveillé au cours de la nuit modérait significativement l'association entre une augmentation de la charge amyloïde et l'oubli en mémoire épisodique chez les mauvais dormeurs (Wilckens et al., 2018).



<u>Figure 13:</u> Résumé des hypothèses sur la directionalité des liens entre sommeil, vieillissement et physiopathologie de la MA.

Les modifications cérébrales liées à l'âge et à la MA surviennent dans des régions sous-tendant une bonne qualité de sommeil. Ainsi, elles entraîneraient des modifications du sommeil (correspondant à une augmentation des niveaux d'éveil, et une diminution du sommeil lent profond), qui pourraient exacerber la progression des pathologies amyloïde et tau, créant ainsi un cercle vicieux précipitant le déclin cognitif.

<u>Abréviations</u> : CCP, cortex cingulaire postérieur ; CPF, cortex préfrontal ; LTM, lobe temporal médian ; SAOS, syndrome d'apnées obstructives du sommeil.

Les illustrations sont empruntées de Pace-Schott et al., (2011) (hypnogramme) et Small et al., (2008) (images de microscopie).

De plus, au-delà de n'être qu'une conséquence de la présence de la pathologie dans des régions sous-tendant le sommeil, plusieurs arguments suggèrent que les troubles du sommeil pourraient également favoriser le développement et la propagation des pathologies amyloïde et tau. En effet, les problèmes de sommeil liés à l'âge incluent une augmentation de la fragmentation du sommeil, et des niveaux d'éveils au cours du sommeil. L'augmentation des niveaux d'éveils ont pour conséquence une augmentation de l'activité neuronale, connue pour être associée à une augmentation des concentrations d'amyloïde et tau dans l'espace interstitiel (Bero et al., 2011; Cirrito et al., 2005; Yamada et al., 2014). De plus, la diminution du temps de sommeil *per se* pourrait diminuer les mécanismes de clairance des métabolites toxiques (Rasmussen et al., 2018; Tarasoff-Conway et al., 2015; Xie et al., 2013), favorisant ainsi le développement des pathologies amyloïde et tau **(Figure 13)**. En effet, l'hypothèse du *système glymphatique* stipule que le sommeil favoriserait le drainage des déchets métaboliques depuis le liquide interstitiel vers les espaces péri-veineux, grâce à la pulsatilité artérielle, un flux convectif de LCS et aux aquaporines localisées sur les cellules gliales (Iliff et al., 2012; Xie et al., 2013). Cependant, les études chez l'animal ainsi que certains aspects théoriques de ce système sont encore débattues (Smith et al., 2017; Smith and Verkman, 2018), et les études pilotes réalisées chez l'homme montrent que les associations entre troubles du sommeil et dépôts amyloïdes seraient davantage sous-tendues par une augmentation de la sécrétion d'Aβ, plutôt qu'une diminution de sa clairance (Lucey et al., 2018). Ainsi, la question de la causalité des liens entre qualité du sommeil, intégrité cérébrale et cognitive reste à l'heure actuelle ouverte et mérite de plus amples investigations.

3. PARTIE EXPERIMENTALE

3.1. PROBLEMATIQUE ET OBJECTIFS

Comme décrit précédemment, il est désormais bien établi que la qualité du sommeil diminue au cours du vieillissement. Les principales modifications du sommeil liées à l'âge incluent une altération marquée du SLP, concentré principalement dans les premiers cycles de sommeil, s'accompagnant d'une augmentation de la fragmentation du sommeil et de la prévalence du SAOS. Ces trois aspects ont été mis en lien avec différentes modifications de l'intégrité cérébrale et cognitive, et les premiers éléments issus d'études menées chez l'animal suggèrent qu'ils pourraient être associés aux mécanismes physiopathologiques sous-tendant la MA. En revanche, à ce jour, la littérature reste hétérogène quant aux mesures et paramètres de sommeil utilisés (la plupart des études ayant été réalisées grâce à des mesures subjectives du sommeil), et modifications cérébrales et cognitives mises en cause. De plus, aucune étude n'a combiné des mesures objectives de sommeil avec plusieurs modalités d'imagerie dans un même échantillon (dont de l'imagerie amyloïde), bien que l'approche de neuroimagerie multimodale se révèle être un outil précieux afin de mieux comprendre les mécanismes sous-tendant les associations observées.

Ainsi, au travers de 3 études originales, ce travail de thèse vise à contribuer à une meilleure compréhension des liens entre les principales modifications du sommeil liées à l'âge, mesurées de façon objective, les perfomances cognitives et les altérations cérébrales structurales, fonctionnelles et moléculaires. Chaque étude de cette thèse se concentre sur un aspect particulier des modifications du sommeil dans le vieillissement, mesuré par actimétrie (étude 1) ou polysomnographie (études 2 et 3). Ainsi, dans une première étude, nous avons étudié les liens entre la fragmentation des premiers cycles de sommeil, durant lesquels la proportion de SL prédomine,

et l'intégrité cérébrale et cognitive, dans un groupe de sujets âgés cognitivement sains et dans un groupe de patients présentant des déficits cognitifs subjectifs ou objectifs, incluant des patients SCD ou MCI. Dans une seconde étude, notre objectif était de mesurer plus finement, au moyen d'analyses spectrales, l'intégrité des rythmes oscillatoires en SL et en SP, et d'établir leurs liens avec le volume, la perfusion et la charge amyloïde cérébrale chez les sujets âgés cognitivement sains. Enfin, dans une troisième étude, notre objectif a été d'établir le profil d'atteintes cognitives et en imagerie multimodale associé à la présence d'un SAOS chez les personnes âgées cognitivement saines. Une meilleure compréhension de l'impact des troubles du sommeil sur les altérations cérébrales liées à l'âge et le risque de démence pourrait permettre de développer de nouvelles stratégies thérapeutiques visant à ralentir le déclin cognitif.

3.2. CONTEXTE GENERAL DE LA THESE

Le présent travail de thèse a été réalisé dans le cadre de deux protocoles plus larges pilotés par le Dr Gaël Chételat au Centre Cyceron à Caen, que nous allons présenter ci-dessous. Ainsi, la première étude de cette thèse s'inscrit dans le cadre du protocole IMAP+, et les études 2 et 3 ont été réalisées grâce aux données issues du protocole Age-Well.

3.2.1. PROTOCOLE IMAP+

Le protocole de recherche clinique IMAP+ (pour Imagerie Multimodale de la Maladie d'Alzheimer à un stade Précoce) a démarré en 2012 au Centre Cyceron à Caen. Le médecin investigateur

principal de l'étude est le Dr Vincent de la Sayette, la coordinatrice scientifique est le Dr Gaël Chételat, et le promoteur est le CHU de Caen.

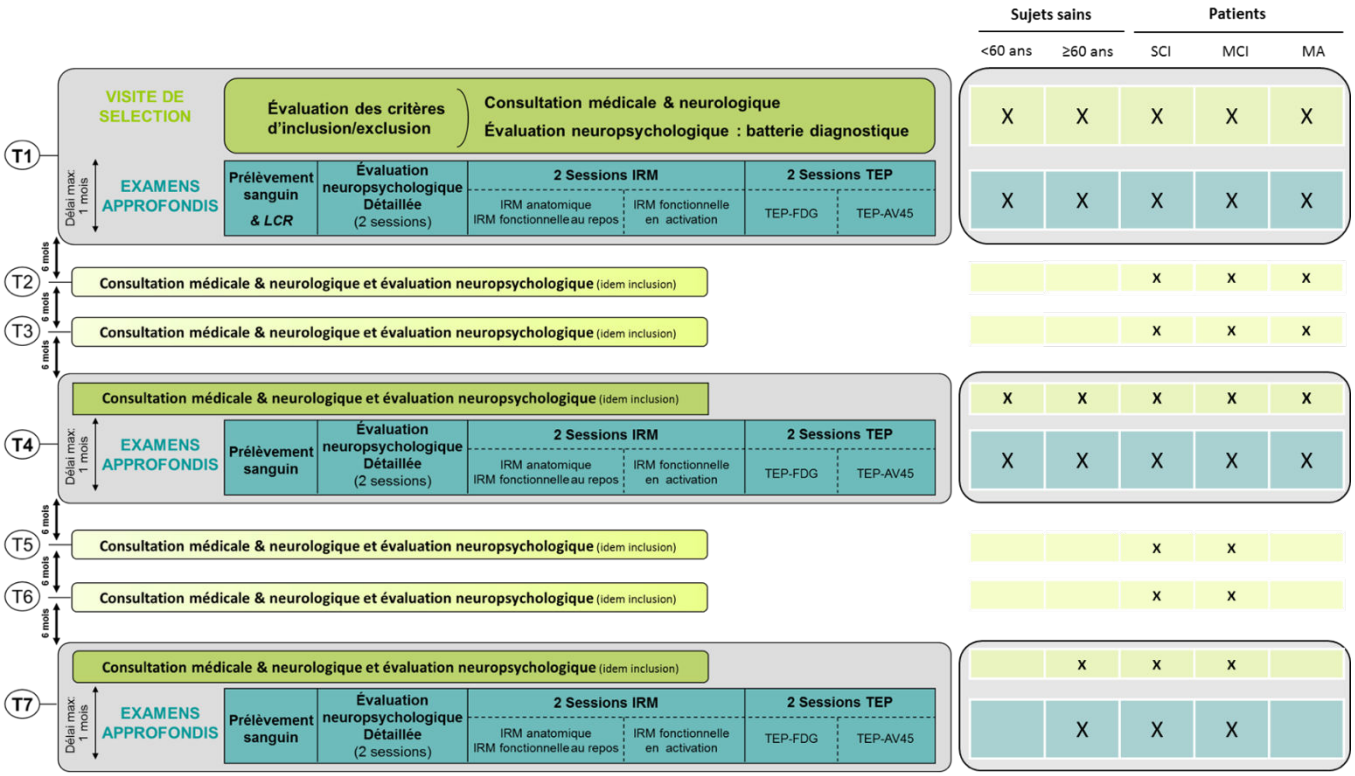


Figure 14: Design général du protocole IMAP+.

Les évaluations cliniques et neuropsychologiques permettant le diagnostic des participants figurent en vert, tandis que les évaluations expérimentales figurent en bleu. A droite sont indiqués les groupes bénéficiant des examens lors des différents suivis longitudinaux.

L'objectif général du protocole IMAP+ est d'identifier des marqueurs de neuroimagerie, de neuropsychologie ou de biologie de la pathologie à un stade pré-démentiel voire asymptomatique associés au déclin cognitif, afin de contribuer au diagnostic précoce et à une meilleure compréhension des mécanismes physiopathologiques de la maladie. Cette étude longitudinale est proposée à des sujets jeunes (18-39 ans), d'âge intermédiaire (40-59 ans) et âgés (plus de 60 ans)

cognitivement sains, ainsi qu'à des patients à différents stades de la MA, incluant des patients avec des déficits cognitifs subjectifs (SCD), des déficits cognitifs légers (MCI), et des patients atteints de MA probable. En baseline ainsi qu'à différents temps de suivi, pouvant aller jusqu'à 36 mois selon la catégorie, les participants réalisent une batterie de tests neuropsychologiques, plusieurs examens de neuroimagerie, et un prélèvement sanguin (voir la **Figure 14** ci-dessus).

Une étude ancillaire sur le sommeil a été intégrée en 2015 et proposée aux sujets d'âge intermédiaire et âgés, ainsi qu'aux patients SCD et MCI inclus dans le protocole IMAP+. Celle-ci comprend des mesures subjectives de sommeil via différents questionnaires, et des mesures objectives, avec un enregistrement actimétrique et un examen de polysomographie à domicile.

Les inclusions dans le protocole IMAP+ sont closes depuis l'automne 2016, et le protocole est encore en cours pour la réalisation de derniers suivis longitudinaux de patients, dont la fin est prévue en automne 2019. L'ensemble des données acquises ont été pré-traitées, contrôlées et analysées en parallèle de la poursuite du recrutement et des suivis de participants et de patients.

3.2.2. PROTOCOLE AGE-WELL

L'étude Age-Well, sur laquelle repose les études 2 et 3 de cette thèse, est un essai clinique randomisé se proposant de comparer les effets d'un entrainement à la méditation ou à l'apprentissage d'une langue étrangère pendant 18 mois sur des mesures comportementales, biologiques et de neuroimagerie, chez des participants de plus de 65 ans. Le médecin investigateur principal de l'étude est le Dr Vincent de la Sayette, la coordinatrice scientifique est le Dr Gaël Chételat, et la promotion est assurée par l'Inserm. Cette étude fait partie du projet européen Medit-Ageing, dont le design général est exposé en **Figure 15** ci-dessous.

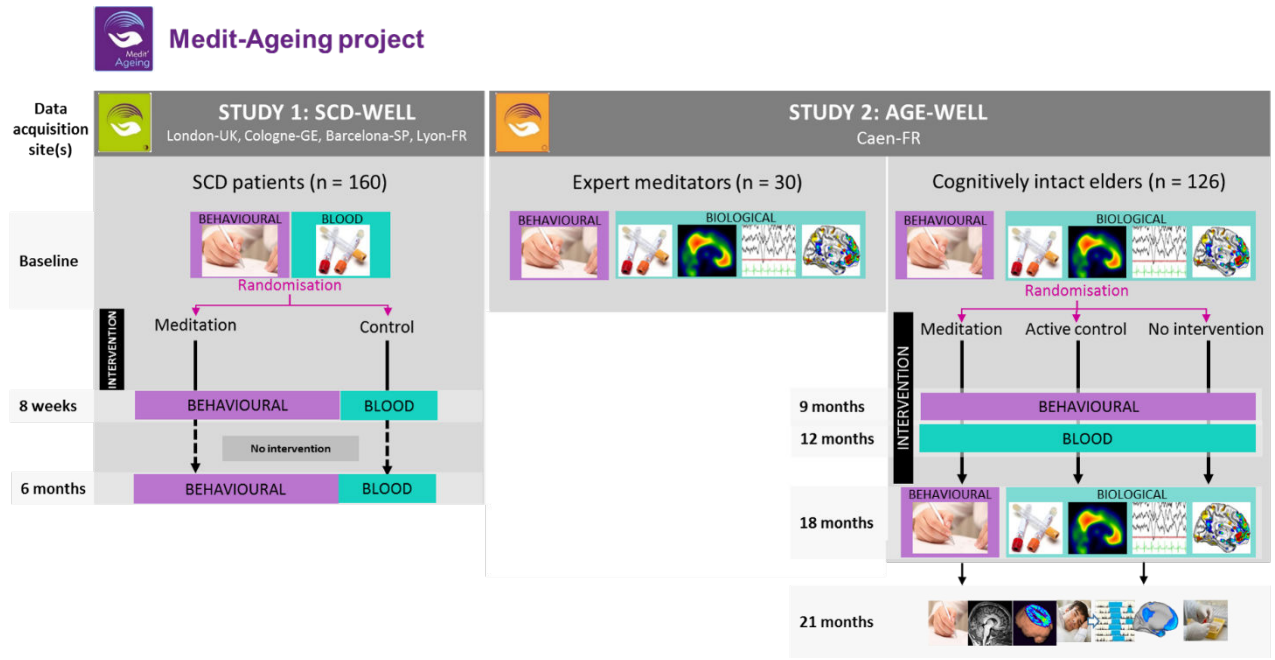


Figure 15: Design général du projet européen Medit-Ageing.
Le projet européen comporte deux études : *SCD-Well*, se déroulant dans 4 pays européen (Royaume-Uni, Allemagne, Espagne et France), dont l'objectif est d'étudier l'effet d'un entrainement de 8 semaines à la méditation chez des patients SCD, et *Age-Well*, se déroulant à Caen (France), ayant pour but l'étude de l'effet d'un entrainement de 18 mois à la méditation ou à l'apprentissage d'une langue étrangère chez des sujets cognitivement sains de plus de 65 ans.

Ce projet comprend également une autre étude intitulée « *SCD-Well* », ainsi que l'étude d'un groupe de méditants experts inclus dans l'étude Age-Well, bien que nous ne détaillerons pas outre mesure ces aspects, dépassant le cadre de ce travail de thèse.

Dans l'étude Age-Well, dont le protocole détaillé est disponible en **Annexe 6.3** (Poisnel et al., 2018), les participants bénéficient d'une série d'examens, incluant des évaluations neuropsychologiques, des examens de neuroimagerie, un prélèvement sanguin, et des examens de sommeil (via des questionnaires, un enregistrement par actimétrie et un examen de polysomnographie). Au total, 137 participants ont été inclus et randomisés entre novembre 2016 et avril 2018, avec une mise à disposition des données de baseline en janvier 2019 pour les analyses. L'ensemble des participants aura terminé son suivi à 18 mois en février 2020. Un suivi à plus long terme (21 mois) sera proposé à l'ensemble des participants.

De manière générale, dans le cadre de ma thèse, j'ai contribué au pré-screening des volontaires de l'étude Age-Well, et participé à l'acquisition, au contrôle qualité et au pré-traitement des données de neuroimagerie et de sommeil à la fois dans le protocole IMAP et dans le protocole Age-Well.

3.3. ÉTUDE 1 : FRAGMENTATION DES PREMIERS CYCLES DE SOMMEIL

Comme abordé précédemment, le vieillissement s'accompagne d'une augmentation de la fragmentation du sommeil et d'une alteration du SLP, particulièrement prépondérant lors des premiers cycles de sommeil (Carrier et al., 2001; Klerman et al., 2013; Mander et al., 2017; Ohayon et al., 2004). Si les modifications du sommeil sont de plus en plus considérées comme un facteur de risque de déclin cognitif (Bubu et al., 2017; Lim et al., 2013; Shi et al., 2018; Taillard et al., 2019), les mécanismes cérébraux sous-tendant cette association sont mal connus, et peu d'études ont été réalisées avec des mesures objectives de sommeil. Ainsi, l'objectif de cette étude était de caractériser les liens entre l'intensité et la variabilité de la fragmentation objective des premiers cycles de sommeil, la structure, le métabolisme et la charge amyloïde cérébrale et les performances cognitives, chez les sujets âgés sains et des patients présentant des déficits cognitifs subjectifs et/ou objectifs (i.e., SCD ou MCI).

Trente sujets âgés sains et 36 patients présentant des déficits cognitifs subjectifs et/ou objectifs (dont 14 patients SCD et 22 patients MCI) issus du protocole IMAP+ ont été inclus dans cette étude. Les participants ont bénéficié d'une évaluation neuropsychologique détaillée, d'une IRM structurale permettant de mesurer le volume de substance grise, d'un examen de TEP couplé au ^{18}F-fluorodeoxyglucose mesurant le métabolisme cérébral du glucose, d'un examen de TEP couplé au ^{18}F-florbetapir permettant de mesurer les dépôts amyloïdes cérébraux, et d'un enregistrement du cycle activité/repos par actimétrie pendant 6 nuits consécutives minimum. Dans un premier temps, nous avons réalisé des analyses de régression multiple entre les paramètres de fragmentation

du sommeil (i.e., l'intensité de la fragmentation des premiers cycles de sommeil, d'une part, et la variabilité des niveaux de fragmentation d'une nuit à l'autre, d'autre part), les différentes données de neuroimagerie et les performances cognitives, au sein de chaque groupe. Dans un second temps, des analyses de médiation ont été réalisées afin de préciser la causalité des associations observées.

Les résultats montrent que chez les sujets âgés cognitivement sains, l'intensité moyenne de la fragmentation du sommeil médie l'association entre l'hypométabolisme du cortex préfrontal ventromédian et des hippocampes, et la diminution des performances exécutives. Dans une moindre mesure, une augmentation de la variabilité de la fragmentation du sommeil, reflétant une qualité de sommeil inconsistante d'une nuit à l'autre, était corrélée à une diminution du volume de substance grise au niveau du thalamus, et une augmentation de la charge amyloïde au niveau du cortex préfrontal ventromédian. Toutefois, ces associations n'étaient pas retrouvées dans le groupe de patients SCD et/ou MCI, puisque seule une corrélation négative entre le métabolisme de l'insula gauche et l'intensité de la fragmentation du sommeil a été retrouvée, sans lien avec l'expression des déficits cognitifs des patients.

De manière intéressante, les régions associées à la fragmentation des premiers cycles de sommeil sont connues pour être impliquées dans la physiologie du sommeil lent, et plus particulièrement dans la génération des ondes lentes (Massimini et al., 2004; Murphy et al., 2009) et des fuseaux de sommeil (Schabus et al., 2007). De plus, il a été montré qu'elles sont sensibles au vieillissement et affectées précocément par les processus physiopathologiques de la MA. En effet, la pathologie amyloïde atteint en premier lieu les zones néocorticales frontales (Thal et al., 2002), et la pathologie tau atteint précocément les structures temporales médiales, dont l'hippocampe (Braak and Braak,

1991). Ainsi, ces résultats suggèrent que la fragmentation objective du sommeil contribuerait directement à la diminution des performances cognitives chez les sujets âgés sains, et que le traitement des troubles du sommeil avant l'apparition des premiers symptômes cognitifs pourrait contribuer à compenser les modifications cérébrales liées à l'âge, et maintenir les performances cognitives. Cependant, avec l'avancée dans la pathologie et l'apparition des premières manifestations cognitives, nous faisons l'hypothèse que les performances cognitives seraient principalement et plus directement sous-tendues par les processus neuropathologiques de la MA, et que l'influence de la fragmentation du sommeil ne serait plus détectable à ce stade.

Cette étude a fait l'objet de trois communications orales en congrès, en 2016 (23ème congrès de l'European Sleep Research Society), 2017 (Alzheimer's Association International Conference) et 2018 (Réunion Francophone sur la Maladie d'Alzheimer et Syndromes Apparentés), et a été publiée en février 2019 dans la revue *Alzheimer's and Dementia : Diagnosis, Assessment & Disease Monitoring*.

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Alzheimer's & Dementia

Cognitive & Behavioral Assessment

Brain and cognitive correlates of sleep fragmentation in elderly subjects with and without cognitive deficits

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Abstract

Introduction: Sleep disturbances are increasingly recognized as a risk factor for Alzheimer's disease. However, no study has assessed the relationships between objective sleep fragmentation (SF) and brain and cognitive integrity across different cognitive stages, from cognitively unimpaired elderly subjects to patients with subjective cognitive decline and/or mild cognitive impairment.
Methods: 30 cognitively unimpaired elderly participants and 36 patients with subjective cognitive decline and/or mild cognitive impairment underwent a neuropsychological evaluation, structural MRI, ^{18}F-fluorodeoxyglucose, and ^{18}F-florbetapir-PET scans, and an actigraphy recording over a minimum of six consecutive nights. Multiple regression and mediation analyses were performed between SF parameters, neuroimaging data, and cognitive scores.
Results: In cognitively unimpaired elderly participants, SF intensity mediated the association between frontohippocampal hypometabolism and lower executive functioning. Moreover, to a lower extent, increased SF variability was related to thalamic atrophy and ventromedial prefrontal amyloid burden. However, in patients with subjective cognitive decline and/or mild cognitive impairment, SF no longer contributed to the expression of cognitive deficits.
Discussion: These findings suggest that SF may directly contribute to lower cognitive performance in cognitively unimpaired elderly subjects. Therefore, treating sleep disturbances before the onset of cognitive deficits may help to cope with brain alterations and maintain cognitive functioning.

Keywords: Sleep; Aging; Subjective cognitive decline; Mild cognitive impairment; MRI; Amyloid; Glucose metabolism; Actigraphy; Sleep fragmentation

1. Introduction

As no curative treatment for Alzheimer's disease (AD) is currently available, it is particularly important to identify modifiable lifestyle factors that might help prevent, delay the onset, or slow down the progression of the disease. In this context, there is a growing interest in better characterizing age-related sleep changes and their associations with AD. Indeed, aging is characterized by a progressive decline in sleep quality, including a decrease in non-rapid eye movement (NREM) sleep, paralleled by greater sleep fragmentation (SF) [1]. Moreover, age-related changes in sleep quality have been related to cognitive decline and increased risk of developing dementia [2–4]. Sleep disturbances are also a core symptom of AD [1]. They worsen with dementia severity and are related to patients' cognitive deficits,

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especially memory impairments [5]. Accumulating evidence indicates that the disruption of slow-wave sleep, the deepest NREM sleep stage predominating during the first part of the night, is associated with increased beta-amyloid (Aβ) deposition in the brain [6–8], a hallmark of AD known to start decades before the apparition of the first cognitive symptoms [9]. Moreover, several self-reported sleep parameters, including longer sleep latency [10,11] and shorter sleep duration [12], have been associated with increased amyloid deposition in frontal areas and/or in the precuneus. In addition to amyloid deposition, sleep disruption may also be associated with neuronal injury, as measured with gray matter atrophy or hypometabolism, both known to be closely related to cognitive decline [13,14]. Previous studies reported that, in cognitively unimpaired elderly subjects, poor self-reported sleep quality is related to reduced gray matter volume in frontal regions and the insula [10,15], and that increased actigraphy-measured sleep fragmentation is associated with atrophy in the orbitofrontal cortex [16].

However, we lack a comprehensive overview of the relationships between objective measures of sleep quality and amyloid deposition, atrophy, and brain glucose metabolism in cognitively unimpaired elderly participants. Furthermore, we have no information about these links in patients with subjective and/or objective cognitive deficits. Clarifying these associations using complementary neuroimaging modalities that reflect different aspects of brain integrity, and across different cognitive stages, would help determining to what extent and at which stage of the disease the treatment of sleep disturbances would be beneficial to prevent cognitive decline.

Thus, the present study aims at investigating and comparing the relationships between objectively measured SF and cognitive, structural, functional, and molecular brain changes in cognitively unimpaired elderly subjects versus in patients with subjective and/or objective cognitive deficits, including patients with subjective cognitive decline (SCD) and mild cognitive impairment (MCI).

2. Materials and methods

2.1. Participants

Sixty-six participants from the IMAP+ study ("Imagerie Multimodale de la Maladie d'Alzheimer à un stade Précoce", Caen, France) were included in the present study. They were all right-handed, native French speakers, with at least 7 years of education, living at home, without history or clinical evidence of neurological or psychiatric disorders, alcohol use disorder or drug abuse, and with a normal somatic examination. The inclusion and group classification of the participants were based on a clinical interview and a standardized neuropsychological assessment, according to internationally agreed criteria, but did not rely on neuroimaging biomarkers, as they were the main outcome measures in our analyses.

Thirty cognitively unimpaired elderly subjects were recruited from the community. They were aged over 60 years, had no memory complaint and never referred to a memory clinic, and performed in the normal range (i.e., within 1.65 standard deviation [SD] of the mean) for their age and education level in all screening tests. In addition, thirty-six patients aged over 50 years were recruited from local memory clinics, to which they attended for self-reported cognitive concerns. During the clinical interview, the physician ensured i) that the complaint was not related to current medication, psychiatric or neurological diseases (including anxiety or depression), or other medical conditions, ii) that independence in daily life was preserved, and iii) that they did not fulfill NINCDS-ADRDA criteria for probable AD [17]. Among the 36 patients, 22 had objective cognitive deficits and met clinical criteria for single or multiple domain amnestic mild cognitive impairment [18], with predominant episodic memory deficits (1.5 SD from the normal mean for age and education). Fourteen patients did not show significant objective cognitive impairment and met criteria for SCD [19]. Clinical diagnosis for patients was assigned by consensus under the supervision of senior neurologists and neuropsychologists.

Once included in the study, all participants performed a detailed neuropsychological assessment, an actigraphy recording, and three neuroimaging scans within a mean interval of 1.9 ± 3.1 months. The IMAP+ study was approved by the local ethics committee (CPP Nord-Ouest III) and registered at http://clinicaltrials.gov (nb. NCT01638949). All participants gave their written informed consent to the study before the examinations.

2.2. Cognitive assessment

Participants underwent a detailed neuropsychological assessment, encompassing multiple domains of cognition (verbal and visual episodic memory, semantic memory, working memory, executive functioning, processing speed, visuospatial abilities, language skills, and praxis), fully described in previous publications [20,21]. In the present study, analyses focused on episodic memory and executive functioning, as they are particularly sensitive to aging and AD [22], and closely related to sleep quality [23]. We used composite scores to reflect cognitive abilities with robust proxies and to minimize the issue of multiple statistical testing (see [24] and Supplementary Material for further details). Higher values always indicated better performance. Furthermore, symptoms of depression and anxiety were assessed using the Montgomery-Asberg Depression Rating Scale [25] and the trait version of the State-Trait Anxiety Inventory [26], respectively.

2.3. Actigraphy recording

2.3.1. Actigraphy data collection

The sleep-wake cycle was recorded in all participants using the MotionWatch 8 wrist-worn triaxial actigraph

(CamNTech Ltd, Cambridge, UK), for at least six consecutive nights (range: 6-8 nights; mean ± SD: 7.05 ± 0.51 nights). Participants were instructed to wear continuously the device on their nondominant wrist until the end of the recording. They had to press the event marker button at lights off and lights on, and to fill in a sleep diary on awakening each morning [27] to facilitate data analysis.

2.3.2. Actigraphy data analysis

Data were analyzed using the MotionWare software (version 1.1.25, CamNTech Ltd, Cambridge, UK) and sampled using a 5-second epoch. A sensitivity threshold of 20 counts was applied to distinguish activity from rest. For each night, the "Lights Off" and "Got Up" markers were placed by the same experimenter in the appropriate position following the event marker put by the participant and cross-validated with the light sensor data and sleep diary information. Then, "Fell Asleep" and "Woke up" markers were automatically adjusted from the combination of the activity data and the "Lights Off" and "Got Up" markers, respectively, allowing the collection of the assumed sleep time. Then, a fragmentation index was calculated as the sum of the percentages of mobile time and immobile bouts below or equal to 1 minute in the assumed sleep period. Two distinct parameters of SF were considered: SF intensity (corresponding to the mean level of fragmentation over the whole recording) and intra-individual SF variability (computed as SF standard deviation across nights) (Fig. 1). These parameters were computed over the first half of the assumed sleep duration for each subject.

2.4. Neuroimaging procedure

Participants underwent a structural T1 MRI, as well as ^{18}F-fluorodeoxyglucose (FDG)- and florbetapir-PET scans, to measure gray matter volume, brain glucose metabolism, and amyloid burden, respectively. All examinations were performed at the Cyceron Center (Caen, France). Details on MRI and PET images acquisition and preprocessing are available in previous publications [28,29] and are fully described in the Supplementary Material. Briefly, T1-weighted images were preprocessed in SPM12. FDG-PET and florbetapir-PET images were preprocessed using MRI data for partial volume effect correction and spatial normalization. Partial volume effects-corrected normalized and scaled florbetapir-PET images were also used to extract the individual global cortical amyloid standard uptake value ratio using a predetermined neocortical mask including the entire gray matter, except the cerebellum, occipital and sensory motor cortices, hippocampi, amygdala, and basal nuclei [30].

2.5. Statistical analyses

2.5.1. Group comparisons

Between-group comparisons for demographics, cognitive scores, and sleep parameters were assessed using Student's t-tests for continuous variables and chi-square tests for categorical variables, with statistical significance set to $P < .05$.

Patients' patterns of atrophy, hypometabolism, and amyloid burden were explored using two-sample t-tests in SPM12, adjusted for age, gender, and body mass index.

2.5.2. Voxelwise regression analyses

Within each group, voxelwise multiple regression analyses were performed between SF parameters and each neuroimaging modality independently in SPM12, controlling

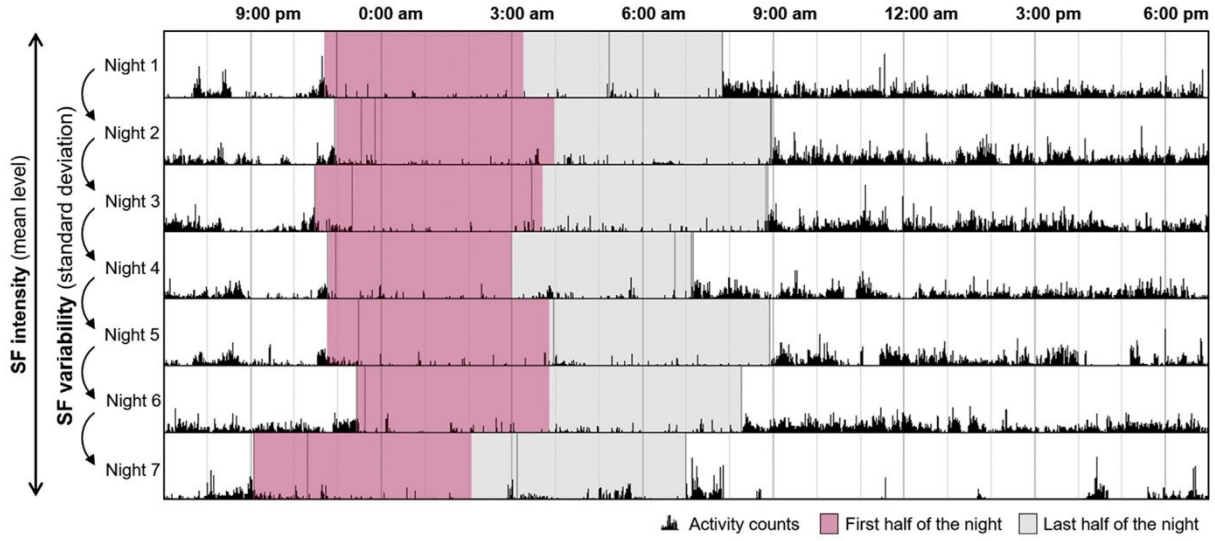

Fig. 1. Illustration of a representative actigraphy recording with computation of SF parameters. SF was computed over the first half of the night. SF intensity corresponded to the mean level of SF over all recorded nights, and SF variability corresponded to the standard deviation of SF across recorded nights. Abbreviation: SF, sleep fragmentation.

for age, gender, body mass index, and the complementary SF parameter (i.e., we controlled for SF variability when SF intensity was the predictive variable, and conversely). Afterward, complementary analyses were performed with the addition of several covariates to the main model. Only results obtained with the initial 4-covariates model are presented, as the main results remained essentially unchanged when adding the Mini-Mental State Examination score, depression score, or sleep medication use as covariates. We report the slight changes observed on these secondary analyses in the Supplementary Material. For all neuroimaging analyses, results were evaluated for significance at $P < .001$ (uncorrected) combined with a minimum cluster size determined by Monte-Carlo simulation using the AlphaSim program to achieve a corrected statistical significance of $P < .05$ (Supplementary Table 1). Results obtained at the same statistical threshold but with a lower cluster size were considered as trends.

2.5.3. Multiple regression analyses

Multiple regression analyses were performed between SF parameters and cognitive scores (i.e., composite scores for executive functioning and episodic memory) within each group. Age and gender were included as covariates in the regression models, and results were considered significant after applying a Bonferroni correction for multiple comparisons: the statistical threshold for significance was set to $P = (.05/\text{number of comparisons})$.

2.5.4. Mediation analyses

When the same SF parameter was significantly associated to both a brain and a cognitive variable, then causal mediation analyses were performed to assess the directionality of the relationships. For this purpose, brain data (i.e., gray matter volume, glucose metabolism, or amyloid values) were extracted in the clusters significantly associated with SF parameters in the voxelwise analyses described previously. Then, two different models were tested to determine whether the brain variable mediated the relationships between sleep and cognition or whether the sleep variable mediated the relationships between the brain variable and cognition. These analyses were performed using the R package "mediation" [31], and we report the average direct effects and average causal mediation effect estimated using nonparametric bootstrapping (5000 bootstrap resamples, $P < .05$) for both models.

3. Results

3.1. Between-group differences

Demographic data, neuropsychological performance, and sleep parameters for each subgroup, as well as between-group differences, are reported in Table 1. The two groups did not differ for age, gender, years of education, body mass index, state-trait anxiety, and sleep parameters. As expected, patients with SCD/MCI presented lower global cognitive functioning (Mini-Mental State Examination

Table 1
Participants characteristics

Variables	Cognitively unimpaired elderly subjects (n = 30)	SCD/MCI patients (n = 36)*	Group comparison†
Demographics			
Age (years ± SD)	73.3 ± 7	71.5 ± 8.2	NS
Gender (% women)	56.7%	38.9%	NS
Education (years ± SD)	12.1 ± 3.5	11.8 ± 3.2	NS
Body mass index (mean ± SD)	24.5 ± 3	24.6 ± 4.5	NS
Florbetapir SUVr (% positive)‡	1 ± 0.2 (30.8 %)	1.2 ± 0.3 (50 %)	$P = .011$
MADRS (mean ± SD)	1 ± 1.9	3.4 ± 3.7	$P = .002$
STAI-B (mean ± SD)	37.4 ± 10	38.8 ± 8.2	NS
Participants on sleep medication (number, (%))§	1 (3.3%)	3 (8.3%)	NS
Cognition			
MMSE (mean ± SD)	28.6 ± 1.2	27.6 ± 2.4	$P = .046$
Mattis total score (mean ± SD)	140.2 ± 3.3	136.2 ± 6.9	$P = .005$
Episodic memory composite score (mean ± SD)	0.0 ± 0.7	−0.8 ± 1.3	$P = .005$
Executive functioning composite score (mean ± SD)	0.0 ± 0.7	−0.8 ± 1.7	$P = .020$
Sleep parameters			
SF intensity (mean ± SD)	30.3 ± 14.7	28 ± 11.1	NS
SF variability (mean ± SD)	10.9 ± 4.7	11.5 ± 5.2	NS

Abbreviations: MADRS, Montgomery and Asberg Depression Rating Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NS, nonsignificant; SCD, subjective cognitive decline; SD, standard deviation; SF, sleep fragmentation; STAI-B, State-Trait Anxiety Inventory form B; SUVr, standard uptake value ratio.

*Owing to missing data in some patients, n = 30 for episodic memory, n = 33 for the MADRS, n = 34 for executive functioning.

†Between-groups differences were assessed using Student's t-tests for all variables, except for gender for which chi-square statistics were used. Statistical significance was set to $P < .05$.

‡n = 26 healthy elderly and 34 patients with valid florbetapir-PET scan. Amyloid positivity was defined as >0.985, based on mean SUVr + 2 SDs in a group of 41 healthy young individuals (aged <40 years).

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

score: t = 2.03, P = .046; Mattis Dementia Rating Scale: t = 2.88, P = .005), episodic memory (t = 2.92, P = .005), and executive performance (t = 2.39, P = .020). They also presented higher depressive symptoms (Montgomery and Asberg depression rating scale: t = −3.27, P = .002). Moreover, patients with SCD/MCI presented significant brain changes compared with cognitively unimpaired elderly subjects including (i) atrophy within the parahippocampal and hippocampal region, (ii) hypometabolism in the precuneus and posterior cingulate cortex, and (iii) widespread amyloid deposition mainly in frontal regions (Supplementary Fig. 1). Consistently, the global cortical amyloid standard uptake value ratio was significantly higher in patients with SCD/MCI compared with cognitively unimpaired elderly subjects (t = −2.61, P = .011).

3.2. Relationships between SF and neuroimaging

Results of significant voxelwise regression analyses are presented in Fig. 2, and detailed peak statistics and coordinates of significant clusters are reported in Supplementary Table 2.

3.2.1. Cognitively unimpaired elderly subjects

SF intensity negatively correlated to brain glucose metabolism in the ventromedial prefrontal cortex, hippocampus and parahippocampus, bilaterally. No significant association was found with gray matter volume or amyloid burden.

SF variability negatively correlated to gray matter volume within the thalamus. Moreover, we observed a trend toward a positive correlation with amyloid burden in the left rectus gyrus. When sleep medication was added as a covariate in the model, both associations became trends (Supplementary Table 3). No association was found between SF variability and brain glucose metabolism.

3.2.2. Patients with SCD/MCI

SF intensity negatively correlated with brain glucose metabolism in the left insula, whereas no significant association was found with gray matter volume or amyloid burden. SF variability was not associated with any neuroimaging modality.

3.3. Relationships between SF and cognition

In cognitively unimpaired elderly subjects, SF intensity was significantly associated to worse performance in executive functioning (Fig. 3A; r = −0.47, P = .01) and episodic memory (Fig. 3B; r = −0.40, P = .03), although this latter did not survive the Bonferroni correction for multiple comparisons. By contrast, SF variability was not related to any cognitive score in this group.

We did not find any significant association between SF parameters and cognitive performance in patients with SCD/MCI (see Supplementary Table 4 for detailed results).

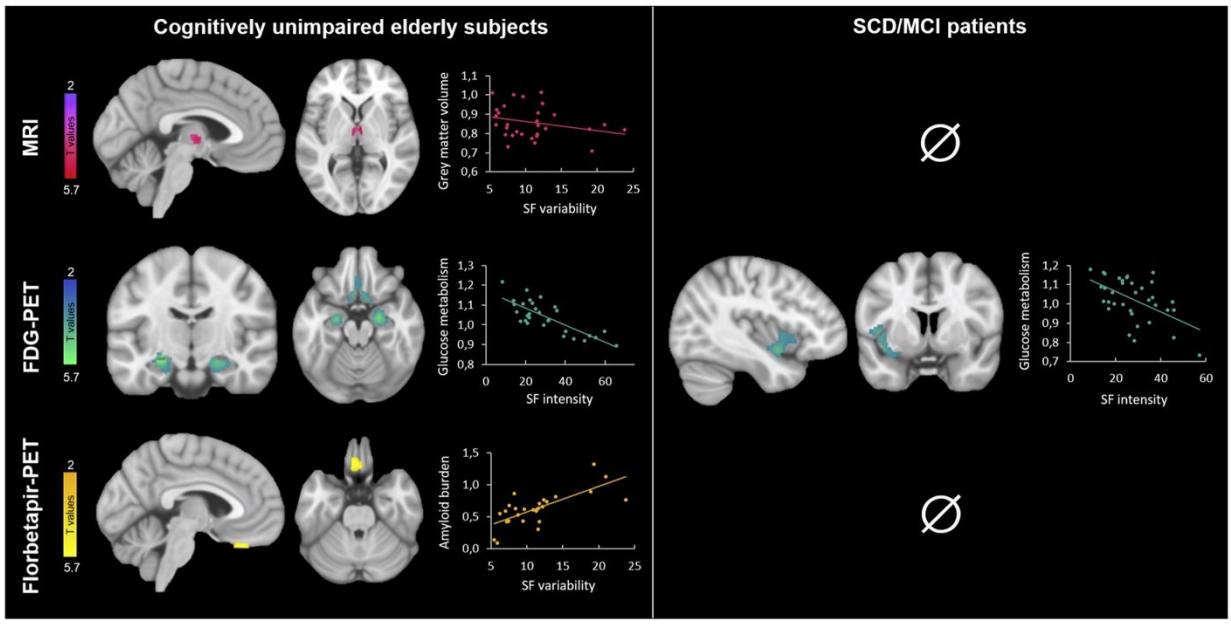

Fig. 2. Neuroimaging correlates of SF. Results of the voxelwise regression analyses between SF parameters and neuroimaging data in cognitively unimpaired elderly participants (left part) and patients with SCD/MCI (right part). Results are presented at $P < .001$ (uncorrected) and adjusted for age, gender, BMI, and the complementary SF parameter (i.e., SF variability when SF intensity was considered, and conversely). Abbreviations: BMI, body mass index; FDG: ^{18}F-fluorodeoxyglucose; MCI, mild cognitive impairment; SCD, subjective cognitive decline; SF, sleep fragmentation.

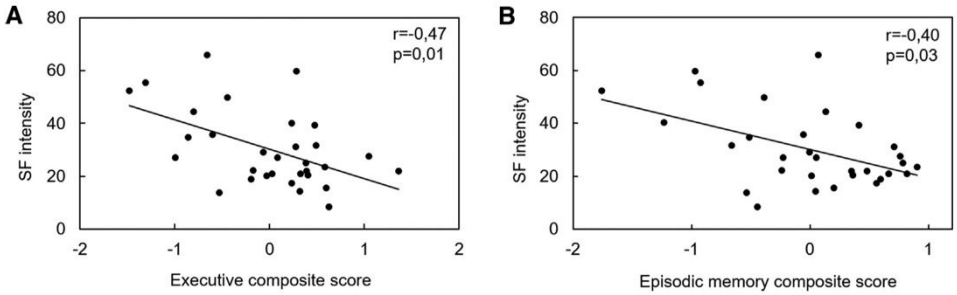

Fig. 3. Significant associations between SF intensity and cognitive performance in cognitively unimpaired elderly subjects. Scatterplots illustrating the associations between SF intensity and (A) executive performance, and (B) episodic memory performance. Partial correlation coefficients and *P*-values adjusted for age and gender are indicated on corresponding graphs. Results were considered significant after applying a Bonferroni correction for multiple testing (alpha = .05/4 = .01). Abbreviation: SF, sleep fragmentation.

3.4. Mediation analyses in cognitively unimpaired elderly subjects

As SF intensity was significantly associated to both executive performance and hippocampal and prefrontal glucose metabolism, these three variables were entered in causal mediation analyses. The results of the two models tested in cognitively unimpaired elderly subjects are summarized in Fig. 4. They showed that SF significantly mediated the relationship between total brain glucose metabolism and executive performance ($P = .02$; Table 2). No other mediation analysis was conducted, as no other sleep variable was significantly associated to both a brain and a cognitive variable.

4. Discussion

The present study aimed at investigating and comparing the brain and cognitive correlates of SF in healthy aging versus in a group of patients with SCD/MCI. In cognitively unimpaired elderly participants, SF intensity was related to frontal and medial temporal metabolism, and to cognitive performance, especially executive functioning. Moreover, SF variability was related to thalamic atrophy and, to a lesser extent, to frontal amyloid deposition. By contrast, in patients with SCD/MCI, we only report a significant association between SF intensity and glucose metabolism in the left insula, whereas no relationship between sleep and cognition was found.

The brain regions found to be associated with the fragmentation of the first hours of sleep include frontal and medial temporal areas, as well as the thalamus in cognitively unimpaired elderly participants, and the insula in patients. These regions are known to be closely involved in sleep physiology. They are largely involved in the generation of NREM-sleep oscillations, such as sleep spindles [32] and slow waves [33,34], that are notably critical for sleep-dependent memory processes [35,36]. Besides, these regions are also known to be particularly sensitive to aging and affected in the early stages of AD. Indeed, on the one hand, the medial prefrontal cortex is one of the first brain regions exhibiting amyloid deposition [37], and is also sensitive to glucose metabolism changes in aging and AD [38–40]. On the other hand, the medial temporal lobe is early affected by tau pathology [41], with atrophy already detectable in the preclinical and prodromal stages [42,43]. The involvement of this common set of brain regions in both sleep physiology and AD pathophysiology might at least partly underlie the (possibly bidirectional) links between sleep problems and AD.

As a first step toward characterizing the directionality of these associations, we performed causal mediation analyses. We showed that the intensity of the fragmentation of the first hours of sleep mediated the relationship between frontohippocampal hypometabolism and lower executive performance. This suggests that sleep disruption resulting from frontohippocampal hypometabolism may directly contribute to cognitive deficits in cognitively unimpaired elderly subjects. Therefore,

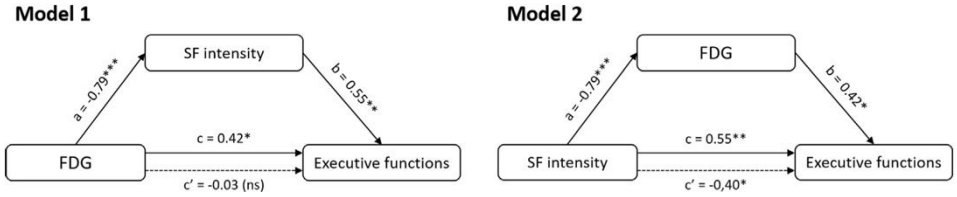

Fig. 4. Causal mediation analyses performed in cognitively unimpaired elderly subjects. Direct effects in filled arrows (simple regressions between variables) are expressed as standardized regression coefficients, and indirect effects in dotted arrows (multiple regressions in which the predictor and the mediator are both added in the model) as partial correlation coefficients. $*P < .05$, $**P < .01$, $***P < .001$. Abbreviations: FDG, ^{18}F-fluorodeoxyglucose; NS, nonsignificant; SF, sleep fragmentation.

Table 2
Detailed statistics of causal mediation analyses in cognitively unimpaired elderly subjects

	ADE			ACME		
Model	Estimate	$CI_{95\%}$	*P*-value	Estimate	$CI_{95\%}$	*P*-value
Model 1	−0.344	[−5.396; 3.526]	.85	4.051	[0.657; 8.723]	.02
Model 2	−0.028	[−0.059; −0.005]	.02	0.002	[−0.016; 0.024]	.87

Abbreviations: ADE, average direct effect; ACME, average causal mediation effect; CI, confidence interval.
In both models, executive functions were entered as the dependent variable. In model 1, brain glucose metabolism was the independent variable and SF intensity the mediator, whereas in model 2, SF intensity was the independent variable and brain glucose metabolism the mediator.

treating sleep disturbances in cognitively unimpaired elderly subjects exhibiting a high level of SF could improve their ability to cope with brain changes and potentially reduce their risk of cognitive decline. Nevertheless, owing to a limited statistical power, mediation analyses were restricted to a single set of variables (i.e., sleep fragmentation, brain glucose metabolism in frontohippocampal areas, and executive functioning), as they were the only ones for which the same sleep parameter was related to both a brain and a cognitive variable. Thus, these analyses are likely to picture only part of the potential associations existing between sleep, brain, and cognitive integrity. They do not preclude that some sleep changes could induce brain alterations that may, in turn, underlie cognitive deficits [44]. Moreover, it is also likely that some brain changes are directly underlying cognitive deficits, independently from sleep disturbances.

Besides the associations between metabolic changes and SF intensity, our results reveal that a higher night-to-night variability of SF was rather associated to structural and molecular brain alterations, namely gray matter atrophy and amyloid deposition. Of note, these results should be taken cautiously as they were only trends when taking into account regular use of sleep medication. This suggests that experiencing inconsistent sleep quality over time might be associated with brain changes that might be less reversible, that is, more durable and that might conduct to long-term cognitive deficits and dementia. This interpretation is in line with existing data showing that a greater variability in sleep quality is related to a higher risk of cognitive impairment and dementia [4,45], as well as other physical and mental health conditions [46,47]. Further investigations need to be conducted to unravel the determinants of this aspect of sleep, such as the use of sleep medication, lifestyle, or psychoaffective factors that might vary from one day to another and induce changes in sleep quality. Addressing this question is essential to be able to take over sleep problems in their entirety in the elderly population.

By contrast to our results in cognitively unimpaired individuals, the relationships between sleep and brain or cognitive variables were almost nonexistent in patients with SCD/MCI—only a link between SF intensity and insula glucose metabolism was found. We hypothesize that while cognitive performances are directly impacted by sleep quality (as probably other lifestyle factors) in asymptomatic individuals, they may be mainly and more directly driven by underlying neuropathological processes (such as amyloid deposition) at a cognitively impaired (SCD/MCI) stage, so that the direct influence of sleep disruption would no longer be detectable. This observation is supported by previous works showing no association between slow-wave sleep fragmentation nor the amount of REM sleep and cognitive performance in patients with MCI [48,49]. Taken together, these results suggest that preserving sleep quality could help to cope with brain alterations and maintain cognitive performance in the normal range, but such interventions may be less efficient once patients experience measurable cognitive deficits.

The present study has some strengths, including an objective sleep assessment over several consecutive nights combined to multimodal neuroimaging data, allowing us to assess for the first time the relationships between sleep fragmentation intensity versus variability on structural, metabolic, and molecular brain alterations in the same sample. Moreover, these associations were evaluated both in cognitively impaired and unimpaired elderly subjects, thus helping to give a more comprehensive picture of their role at different cognitive stages. However, some limitations must be mentioned. First, our study is limited by the small sample size and the cross-sectional nature of the analyses. Further analyses should be conducted using a longitudinal design, together with larger sample sizes to complement our mediation analyses and assess the nature and directionality of the relationships between sleep and brain and cognitive integrity more exhaustively. Second, we were not able to characterize the origin of sleep fragmentation (e.g., obstructive sleep apnea, periodic limb movements, or restless legs syndrome), as participants did not undergo polysomnography recordings. Further studies should aim at determining the relative contribution of the multiple factors that can cause sleep fragmentation, such as sleep disorders or lifestyle risk factors. In addition, polysomnography will also be necessary to specifically assess changes in NREM-sleep oscillations, and to test the potential impact of other sleep alterations such as REM-sleep disruption [50].

Our interpretation of the data is that the fragmentation of the first hours of sleep is associated with an alteration of brain regions typically affected in aging and AD, and may directly contribute to lower cognitive performance. However, in patients with SCD/MCI, sleep disruption may no longer contribute to the expression of cognitive deficits. Therefore, preserving sleep quality in cognitively unimpaired elderly subjects may help to cope with brain changes and maintain cognitive functioning.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dadm.2018.12.009.

RESEARCH IN CONTEXT

1. Systematic Review: In the existing literature, sleep disturbances are increasingly recognized as a risk factor for Alzheimer's disease. However, no previous study has assessed the associations between sleep disruption, brain and cognitive integrity across different cognitive stages.
2. Interpretation: We showed that the disruption of the first hours of sleep is related to the alteration of brain regions typically affected in aging and Alzheimer's disease, and may directly contribute to lower cognitive performance in cognitively unimpaired elderly participants. However, this is no longer the case in patients with subjective cognitive decline and/or mild cognitive impairment.
3. Future Direction: These findings have important clinical implications, as they suggest that treating sleep disturbances before the onset of cognitive deficits may help to cope with brain changes and maintain cognitive performance. Further studies need to be conducted on larger samples and using polysomnography to assess changes in sleep architecture and microstructure more specifically.

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Supplementary Material

Supplementary methods

Neuropsychological scores

Neuroimaging data acquisition and pre-processing

Supplementary Figures

Supplementary Figure 1: Patterns of atrophy, hypometabolism and amyloid de position in SCD/MCI patients compared to cognitively unimpaired elderly subjects.

Supplementary Tables

Supplementary Table 1: Determination of minimal cluster sizes for neuroimaging analyses.

Supplementary Table 2: Result of voxel-wise multiple regressions between SF parameters and neuroimaging data with 4 covariates.

Supplementary Table 3: Result of voxel-wise multiple regressions between SF parameters and neuroimaging data with 5 covariates.

Supplementary Table 4: Relationships between SF parameters and neuropsychological scores in cognitively unimpaired elderly subjects and SCD/MCI patients.

Neuropsychological scores

To obtain more robust proxies of cognitive abilities and minimize the issue of multiple statistical testing, composite cognitive scores were used instead of multiple (sub)tests, as described in (Mander et al., 2013, 2015; Molano et al., 2017; Wilckens et al., 2018). For that purpose, performance from different tasks that showed neither ceiling nor floor effects were z-transformed and averaged as follows:

- **Executive functions**
  - TMT test (time difference between TMT part B and part A)*
  - Stroop test (time difference between the interference and color cards)*
  - Verbal fluency (number of words beginning with ‘‘p’’ in 2 min)
- **Episodic memory**
  - 3 consecutive free recalls + delayed free recall from the Free and Cued Selective Reminding Test
  - Free recall of the BEM (*Batterie d’Efficience Mnésique*) figure
  - 2 free recalls from the *Encoding Storage Retrieval* (ESR) paradigm (two 16-word lists, one being encoded incidentally and superficially, the other after deep and intentional encoding)
  - 2 free recalls from a visual version of the ESR paradigm (based on two lists of nonfigurative graphical signs)

* note that before averaging, Z-scores derived from reaction times were reversed so that increasing values always indicated better performances.

Neuroimaging data acquisition and pre-processing

1.1.1. MRI data acquisition and pre-processing

A high-resolution T1-weighted anatomical image was acquired on a 3T Philips Achieva MRI 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 = 256×256 mm²; in-plane resolution = 1×1 mm²). The T1-weighted images were iteratively segmented, spatially normalized to the Montreal Neurological Institute (MNI) space, modulated to correct for non-linear warping effects, and smoothed with a 8-mm full width at half maximum (FWHM) Gaussian kernel using the voxel-based morphometry toolbox (VBM12) implemented in SPM12 software (Statistical Parametric Mapping, www.fil.ion.ucl.ac.uk/spm). Images were then masked to exclude non-grey matter voxels from the analyses.

1.1.2. PET data acquisition and pre-processing

FDG- and Florbetapir-PET scans were acquired in two separate sessions, with a Discovery RX VCT 64 PET-CT scanner (General Electric Healthcare) with a resolution of 3.76 x 3.76 x 4.9 mm (field of view = 157 mm). Forty-seven planes were obtained with a voxel size of 1.95 x 1.95 x 3.2 mm. A transmission scan was performed for attenuation correction before the PET acquisition. For FDG-PET, participants were fasted for at least 6 hours before scanning. After a 30-min resting period in a quiet and dark environment, ≈180 MBq of FDG were intravenously injected as a bolus. A 10-min PET acquisition scan began 50 minutes after injection. For Florbetapir-PET, each participant underwent a 20-min PET scan, beginning 50 min after intravenous injection of ≈ 4 MBq/kg of Florbetapir. FDG- and Florbetapir-PET data were first corrected for partial volume effects (PMOD Technologies Ltd, Adliswil, Switzerland), coregistered onto their corresponding MRI, and then spatially normalized using the deformation parameters derived from the MRI

procedure. The resulting images then underwent quantitative scaling, using cerebellar grey matter as a reference. Finally, both FDG-PET and Florbetapir-PET resulting images were smoothed using a 10-mm FWHM Gaussian kernel and masked to exclude non-grey matter voxels from the voxelwise analyses. PVE-corrected normalized and scaled Florbetapir-PET images were also used to extract the individual global cortical amyloid standard uptake value ratio (SUVr) using a predetermined neocortical mask including the entire grey matter, except the cerebellum, occipital and sensory motor cortices, hippocampi, amygdala and basal nuclei (Perrotin et al., 2017).

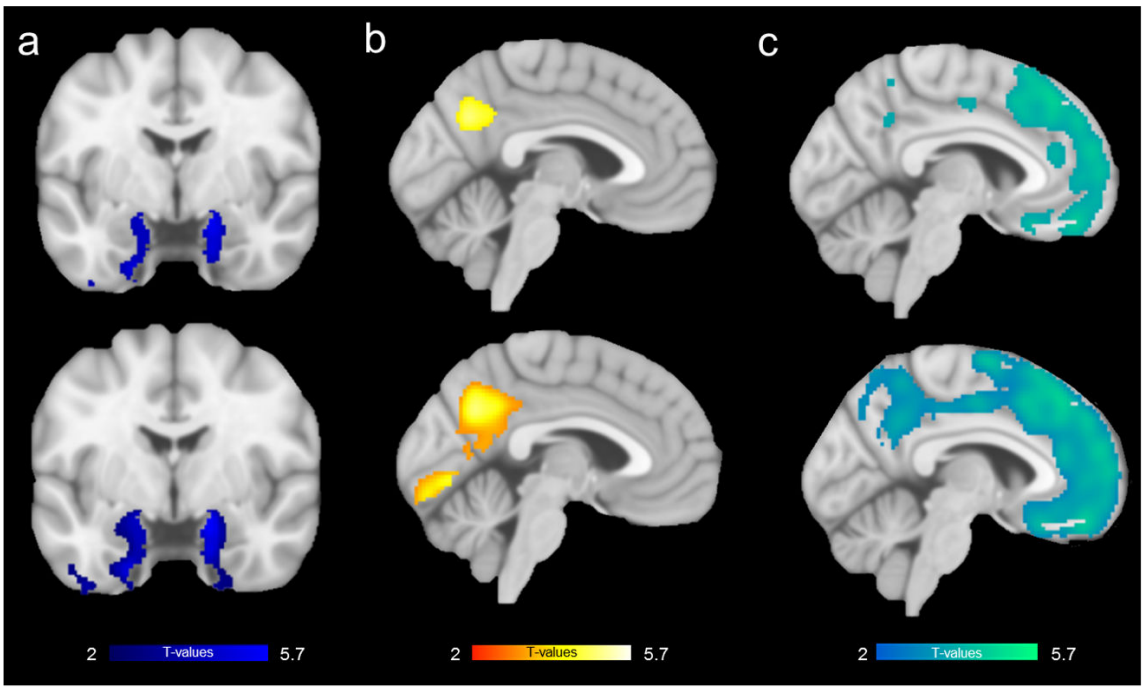
Supplementary Table 1: Determination of minimal cluster sizes for neuroimaging analyses.

Statistical design	Minimal cluster sizes (k voxels)		
	MRI	**FDG-PET**	**Florbetapir-PET**
Group comparisons	141	145	132
Multiple regressions in cognitively unimpaired elderly subjects	127	124	118
Multiple regressions in SCD/MCI patients	130	111	145

Abbreviations: FDG, ^{18}F-fluorodeoxyglucose; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography; SCD, subjective cognitive decline.

Minimal cluster sizes (k) were determined for each statistical design at the P<.001 (uncorrected) level by Monte-Carlo simulation using the Alphasim program, in order to achieve a corrected statistical significance of P<.05.

<u>Supplementary Figure 1:</u> Patterns of atrophy, hypometabolism and amyloid deposition in SCD/MCI patients compared to cognitively unimpaired elderly subjects.



<u>Abbreviations</u>: BMI, body mass index; MCI, mild cognitive impairment; SCD, subjective cognitive decline.

Results of the two-sample t-tests exhibiting patterns of **(a)** atrophy, **(b)** hypometabolism, and **(c)** amyloid deposition, in SCD/MCI patients compared to healthy elderly subjects. Results are presented at the P<.001 uncorrected level in the top line, and the P<.005 uncorrected level in the bottom line, and were adjusted for age, gender and BMI.

Supplementary Table 2: Result of voxel-wise multiple regressions between SF parameters and neuroimaging data with 4 covariates.

Brain areas	Cluster extent		MNI coordinates (mm)			T-value
	Voxels	mm^3	x	y	z	
Cognitively Unimpaired Elderly Subjects						
SF intensity and FDG-PET (n=30)						
R caudate, R hippocampus, R parahippocampal gyrus, B rectus gyri, B anterior cingulate gyri, B frontal medial orbital gyri	789	6 312	8	6	-6	5.73
L hippocampus, L amygdala	247	1 976	-24	-14	-16	5.40
SF variability and MRI (n=30)						
B thalamus	149	503	4	-8	0	5.22
SF variability and Florbetapir-PET (n=26)						
L rectus gyrus	80	640	-6	32	-28	4.57
SCD/MCI Patients						
SF intensity and FDG-PET (n=35)						
L insula	301	2 408	-38	0	-12	4.48

Abbreviations: B, bilateral; BMI, body mass index; FDG, ^{18}F-fluorodeoxyglucose; L, left; MCI, mild cognitive impairment; R, right; SCD, subjective cognitive decline; SF, sleep fragmentation. Voxel-wise multiple regressions were corrected for age, gender, BMI and the complementary SF parameter. Brain regions listed were significant at P<.001 (uncorrected). MNI coordinates are given for the main peak of each significant cluster. In cluster labelling, the first listed region corresponds to the label of the peak voxels, and the following regions are other regions included in the cluster.

Supplementary Table 3: Result of voxel-wise multiple regressions between SF parameters and neuroimaging data with 5 covariates.

Brain areas	Cluster extent		MNI coordinates (mm)			T-value
	Voxels	mm^3	x	y	z	
Cognitively Unimpaired Elderly Subjects						
SF intensity and FDG-PET (n=30)						
R caudate, R hippocampus, R parahippocampal gyrus, B rectus gyri, B anterior cingulate gyri, B frontal medial orbital gyri	901	7 208	8	6	-6	5.89
L hippocampus, L amygdala	248	1 984	-24	-14	-16	5.30
SF variability and MRI (n=30)						
B thalamus	95	321	4	-8	0	4.23
SF variability and Florbetapir-PET (n=26)						
L rectus gyrus	32	256	-6	32	-28	3.94
SCD/MCI Patients						
SF intensity and FDG-PET (n=35)						
L fusiform gyrus, parahippocampus, hippocampus	111	888	-22	-30	-20	4.82
L insula	411	3 288	-38	0	-12	4.62

Abbreviations: B, bilateral; BMI, body mass index; FDG, ^{18}F-fluorodeoxyglucose; L, left; MCI, mild cognitive impairment; R, right; SCD, subjective cognitive decline; SF, sleep fragmentation. Voxel-wise multiple regressions were corrected for age, gender, BMI, the complementary SF parameter and regular us of sleep medication. Brain regions listed were significant at P<.001 (uncorrected). MNI coordinates are given for the main peak of each significant cluster. In cluster labelling, the first listed region corresponds to the label of the peak voxels, and the following regions are other regions included in the cluster.

Supplementary Table 4: Relationships between SF parameters and neuropsychological scores in cognitively unimpaired elderly subjects and SCD/MCI patients.

Cognitive score	Cognitively unimpaired elderly subjects (n=30)		SCD/MCI patients (n=36)*	
	SF intensity	SF variability	SF intensity	SF variability
Episodic memory composite score	r=-0.40 P=.03	r=-0.11 P=.56	r=-0.04 P=.85	r=0.08 P=.67
Executive functioning composite score	**r=-0.48** **P=.01**	r=-0.11 P=.57	r=0.15 P=.46	r=0.144 P=.47

Abbreviations: MCI, mild cognitive impairment; MMSE, mini-mental state examination; SCD, subjective cognitive decline; SF, sleep fragmentation.

R-values correspond to partial correlation coefficients, controlling for age and gender. Results in bold are still significant after applying a Bonferroni correction for multiple testing within each group (alpha = .05/4 = .01).

* Due to missing data, n=33 for the Mattis total score, n=34 for the executive functioning composite score, n=30 for the episodic memory composite score.

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3.4. ÉTUDE 2 : ANALYSE SPECTRALE DU SOMMEIL LENT ET PARADOXAL

Si les résultats de la première étude de cette thèse confirment que l'altération des premiers cycles de sommeil est associée à l'intégrité de régions cérébrales impliquées dans les rythmes oscillatoires du sommeil lent chez les sujets âgés cognitivement sains, des mesures plus fines sont nécessaires afin de préciser leur implication. Ainsi, dans la continuité de la première étude, nous avons donc cherché à mesurer par PSG la puissance spectrale des différents rythmes oscillatoires au cours du sommeil lent (SL), mais aussi en sommeil paradoxal (SP), dont les études récentes montrent qu'il serait prédictif du déclin cognitif (Pase et al., 2017; Song et al., 2015). L'objectif de cette étude a donc été d'explorer les liens entre les altérations des rythmes du SL et du SP, et l'intégrité cérébrale structurale, fonctionnelle et moléculaire, chez les sujets âgés cognitivement sains.

Cette étude a été réalisée auprès de 125 sujets âgés cognitivement sains inclus dans l'étude Age-Well, ayant bénéficié d'une évaluation neuropsychologique, d'une IRM structurale, d'un examen de TEP couplée au ^{18}F-florbetapir (avec une acquisition précoce reflétant la perfusion cérébrale et une acquisition tardive reflétant la charge amyloïde cérébrale), et d'un examen de PSG. Les données issues des analyses spectrales ont été obtenues grâce à l'algorithme automatique ASEEGA®, et nous nous sommes intéressés aux valeurs normalisées de puissance spectrale dans les bandes de fréquence delta (0.1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz) et beta (16-50 Hz), en SL et en SP. Des analyses de régression multiple « *voxel-wise* » ont été réalisées entre les valeurs issues des analyses spectrales et les données de neuroimagerie (i.e., volume, perfusion et charge amyloïde

cérébrales), en contrôlant pour l'âge, le sexe, le niveau d'éducation, l'index d'apnées-hypopnées, la prise de médicaments pouvant interférer avec la qualité du sommeil, et le statut APOE4.

Les résultats principaux montrent qu'une diminution de la puissance spectrale du rythme delta en SL est associée à une diminution du volume et de la perfusion dans les aires fronto-cingulaires, sans lien avec la charge amyloïde. En parallèle, la diminution de la puissance spectrale du rythme theta en SP est associée à une diminution de volume de substance grise dans les régions frontales, temporales, occipitales et l'insula, ansi qu'à une augmentation de la perfusion cérébrale dans les aires fronto-pariétales, et une augmentation de la charge amyloïde néocorticale, notamment dans les aires fronto-cingulaires et temporo-pariétales.

Ainsi, nos résultats montrent que l'altération des rythmes du SL et du SP est associée à des modifications structurales et fonctionnelles dans des régions sensibles au vieillissement et à la MA, incluant notamment les aires préfrontales, le cortex cingulaire antérieur et postérieur, et le précunéus. De plus, si nos résultats ne mettent pas en évidence d'association significative entre le sommeil lent et la charge amyloïde, ils révèlent en revanche pour la première fois que les modifications de la microstructure du SP sont associées à une charge amyloïde néocorticale plus importante. Ainsi, les modifications du SP pourraient être un marqueur précoce de l'appartenance au continuum Alzheimer.

L'article correspondant à cette étude est actuellement en préparation.

Multimodal neuroimaging correlates of NREM and REM sleep EEG spectral power in ageing.

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Abstract:

Sleep changes are a major feature of the ageing process, and are increasingly recognized as a risk factor for cognitive decline. However, little is known about the brain mechanisms underlying the associations between sleep changes and cognitive decline, and recent research has essentially focused on slow wave sleep alterations. Our objective was to provide an overview of the relationships between changes in quantitative EEG of non-rapid eye movement (NREM) and rapid eye movement (REM) sleep, and gray matter (GM) volume, perfusion, and amyloid burden in ageing. We included 125 cognitively unimpaired older adults, from the Age-Well randomized controlled trial. All participants underwent a detailed neuropsychological assessment, an ambulatory polysomnography recording, and MRI and Florbetapir-PET scans at the Cyceron Center (Caen, France). Normalized EEG spectral power values were obtained using the ASEEGA® algorithm, for delta (0.1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz) and beta (16-50 Hz) frequency bands. Voxel-wise multiple regression analyses were conducted between sleep EEG spectral power values and neuroimaging data (i.e., GM volume, perfusion and amyloid burden), separately for NREM and REM sleep, controlling for age, gender, education, the apnea-hypopnea index, sleep medication use, and the Apolipoprotein E ε4 status. We show that lower NREM sleep delta power was related to decreased GM volume and perfusion in fronto-cingulate areas. Besides, decreased REM sleep theta power was associated with lower GM volume in frontal, temporal, occipital and insular cortices, increased perfusion in frontal and parietal regions, and increased amyloid burden in frontal, cingulate, parietal and temporal areas. Thus, our results show that both NREM and REM sleep alterations are associated with structural and functional changes in regions known to be sensitive to ageing and Alzheimer's disease (AD). Importantly, REM sleep changes were

associated with greater neocortical amyloid burden, such that older individuals exhibiting REM sleep alterations may be more at risk of belonging to the Alzheimer's continuum.

1. Introduction

Sleep quality undergoes substantial changes with aging (Mander *et al.*, 2017). Indeed, sleep becomes lighter and more fragmented with age, with a marked alteration of slow wave sleep (SWS), contrasting with a relative preservation of rapid-eye movement (REM) sleep (Carrier *et al.*, 2001; Ohayon *et al.*, 2004; Petit *et al.*, 2004). Regarding sleep microstructure, the ageing process is accompanied by a decrease in delta, theta and sigma rhythm both during non-rapid eye movement (NREM) and REM sleep (Dijk *et al.*, 1989; Landolt *et al.*, 1996; Carrier *et al.*, 2001; Landolt and Borbély, 2001; Martin *et al.*, 2013; Varga *et al.*, 2016). In patients with an Alzheimer's clinical syndrome of dementia, NREM-sleep alterations are an exaggeration of what is observed in normal aging (Petit *et al.*, 2004). Moreover, they show a significant reduction of the proportion of REM sleep, with a global slowing of REM sleep rhythms (Petit *et al.*, 1993; Hassainia *et al.*, 1997; Petit *et al.*, 2004). Interestingly, the reduction of REM sleep seems to be associated with cognitive decline and a higher risk of converting to Alzheimer's clinical syndrome of MCI or dementia (Song *et al.*, 2015; Pase *et al.*, 2017). Results are less consistent when considering the few studies that have explored age-related changes in sleep microstructure, as both increases (Djonlagic *et al.*, 2019) and decreases in sleep EEG power values (Taillard *et al.*, 2019) have been related to the risk of presenting an Alzheimer's clinical syndrome of MCI or dementia. However, the brain mechanisms underlying the associations between polysomnography-measured sleep changes, cognitive decline and the risk of Alzheimer's clinical syndrome of MCI and dementia are also largely unclear. If decreased NREM slow wave activity (i.e., activity in the delta frequency range

[0.1-4 Hz]) has been associated with gray matter (GM) atrophy (Mander *et al.*, 2013; Dube *et al.*, 2015; Latreille *et al.*, 2019), hypometabolism (Wilckens *et al.*, 2016) and increased amyloid burden (Mander *et al.*, 2015) within prefrontal regions, the other frequency bands have been much less studied, especially during REM sleep (Latreille *et al.*, 2019).

Taken together, the age-related reduction of NREM sleep delta power has been reliably associated with structural, functional and molecular alterations of frontal regions (Mander *et al.*, 2013, 2015; Dube *et al.*, 2015; Latreille *et al.*, 2019), and consecutive memory impairment. However, given the ability of REM sleep alterations to predict cognitive decline, it appears necessary to deepen our understanding of the structural, functional and molecular correlates of both NREM and REM sleep oscillations. Thus, our objective was to explore the associations between GM volume, perfusion and amyloid burden and NREM and REM sleep power spectral values in a sample of cognitively unimpaired older adults.

2. Materials & Methods

2.1. Participants

One hundred and twenty-five cognitively unimpaired older participants were included in the present study **(see Figure 1 and Table 1)**. All participants were enrolled in the on-going Age-Well randomized controlled trial (RCT) of the Medit-Ageing European Project, sponsored by the French Institute of Health and Medical Research (Institut National de la Santé et de la Recherche Médicale, INSERM). Data from the baseline visit of the RCT were used in the analyses. The full protocol, including detailed inclusion and exclusion criteria, have been described in Poisnel *et al.*, 2018. Briefly, participants were all recruited from the general population, aged over 65 years old, native

French speakers, retired for at least one year, had at least 7 years of education, and performed within the normal range for age and educational levels on standardized cognitive tests of a neuropsychological diagnostic battery. Main exclusion criteria were safety concerns in relation to 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 that may interfere with cognitive functioning. At baseline, in a maximum period of 3 months, participants underwent a comprehensive neuropsychological assessment, an ambulatory polysomnography (PSG) recording, Apolipoprotein E (APOE) genotyping, structural MRI and ^{18}F-Florbetapir PET scans. Participants' characteristics are displayed in **Table 1**. All participants gave their written informed consent prior to the examinations, and the Age-Well RCT was approved by the ethics committee (CPP Nord-Ouest III, Caen; trial registration number: EudraCT: 2016-002441-36; IDRCB: 2016-A01767-44; ClinicalTrials.gov Identifier: NCT02977819).

2.2. Polysomnography recording

Participants underwent an ambulatory polysomnography (PSG) recording at home using a Siesta® device (Compumedics, Australia). Sixty-eight percent of the sample benefited from a habituation night, which was not included in the analyses (n=85 over 125). The PSG examination consisted in recording the electroencephalogram (EEG), electrooculogram (EOG), electrocardiogram (ECG), chin electromyogram (EMG), respiratory movements using thoracic and abdominal belts, respiratory airflow using nasal and oral thermistors, and oxygen saturation using a finger pulse oximeter. For the EEG recording, twenty electrodes were placed over the scalp according to the international 10-20 system (Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, T3, T4, P3, P4, Pz, O1, O2,

vertex ground, and a bi-mastoid reference), with impedances kept below 5 kΩ. The EEG signal was digitalized at a sampling rate of 256 Hz, high-pass and low-pass filters were applied, respectively at 0.3Hz, and 35Hz. Then, the recordings were visually scored in 30-second epochs according to the internationally agreed scoring rules of the American Academy of Sleep Medicine (Berry *et al.*, 2017), allowing the computation of standard sleep parameters and respiratory parameters, including the apnea-hypopnea index (AHI), corresponding to the sum of apneas and hypopneas per hour of sleep **(Table 1)**.

2.3. Spectral analyses

Quantitative EEG analyses were based on automatic scoring by the ASEEGA algorithm, after automatic artefact rejection (version 4.1.71, PHYSIP, France; see Berthomier *et al.*, 2007 for a validation of this algorithm). The mean accordance rate with visual scoring was 75,5%, with a Cohen's kappa coefficient of 0,66, corresponding to a strong agreement. Absolute EEG spectral power was calculated on artefact-free 30-s epochs on the Cz-Pz derivation, using a fast Fourier transform with Hanning window, in the following frequency bands: delta (0.1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), and beta (16-50 Hz), for all REM and NREM epochs. Additionally, we also computed absolute EEG spectral power in the delta range for N3 epochs, to measure slow wave activity more specifically. Absolute EEG spectral power values were then normalized to the global spectral power for each epoch, and log-transformed normalized EEG power values were used in the analyses.

2.4. Neuroimaging examinations

Participants underwent three neuroimaging examinations in separate sessions, at the Cyceron Center (Caen, France), on the same MRI and PET cameras (Philips Achieva 3.0T and a GE Healthcare Discovery RX VCT 64 PET-CT scanners, respectively) (see Poisnel *et al.*, 2018).

2.4.1. Structural MRI

A high-resolution T1-weighted anatomical image was acquired using a 3D fast-field echo sequence (3D-T1-FFE sagittal, repetition time =7.1 ms, echo time = 3.3 ms, flip angle = 6°, 180 slices with no gap, slice thickness = 1mm, field of view = 256x256 mm^2, in-plane resolution= 1x1x1 mm^3). During the MRI session, subjects were equipped with earplugs and their head was stabilized with foam pads in order to minimize head motion. T1-weighted images were segmented using FLAIR images (3D-IR sagittal, TR/TE/TI = 4800/272/1650 ms ; flip angle = 40°; 180 slices with no gap; slice thickness = 1 mm; field of view = 250x250 mm^2; in-plane resolution = 0.98x0.98 mm^2), spatially normalized to the Montreal Neurological Institute (MNI) template, modulated using the SPM12 segmentation procedure (http://www.fil.ion.ucl.ac.uk) and smoothed with an 8 mm full-width at half-maximum (FWHM) Gaussian filter. Images were then masked to exclude non-grey matter voxels from the analyses.

2.4.2. PET imaging

Florbetapir-PET scans were acquired in two separate sessions with a resolution of 3.76 × 3.76 × 4.9 mm^3 (field of view = 157 mm). Forty-seven planes were obtained with a voxel size of 1.95 × 1.95 × 3.27 mm^3. A transmission scan was performed for attenuation correction before the PET acquisition. Each participant underwent a 10 min PET scan beginning at the intravenous injection of ~4MBq/Kg of Florbetapir, and a 10 min PET scan beginning 50 min after the intravenous

injection. Early Florbetapir-PET, reflecting brain perfusion, was reconstructed from 1 to 6 min. Late-Florbetapir acquisition reflected brain amyloid burden.

PET images were coregistered on their corresponding anatomical MRI, voxel-wise corrected for partial volume effects using the three-compartmental voxel-wise Müller-Gärtner method, and were then normalized to the MNI template using deformation parameters derived from the anatomical MRI. Resulting images were scaled using cerebellar grey matter as a reference. A smoothing kernel of 10 mm Gaussian filter was applied and images were masked to exclude non-grey matter voxels from the analyses. PVE-corrected normalized and scaled images were also used to extract the individual global cortical amyloid standard uptake value ratio (SUVr) using a predetermined neocortical mask including the entire grey matter, except the cerebellum, occipital and sensory motor cortices, hippocampi, amygdala and basal nuclei (La Joie *et al.*, 2013).

2.5. Statistical analyses

Voxel-wise multiple regression analyses were performed using SPM12, between neuroimaging data (i.e., GM volume, perfusion and amyloid burden) and sleep EEG spectral power values (i.e., delta, theta, alpha and beta power in NREM and REM sleep), separately. In case no significant associations were found with NREM delta power values, we performed additional analyses with N3 delta power, reflecting slow wave activity more specifically. Age, gender, education, AHI, sleep medication use, and the APOE4 status were included as covariates. Results were considered significant at a $p<0,005$ (uncorrected) threshold combined with a cluster-level threshold of $p<0.05$ corrected for family-wise errors (FWE).

3. Results

3.1. Multimodal neuroimaging correlates of NREM-sleep spectral power

NREM delta power was positively associated to both GM volume and perfusion in the anterior and middle cingulate, precuneus and superior frontal areas, bilaterally (see Table 2 and Figure 2). Moreover, NREM alpha power was negatively associated with GM volume in the middle and posterior cingulate cortex, and NREM beta power negatively correlated with GM volume in the anterior cingulate cortex and medial prefrontal areas (Table 2). No significant association was observed between amyloid burden and delta spectral power during NREM or N3 sleep, nor with any other frequency band during NREM sleep.

3.2. Multimodal neuroimaging correlates of REM sleep spectral power

REM sleep theta power was positively associated with GM volume in temporal, occipital, frontal and insula regions (Table 2 and Figure 3). In addition, REM sleep theta power was negatively associated with perfusion in frontal, middle cingulate and parietal cortices, and with amyloid burden mainly in the precuneus, posterior and middle cingulate, superior frontal, and lateral temporal areas (Table 2 and Figure 3). Finally, REM sleep theta power was negatively associated with frontal, parietal, and temporal amyloid burden (Table 2 and Figure 3).

We also found that REM sleep beta power was negatively associated with perfusion within anterior and middle cingulate, and superior frontal areas (Table 2). Lastly, REM sleep delta power was positively associated with perfusion within fronto-parietal areas, including the superior, middle and

inferior frontal gyri, anterior, middle and posterior cingulate gyri, and the precuneus (Table 2 and Figure 2).

4. Discussion

The goal of the present study was to establish the brain structural, functional and molecular correlates of NREM and REM sleep EEG spectral power values. Taken together, our results mainly show that decreased NREM sleep delta power was associated with GM atrophy and hypoperfusion in fronto-cingulate areas, but not with amyloid burden. Besides, decreased REM sleep theta power was related to lower GM volume in frontal, temporal, occipital and insular cortices, increased perfusion in fronto-parietal areas and amyloid burden in fronto-cingulate, parietal and temporal regions.

One of our main observations is that reduced volume and perfusion of fronto-cingulate regions is associated with decreased EEG spectral power during NREM sleep. This result appeared to be strongly driven by decreased power in the delta band, which was related to both lower GM volume and perfusion in this area, while increased NREM alpha and beta power were only associated to reduced GM volume in the posterior and anterior parts of the cingulate cortex, respectively. Delta activity is known to originate from medial prefrontal and anterior cingulate areas (Murphy *et al.*, 2009), and to propagate along an anteroposterior axis (Massimini *et al.*, 2004). Many studies reported an age-related decrease of delta power (Carrier *et al.*, 2001; Landolt and Borbély, 2001; Latreille *et al.*, 2019; Taillard *et al.*, 2019), that is likely to be underlied by GM atrophy occurring with aging in regions implicated in slow wave generation and propagation (Mander *et al.*, 2013;

Dube *et al.*, 2015; Latreille *et al.*, 2019), including anterior cortical areas, as well as parietal, temporal and insular regions. Our results support the current knowledge about NREM sleep delta power structural correlates, and extend them to functional data, as we show that preserved brain perfusion in the same cortical areas is related to preserved NREM sleep delta power. Interestingly, in line with the results of Latreille *et al.* (2019), we show that decreased power in the delta band is associated with fronto-cingulate hypoperfusion both for NREM and REM sleep. Furthermore, the age-related decrease of delta activity has been related to impaired sleep-dependant memory consolidation (Mander *et al.*, 2013) and an increased risk of cognitive impairment (Taillard *et al.*, 2019).

Of note, although we expected NREM sleep delta power to be associated with amyloid levels, no significant association was found in our sample, even when considering specifically delta power during N3 sleep. Previous studies measuring amyloid burden using PET-imaging have revealed significant associations with self-reported sleep parameters such as sleep duration, sleep latency, or excessive daytime sleepiness (Spira *et al.*, 2013; Branger *et al.*, 2016; Brown *et al.*, 2016; Carvalho *et al.*, 2018). Importantly, self-reported sleep parameters are known to frequently differ from objective sleep measures (Van Den Berg *et al.*, 2008; Landry *et al.*, 2015; Åkerstedt *et al.*, 2016), and to be influenced by several factors, including anxiety or depressive symptoms (Baillet *et al.*, 2016). When considering objectively-measured sleep quality, associations between SWS and amyloid levels have mainly been demonstrated using CSF measures (Liguori *et al.*, 2014; Varga *et al.*, 2016; Ju *et al.*, 2017), that are much more dynamic, such that amyloid levels are more directly related to sleep quality on the night preceding the lumbar puncture. At the voxel-wise level, no previous study has found significant associations between polysomnography-measured sleep

quality and PET-measured amyloid burden, reflecting the accumulation of amyloid deposition over a long period. Only one study focused on amyloid burden in the medial prefrontal cortex using a region of interest approach, and revealed a significant negative association with slow wave activity measured in the same area (Mander *et al.*, 2015). We can hypothesize that this link is specific to prefrontal regions, as our results suggest that it is no longer evident for slow wave activity measured over central derivations.

By contrast, our results show that decreased REM sleep theta power was associated with greater neocortical amyloid deposition and brain perfusion, essentially in frontal and parietal areas, as well as lower GM volume mainly in frontal and temporal regions. REM sleep alteration is a specific feature of Alzheimer's clinical syndrome of dementia (Petit *et al.*, 1993, 2004; Hassainia *et al.*, 1997). Moreover, in older adults, a decrease in REM sleep duration is predictive of the conversion to Alzheimer's clinical syndrome of MCI and dementia (Song *et al.*, 2015; Pase *et al.*, 2017). If the mechanisms underlying this relationship between REM sleep and Alzheimer's disease are still not well understood, a previous study has shown that lower levels of Aβ42 in the CSF were associated with a decreased proportion of REM sleep, in patients with an Alzheimer's clinical syndrome of dementia (Liguori *et al.*, 2014). Our findings go further by providing evidence that cognitively unimpaired older individuals with decreased REM sleep theta power exhibit amyloid burden in AD-sensitive regions, notably the posterior cingulate and precuneus areas, and may therefore be more likely to belong to the Alzheimer's continuum. Thus, REM sleep changes could represent an early biomarker of the presence of amyloid pathology, and our results support the hypothesis that older adults exhibiting REM sleep changes could represent a sub-population particularly at risk of cognitive decline.

The present study has some strengths, including analyses performed on a large sample of cognitively normal individuals who underwent multimodal neuroimaging, with analyses controlled for multiple confounders, such as sleep apneas or the ApoE4 status. However, our study also present some limitations. Indeed, measures of sleep EEG spectral power were computed only on the Cz-Pz derivation. Especially for amyloid burden, further explorations are needed on other derivation, notably over frontal regions. Finally, studies combining both amyloid and tau-PET are needed in order to determine their specific contribution to REM sleep alterations. To conclude, we show that both NREM and REM sleep alterations are associated with structural and functional changes in regions known to be sensitive to ageing and Alzheimer's disease, including fronto-cingulate areas. Importantly, REM sleep changes were associated with greater neocortical amyloid burden, such that older individuals exhibiting REM sleep alterations may be more at risk of belonging to the Alzheimer's continuum.

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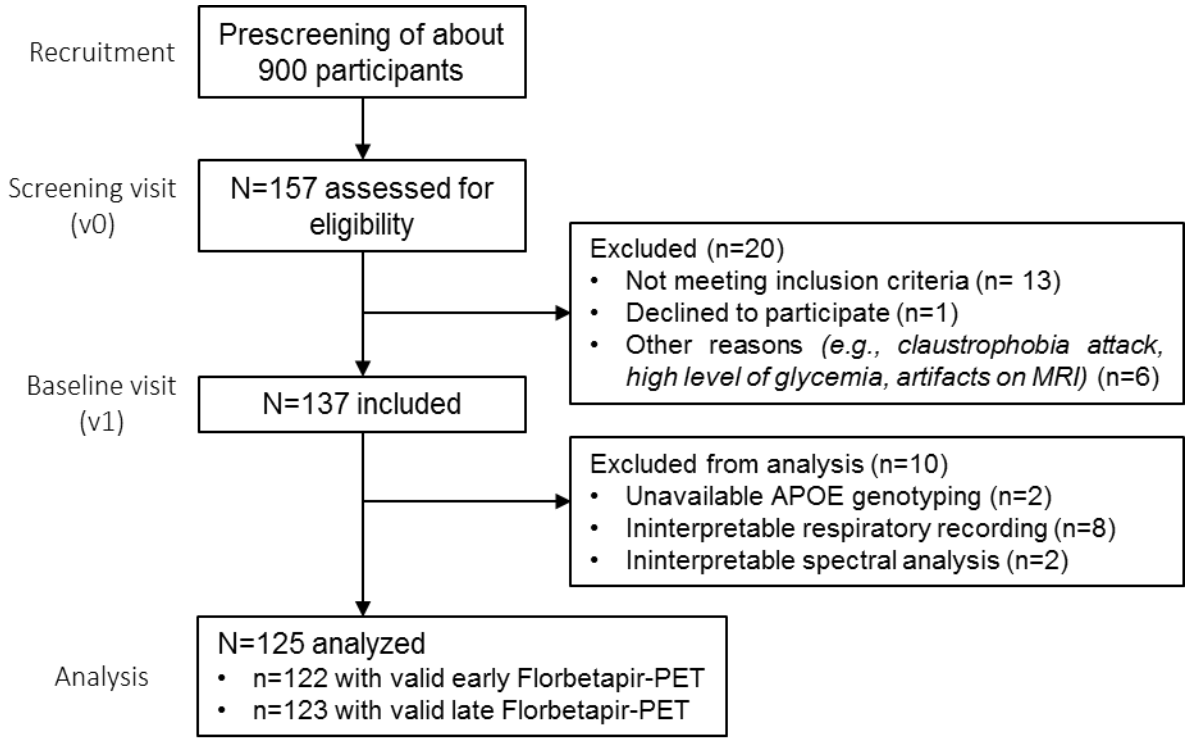
Figure 1: Flowchart of the inclusion process.



Abbreviations: APOE, Apolipoprotein E; MRI, Magnetic Resonance Imaging; PET, Positons Emission Tomography.

Table 1: Participants' characteristics.

	Mean	SD	Range
Demographics			
Age: years	69.08	3.87	64 - 83
Gender: number (%) of women	78 (62.40)	N/A	N/A
Education: years	13.06	3.09	7 - 22
MMSE	28.99	1.06	26 - 30
GDS	1.30	1.76	0 - 11
STAI-B	34.51	7.06	20 - 54
Body mass index: kg/m²	26.27	4.32	18.10 - 44.18
Current sleep medication use: number (%) [1]	11 (8.80)	N/A	N/A
Florbetapir SUVr [2]	0.97	0.21	0.72 - 1.76
Amyloid positive participants: number (%) [3]	27 (21.77)	N/A	N/A
APOE4 carriers: number (%)	35 (28.00)	N/A	N/A
Sleep			
Total Sleep Time: min	360.27	64.79	192 - 550.50
Sleep efficiency: %	77.03	9.99	49.60 - 96.60
NREM-1: min (% TST)	48.97 (13.74)	26.19 (7.33)	9 (3.5) - 142.50 (43.90)
NREM-2: min (% TST)	173.73 (48.23)	46.11 (9.05)	88 (24.40) – 313.50 (69.70)
NREM-3: min (% TST)	70.96 (19.80)	35.793 (9.70)	0 (0) – 188.50 (48.10)
REM sleep: min (% TST)	66.61 (18.23)	24.45 (5.54)	0 (0) – 120 (33.30)
Apnea-Hypopnea index: number of events/h	25.38	14.83	0.7 – 56.20

Abbreviations: APOE4, Apolipoprotein E allele ε4; GDS, Geriatric Depression Scale; min, minutes; MMSE, Mini Mental State Examination; N/A, not applicable; NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep; SD, standard deviation; STAI-B, State-Trait Inventory form B; SUVr, Standard Uptake Value ratio; TST, Total Sleep Time.

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

[2] n= 123 participants with a valid Florbetapir-PET scan.

[3] The threshold for amyloid positivity was defined as >0.99, and corresponded to the 99.9th percentile of the neocortical SUVr distribution among 45 healthy young individuals, aged <40 years.

Table 2: Results of voxel-wise multiple regressions analyses between sleep EEG power spectral values and neuroimaging data.

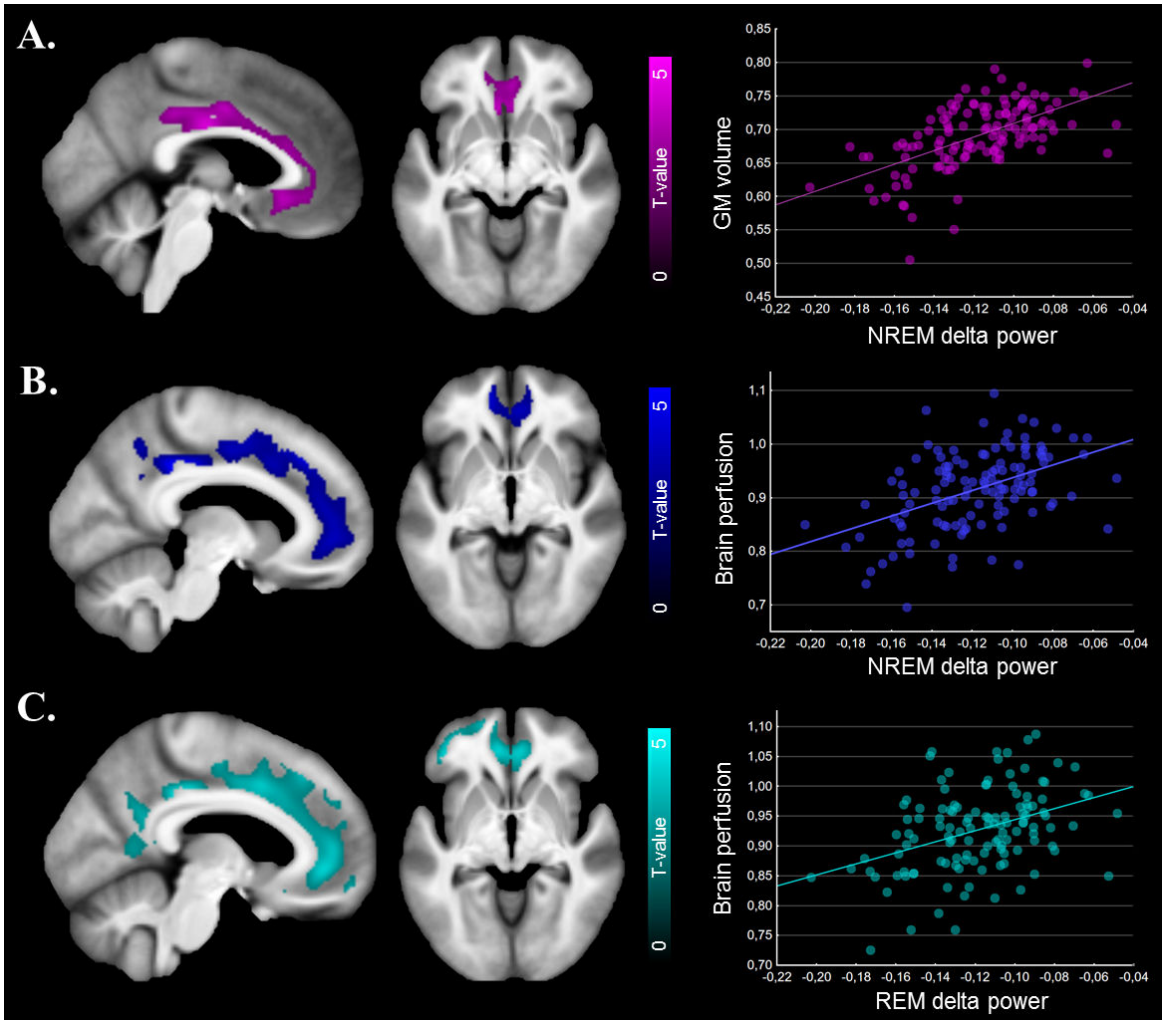
Frequency band	Correlation	Brain region	Cluster extent		MNI coordinates			T-value	$p_{FWE\text{-}corrected}$
			Nb of voxels	mm^3	x	y	z		
		GM volume							
NREM Alpha	-	B middle cingulate, R posterior cingulate	1211	4087	-8	-38	38	5.37	0.006
NREM Beta	-	B anterior cingulate, frontal medial orbital, R rectus, medial superior frontal	1518	5123	4	36	-6	4.28	0.001
NREM Delta	+	B anterior and middle cingulate, R precuneus and posterior cingulate	3830	12926	-6	-34	38	5.25	<0.001
		R middle and superior frontal	1039	3506	34	21	44	4.59	0.013
		L middle and superior frontal	897	3027	-32	44	24	4.22	0.028
REM Theta	-	L inferior temporal, middle temporal, and fusiform	1616	5454	-45	12	-42	5.26	0.001
		R middle, superior and inferior occipital, middle temporal, angular	2846	9605	50	-72	28	4.87	<0.001
		L middle and superior temporal, inferior, middle and superior occipital, and angular	3273	11046	-66	-27	2	4.66	<0.001
		L inferior, middle and superior frontal, medial orbital frontal	2667	9001	-54	33	8	4.59	<0.001
		R superior and middle temporal	1602	5407	50	15	-34	4.54	0.001
		R middle and inferior frontal	926	3125	38	45	32	4.19	0.025
		L insula	1469	4958	-36	26	-3	4.13	0.002
		Brain perfusion							
NREM Delta	+	B anterior and middle cingulate, superior frontal, precuneus.	4627	15616	-8	-38	36	4.80	<0.001
REM Beta	-	B anterior cingulate, L superior frontal	1970	6649	8	42	2	4.16	0.035
		B middle cingulate, L anterior cingulate	2685	9062	9	-21	40	3.75	0.009
REM Delta	+	L inferior, middle and superior frontal	4111	13875	-42	36	4	5.30	0.001
		B anterior, middle, posterior cingulate, precuneus, inferior rostral, L superior frontal	9047	30534	-10	51	16	4.90	<0.001
REM Theta	-	B superior frontal, L middle frontal, middle cingulate, precentral, postcentral, supramarginal, superior parietal lobule	3789	12788	-32	20	45	5.60	0.005
		Amyloid burden							
REM Theta	-	R precentral, postcentral, superior parietal lobule, cuneus, calcarine, B precuneus, posterior cingulate, middle cingulate, superior frontal.	21848	73737	54	-4	34	4.32	<0.001
		R fusiform, inferior occipital, middle temporal, superior temporal, transverse temporal.	5086	17165	34	-45	-10	4.25	0.028

Abbreviations: AHI, Apnea-Hypopnea Index; APOE4, Apolipoprotein E allele ε4; B, bilateral; FWE, family-wise error; L, left; MNI, Montreal Neurological Institute; MRI, Magnetic Resonance

Imaging; NREM, non-rapid eye movement; PET, Positons Emission Tomography; R, right; REM, rapid eye movement.

Results are presented at the $p<0.005$ (uncorrected) level combined with a FWE cluster-level correction, controlling for age, sex, education, the AHI, the APOE4 status and sleep medication use.

<u>Figure 2</u>: Structural and functional correlates of NREM and REM sleep delta spectral power in cognitively unimpaired older adults.

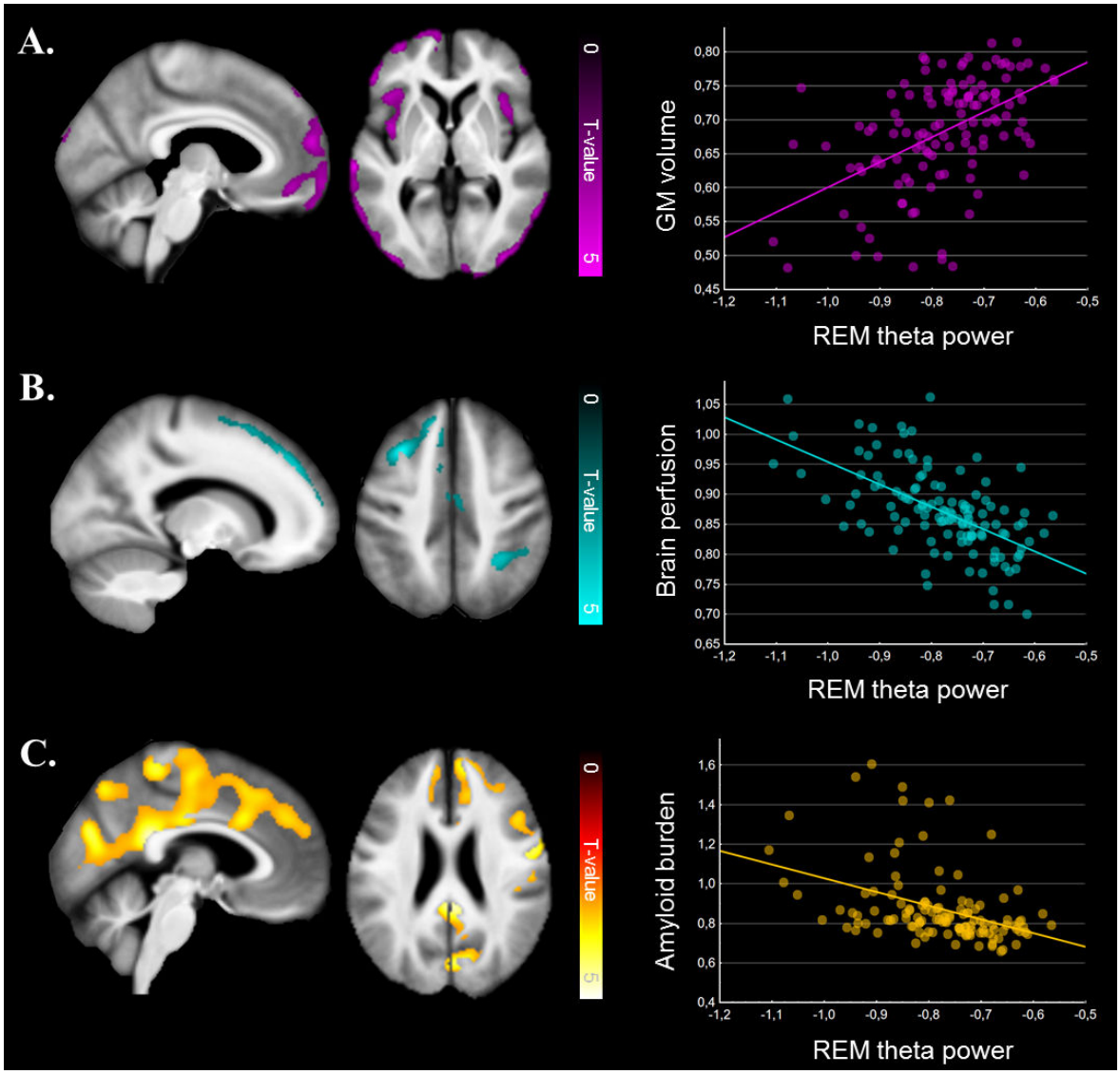


<u>Abbreviations</u>: AHI, Apnea-Hypopnea Index; APOE4, Apolipoprotein E allele ε4; FWE, family-wise error; GM, gray matter; NREM, non-rapid eye movement; REM, rapid eye movement.

Results of voxel-wise multiple regressions showing significant positive correlations between **(A)** NREM delta power and GM volume, **(B)** NREM delta power and brain perfusion, and **(C)** REM delta power and brain perfusion. Results are presented at the $p<0.005$ (uncorrected) level, combined

with a FWE cluster-level correction, controlling for age, sex, education, the AHI, the APOE4 status and sleep medication use.

<u>Figure 3</u>: Structural, functional and molecular correlates of REM sleep theta spectral power in cognitively unimpaired older adults.



<u>Abbreviations</u>: AHI, Apnea-Hypopnea Index; APOE4, Apolipoprotein E allele ε4; FWE, family-wise error; GM, gray matter; REM, rapid eye movement.

Results of voxel-wise multiple regressions showing significant associations between REM-sleep theta power and **(A)** GM volume, **(B)** brain perfusion, and **(C)** amyloid burden. Results are

presented at the $p<0.005$ (uncorrected) level, combined with a FWE cluster-level correction, controlling for age, sex, education, the AHI, the APOE4 status and sleep medication use.

3.5. ÉTUDE 3 : SYNDROME D'APNEES OBSTRUCTIVES DU SOMMEIL

La fragmentation du sommeil est l'une des modifications majeures du sommeil survenant dans le vieillissement. L'une des causes principales de la fragmentation du sommeil chez le sujet âgé est l'augmentation substantielle de la prévalence du syndrome d'apnées obstructives du sommeil (SAOS) avec l'âge (Senaratna et al., 2017). En effet, le SAOS à été associé à un risque accru de déclin cognitif (Leng et al., 2017; Osorio et al., 2015; Yaffe et al., 2011). Cependant, les mécanismes cérébraux sous-tendant cette association restent à ce jour mal compris, et les corrélats cérébraux du SAOS sont hétérogènes. Cependant, les études actuelles ont principalement été réalisées chez des patients relativement jeunes présentant un SAOS sévère, et aucune étude n'ayant combiné plusieurs modalités d'imagerie dans une même étude, spécifiquement chez les suejts âgés. Ainsi, l'objectif principal de cette troisième étude était de préciser la nature des altérations cérébrales et cognitives associées à la présence d'un SAOS dans le vieillissement, en utilisant une approche de neuroimagerie multimodale. Des analyses secondaires ont été réalisées dans le but d'identifier (i) les aspects du SAOS (i.e., la fréquence des évènements respiratoires, la fragmentation du sommeil associée, ou la sévérité des épisodes hypoxiques associés) les plus prédictifs des altérations observées, et (ii) les liens éventuels avec les performances cognitives.

Dans cette étude, nous avons inclus 127 sujets âgés cognitivement sains issus de la cohorte Age-Well, ayant réalisé une évaluation neuropsychologique, une IRM structurale, un examen de TEP couplée au ^{18}F-florbetapir, un examen de TEP couplé au ^{18}F-fluorodeoxyglucose (pour un sous-échantillon de 87 participants), et d'un examen de PSG. Les enregistrements de sommeil ont été

scorés visuellement selon les critères internationaux de l'*American Academy of Sleep Medicine* (ref 2017), et sur la base de l'index d'apnées-hypopnées (IAH), les participants ont été classifiés comme négatifs (IAH<15) ou positifs (IAH≥15) pour la présence d'un SAOS.

Afin de caractériser le profil d'atteintes cérébrales associé à la présence d'un SAOS, nous avons tout d'abord réalisé des comparaisons inter-groupes en cerveau entier pour chaque modalité d'imagerie, en contrôlant pour l'âge, le sexe, le niveau d'éducation, l'indice de masse corporelle, la prise de médicaments ayant un impact sur la qualité du sommeil, et le statut APOE4. Dans un second temps, des régressions pas-à-pas ont été réalisées dans le but de déterminer les aspects du SAOS expliquant le plus les altérations cérébrales observées, puis des analyses de corrélations partielles ont permis d'explorer les associations avec les performances cognitives (mesurées grâce à des scores composites représentatifs des principales sphères cognitives), en contrôlant pour les mêmes covariables que dans l'analyse principale.

Les résultats montrent que les sujets âgés cognitivement sains possédant un SAOS présentent une augmentation du volume de substance grise, du métabolisme et de la perfusion cérébrale, ainsi que de la charge amyloïde principalement au niveau du cortex cingulaire postérieur et du précunéus. De manière intéressante, ces altérations cérébrales semblent particulièrement sous-tendues par la sévérité des épisodes hypoxiques, mais aucun lien significatif n'a été retrouvé avec les performances cognitives, la plainte cognitive, les difficultés auto-rapportées de sommeil (mesurées avec l'Index de Qualité de Sommeil de Pittsburgh), ni les symptômes de somnolence diurne excessive (mesurés grâce à l'échelle de somnolence d'Epworth).

Ces résultats suggèrent que la présence d'un SAOS est associée à une hyperactivité neuronale et une augmentation de la charge amyloïde, dans une région typiquement touchée par les processus physiopathologiques caractéristiques de la MA, à un stade asymptomatique.

Cette étude a fait l'objet d'une communication orale en 2019 (Alzheimer's Association International Conference), et l'article correspondant est actuellement soumis.

Association of sleep-disordered breathing with gray matter volume, perfusion, glucose metabolism and β-amyloid deposition in older adults

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Declarations of interest: none.

Key points:

- **Question:** Which brain changes are associated with sleep-disordered breathing (SDB) in aging?
- **Findings:** In this cross-sectional study of 127 cognitively unimpaired older individuals, the presence of SDB was associated with increased gray matter volume, metabolism, perfusion and amyloid burden in the posterior cingulate cortex and precuneus. There were no association with cognitive performance, cognitive or sleep complaint, or excessive daytime sleepiness.
- **Meaning:** SDB-related alterations include amyloid deposition in brain regions typically involved in Alzheimer's disease (AD), which might explain why SDB is associated with increased risk for developing Alzheimer's clinical syndrome at a younger age.

Abstract:

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

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

Design and Setting: This cross-sectional study was conducted using data from the Age-Well randomized controlled trial of the Medit-Ageing European project, acquired between 2016 and 2018 at the Cyceron Center (Caen, France).

Participants: 127 cognitively unimpaired older participants underwent a detailed neuropsychological assessment, polysomnography recording, MRI and Florbetapir-PET scans, and an FDG-PET scan (for a subsample of 87 participants). Based on the apnea-hypopnea index (AHI), participants were classified as SDB- (AHI<15) or SDB+ (AHI≥15).

Main outcomes and measures: Voxel-wise between-group comparisons were performed for each neuroimaging modality in order to picture changes in gray matter (GM) volume, perfusion, glucose metabolism and amyloid deposition associated with the presence of SDB, controlling for age, gender, education, body mass index, sleep medication use and Apolipoprotein E ε4 status. Secondary analyses aimed at (i) identifying which SDB parameter(s) (sleep fragmentation, hypoxia severity or the frequency of respiratory disturbances) best explained the observed brain changes, and (ii) assessing whether SDB severity and/or SDB-related brain changes are associated with cognitive and behavioral changes, adjusting for the same covariates.

Results: SDB+ participants showed increased GM volume, metabolism, perfusion, and amyloid burden overlapping mainly over the posterior cingulate cortex and precuneus. No association was found with cognition, cognitive complaint, subjective sleep quality or excessive daytime sleepiness symptoms.

Conclusions and relevance: SDB-related changes occur in AD-sensitive brain regions and include amyloid deposition. Neuronal hyperactivity and amyloid deposition in the posterior cingulate cortex and precuneus in asymptomatic older adults could be the mechanism linking SDB to increased AD risk. These results support the fact that SDB may be a risk factor for the development of AD.

1. Introduction

Sleep-disordered breathing (SDB) is a respiratory disorder characterized by recurrent upper airway collapse during sleep, associated with arousals and hypoxia episodes[1,2], affecting around 30 to 80% of older adults, depending on SDB definition criteria[3,4]. Moreover, patients with the Alzheimer's clinical syndrome are more likely to suffer from SDB compared to cognitively unimpaired older individuals[5], and untreated SDB is associated with cognitive decline and conversion to the Alzheimer's clinical syndrome of Mild Cognitive Impairment (MCI) or dementia at a younger age[6–8]. Growing efforts have been deployed to better characterize the brain alterations associated with SDB towards highlighting the brain mechanisms that may underlie the association between SDB and dementia risk. Previous studies yet provided heterogeneous results, showing both SDB-related decreases[9–11] and increases[12,13] in gray matter (GM) volume or thickness in various brain areas including frontal, temporal and parietal regions. Similarly, both decreased[14–16] and increased[15,17] perfusion has been reported in SDB patients compared to controls. These discrepancies are likely to be explained by the small sample sizes in most studies; they might as well reflect differences in the characteristics of SDB patients (e.g. age, SDB severity and scoring rules) and/or the lack of control for possibly biasing covariates, especially in studies performing between-group comparisons. Finally, SDB has been related to increased amyloid and tau levels in the blood and cerebrospinal fluid (CSF), both cross-sectionally and longitudinally[18–21]. Only one study to date assessed the link with brain amyloid deposition on a relatively small sample of patients with SDB (n=19), all aged below 65 years old[22]. They found increased amyloid burden in the precuneus and posterior cingulate cortex, without structural changes, in SDB patients compared to controls. There is however no previous study using a multimodal neuroimaging approach in

order to better characterize brain alterations associated with the presence of SDB within a large sample of older SDB patients with normal cognitive performance.

Our main objective was thus to provide a comprehensive picture of structural, functional and molecular brain changes associated with the presence of SDB in cognitively unimpaired older adults. We investigated SDB-related changes in GM volume, perfusion, glucose metabolism and cortical amyloid burden, for the first time altogether in the same study, towards providing significant advances in our understanding of the brain mechanisms underlying the relationships between SDB and AD. As a secondary objective, we aimed at specifying which aspect of SDB severity (sleep fragmentation, hypoxia severity or the frequency of respiratory events) mostly underlie brain changes. Lastly, we investigated the possible link between SDB severity and/or SDB-related brain changes and cognitive performance.

2. Materials & Methods

2.1. Participants

We included 127 cognitively unimpaired older adults from the baseline visit of the on-going Age-Well randomized controlled trial (RCT) of the Medit-Ageing European project[23] (flow diagram in **Fig. 1**), sponsored by the French National Institute of Health and Medical Research (Institut National de la Santé et de la Recherche Médicale, INSERM). Briefly, participants were recruited from the general population, aged over 65 years old, native French speakers, retired for at least one year, with at least 7 years of education, and performing within the normal range for age and educational levels on standardized cognitive tests of a neuropsychological diagnostic battery. Main exclusion criteria were safety concerns in relation to 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 that may interfere with cognitive functioning.

Participants meeting inclusion criteria performed a detailed cognitive assessment, a polysomnography recording, structural MRI, ^{18}F-Florbetapir and ^{18}F-fluorodeoxyglucose (FDG)-PET scans and ApoE genotyping within a maximum period of 3 months. All participants gave their written informed consent prior to the examinations, and the Age-Well RCT was approved by the ethics committee (CPP Nord-Ouest III, Caen; trial registration number: EudraCT: 2016- 002441-36; IDRCB: 2016-A01767-44; ClinicalTrials.gov Identifier: NCT02977819).

2.2. Cognitive and behavioral assessment

After inclusion, a detailed neuropsychological evaluation was performed, encompassing global cognitive functioning, processing speed, attention, working memory, executive functions and episodic memory (see Poisnel *et al.* 2018 for the protocol description[23]). For each cognitive domain, a composite score was computed (see **Supplementary Material** for further details). In addition, cognitive complaint was assessed using the global score at the Cognitive Difficulties Scale[24]. Moreover, global self-reported sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI)[25], and excessive daytime sleepiness symptoms were measured using the Epworth Sleepiness Scale (ESS)[26].

2.3. Neuroimaging examinations

All participants underwent the acquisition of a high-resolution T1-weighted anatomical image to measure GM volume, and a Florbetapir-PET scan, with an early acquisition (beginning at the

intravenous injection) reflecting brain perfusion, and a late acquisition (beginning 50 mn after injection) reflecting amyloid burden. A subset of participants (n=87) also underwent a ^{18}F-fluorodeoxyglucose (FDG)-PET scan, to measure brain glucose metabolism. All participants were scanned in three different sessions at the Cyceron Center (Caen, France) on the same MRI (Philips Achieva 3.0T) and PET (Discovery RX VCT 64 PET-CT, General Electric Healthcare) scanners. The detailed acquisition and pre-processing procedure is available in the **Supplementary Material** (see also [23]).

2.4. SDB characterization

Participants underwent an ambulatory polysomnography (PSG) recording in their habitual home environment using a Siesta® device (Compumedics, Australia). Twenty EEG electrodes were placed over the scalp (Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, T3, T4, P3, P4, Pz, O1, O2, vertex ground, and a bi-mastoid reference) according to the international 10-20 system, with impedances kept below 5 kΩ. The electrooculogram, electrocardiogram, chin electromyogram, respiratory movements using thoracic and abdominal belts, respiratory airflow using nasal and oral thermistors, and oxygen saturation using a finger pulse oximeter were also recorded. Sixty-eight percent of the participants (n=86 over 127) underwent two PSG recordings, including a habituation night which was not included in the analyses. The remaining 39 participants only had one PSG recording. The EEG signal was digitalized at a sampling rate of 256 Hz. High-pass and low-pass filters were applied, respectively at 0.3Hz and 35Hz. PSG recordings were manually scored in 30-s epochs following the recommended standard criteria of the American Academy of Sleep Medicine[1], allowing the computation of standard sleep parameters and respiratory parameters. Sleep apnea was defined by a ≥90% drop of nasal pressure for a minimum of 10 seconds, whereas

sleep hypopnea was characterized by a ≥30% drop of nasal pressure for a minimum of 10 seconds, associated with an arousal or a ≥3% oxygen desaturation. In order to characterize brain changes associated with the presence of SDB, participants were classified into two groups based on the apnea-hypopnea index (AHI), corresponding to the sum of apneas and hypopneas per hour of sleep: the SDB- group (AHI<15; n=31), and the SDB+ group (AHI≥15; n=96)[6,27,28]. The sub-sample of 87 participants who also had a FDG-PET scan was composed of 69 SDB+ and 18 SDB- participants, such that the proportions of SDB+ versus SDB- participants was comparable between the two samples (χ^2=0.26, p=0.61). Additionally, we aimed at further specifying which aspect of SDB severity was related to brain changes and if these were associated with cognitive performance. For these secondary objectives, we considered the frequency of SDB (as reflected by the AHI), as well as two additional scores: i) a sleep fragmentation composite score, corresponding to the average of the Z-scores of the respiratory arousal index, the number of shifts to non-REM sleep stage 1, and the number of nocturnal awakenings, and ii) a hypoxia composite score, corresponding to the average of the Z-scores of the oxygen desaturation index, the proportion of total sleep time with oxygen desaturation ≤90%, and the minimal oxygen saturation.

2.5. Statistical analyses

2.5.1. Between-group differences

Between-groups differences for demographical, sleep, and cognitive variables were assessed using Student t-tests for continuous variables, and chi-square statistics for categorical variables, with statistical significance set to p<0.05.

Voxel-wise group differences in GM volume, perfusion, glucose metabolism and amyloid burden were explored using ANCOVAs in SPM12, controlling for age, sex, education, body mass index

(BMI), sleep medication use, and the Apolipoprotein E ε4 (ApoE4) status. Voxel-wise analyses were performed using a voxel-level p(uncorrected)<0.005 threshold and applying a cluster-level threshold of p<0.05 corrected for family-wise errors.

2.5.2. Stepwise regression analyses

As a second step, we aimed at further assessing which aspect of SDB severity was more specifically involved in the SDB-related brain changes highlighted in the previous analyses. For this purpose, neuroimaging signal values (e.g., GM volume, perfusion, glucose metabolism and amyloid burden) were extracted from the significant clusters obtained in the voxel-wise group comparisons described above. Then, stepwise regression analyses were performed on the whole sample of participants in order to determine which aspect(s) of SDB severity (i.e., the frequency of respiratory disturbances, associated sleep fragmentation and/or hypoxia severity) is the best predictor of the observed brain changes. Nine measures were entered in the model as independent variables (i.e., the three measures of SDB severity, as well as age, gender, education, BMI, sleep medication use and the ApoE4 status), while the dependant variable was each brain alteration tested separately.

2.5.3. Partial correlation analyses

Partial correlations were then performed on the whole sample of participants in order to assess potential associations between (i) the three measures of SDB severity, and (ii) SDB-related brain changes, with cognitive and behavioural variables. These analyses were controlled for age, gender, education, BMI, sleep medication use and ApoE4 status, and considered significant at a p<0.05 threshold, after applying a Bonferroni correction for multiple comparisons (i.e., the statistical threshold for significance was set to P≤(.05/number of comparisons)).

3. Results

3.1. Participants' characteristics

Participants' characteristics, including demographical variables, neuropsychological scores and sleep parameters, as well as between-group differences, are provided in **Table 1**. Participants with SDB did not differ from controls for age, gender, education, depression and anxiety scores, current use of sleep medication, and the proportion of ApoE4 carriers. As expected, SDB+ participants presented significantly higher BMI ($t=2.24$, $p=0.03$), AHI ($t=8.64$, $p<0.001$), levels of sleep fragmentation ($t=5.96$, $p<0.001$) and hypoxia ($t=3.68$, $p<0.001$). Interestingly, no between-group differences were observed for global subjective sleep quality, daytime sleepiness symptoms and objectively-measured total sleep time, sleep efficiency and sleep latency on the PSG night. Moreover, cognitive performance and cognitive complaint were comparable between the two groups.

3.2. Brain changes associated with the presence of SDB

Results of between-group comparisons for neuroimaging data are presented in **Fig. 2**. Cluster peak coordinates and statistics, including effect sizes, are detailed in the **Supplementary Table 1**. Compared to the SDB- group, SDB+ participants presented increased GM volume in the precuneus and posterior cingulate cortex, bilaterally (**Fig. 2A**, Cohen's $d=0.75$). They also showed widespread bilateral increase in brain perfusion in parieto-occipital regions (including the precuneus, posterior cingulate, calcarine, and lingual areas) (**Fig. 2B**, Cohen's $d=0.86$). In the subsample of participants who also had an FDG-PET scan, SDB+ participants presented increased glucose metabolism in the precuneus, posterior cingulate, and lingual areas, bilaterally (**Fig. 2C**, Cohen's $d=1.04$). Finally,

SDB+ participants showed higher amyloid burden in the left precuneus, posterior cingulate, calcarine, and cuneus regions (**Fig. 2D**, Cohen's d=0.83) compared to SDB- participants. Moreover, there was a trend towards a higher neocortical amyloid SUVr (t=1.81, p=0.07) and a higher proportion of amyloid positive participants in the SDB+ group (p=0.08) **(Table 1)**. SDB+ participants did not exhibited any decreases in GM volume, perfusion, metabolism or amyloid burden.

Of note, there was an overlap between all four neuroimaging modalities (i.e., increased GM volume, perfusion, metabolism, and amyloid burden) over the posterior cingulate cortex and the precuneus. Moreover, the overlap between the patterns of increased brain perfusion, metabolism and amyloid burden was particularly pronounced, mainly over the posterior cingulate cortex, the precuneus, and the cuneus **(Fig. 3)**.

3.3. Links between SDB-related brain changes and measures of SDB severity.

In order to determine which aspects of SDB severity are the most predictive of SDB-related brain changes, forward stepwise regression were performed **(Table 2)**. The best predictors of amyloid burden were the hypoxia composite score, explaining 7.7% of the variance (β coefficient=0.278, p=0.002), followed by the ApoE4 status, explaining 3.4% of the variance (β coefficient=0.183, p=0.001). No other variable entered the model. The BMI was the most predictive variable of cerebral hypertrophy, explaining 5.3% of the variance (β coefficient=-0.230, p=0.012), followed by the AHI, explaining 3.9% of the variance (β coefficient=0.200, p=0.004). No variable significantly predicted brain perfusion or metabolism. Backward stepwise regression analyses led to the same conclusions.

3.4. Links with cognition, cognitive complaint and self-reported sleep

Lastly, we aimed at exploring the cognitive and behavioral correlates of SDB severity and associated brain changes. No significant associations surviving the Bonferroni correction for multiple comparisons were observed (see **Supplementary Table 2**), such that neither measures of SDB severity, nor SDB-related brain alterations, were related to cognitive performance, cognitive complaint, self-reported sleep complaint or symptoms of sleepiness.

4. Discussion

The main goal of the present study was to provide a comprehensive overview of structural, functional and molecular brain changes in cognitively unimpaired older participants with SDB. Our results show that SDB+ participantspresented increased GM volume, perfusion and metabolism, in parieto-occipital regions, including the precuneus and posterior cingulate cortex, compared to SDB- participants. SDB+ participants also showed increased amyloid deposition in the same brain areas, mainly associated with the severity of hypoxia. Neither SDB severity, nor SDB-related brain changes, were associated with cognitive performance, cognitive complaint, self-reported sleep quality and sleepiness.

The cerebral pattern in older participants with SDB was characterized by increased GM volume, perfusion and metabolism. Our results are in line with several other studies showing GM hypertrophy and hyperperfusion[12,15,17,29,30]. Nevertheless, other groups have rather reported GM atrophy, hypoperfusion and hypometabolism in participants with SDB[9–11,14,16]. Part of these discrepancies across studies are likely to be the consequence of methodological differences, as

most of studies have been performed on smaller samples of young and middle-aged participants with severe SDB (AHI>30). Alternatively, it is possible that studies including participants with less severe SDB (i.e., from the moderate SDB stage corresponding to an AHI>15), as done in the present study and in others[12,15], are more able to capture earlier brain changes associated with the presence of SDB. Indeed, it has been hypothesized that GM hypertrophy and hyperperfusion are the result of astrogliosis, microgliosis and neuroinflammatory processes[29,31–33], which may precede and promote the development of further neuronal injury, such as hypoperfusion, hypometabolism and atrophy[34].

Moreover, our results show that participants with SDB also exhibited increased amyloid burden in parieto-occipital regions. This result is in line with the current knowledge about the associations between the presence of SDB and lower serum and CSF amyloid levels[18,35]. Furthermore, it unravels the regional pattern of amyloid deposition in cognitively unimpaired individuals with SDB, extending the findings of Yun and colleagues[22] to a larger and older sample of individuals with SDB. In our study, increased amyloid burden in the posterior cingulate cortex and the precuneus significantly correlated with the severity of hypoxia. This finding is consistent with animal studies, showing that hypoxia promotes the cleavage of the amyloid precursor protein by the β- and γ-secretase enzymes, leading to increased Aβ levels[36–38].

Importantly, our results show *in vivo* for the first time that increased GM volume, perfusion, and metabolism co-localize with increased amyloid burden in cognitively unimpaired older participants with SDB. We believe these overlapping patterns reinforce the likelihood of common underlying mechanisms. Indeed, it has been demonstrated that higher neuronal activity is associated with

increased Aβ production[39–42]. In addition, several studies have shown that neuroinflammatory processes play a central role in AD progression, and are associated with higher levels of amyloid deposition[43]. Thus, SDB-related neuroinflammatory processes and associated GM hyperactivity are likely to promote amyloid deposition in the same area.

In our study, brain changes associated with the presence of SDB were not associated with cognitive performance, cognitive complaint, subjective sleep quality or symptoms of excessive daytime sleepiness. We believe that this finding reinforces our hypothesis according to which increased GM volume, perfusion, metabolism and amyloid deposition represent early and asymptomatic brain changes. Studies exploring the associations between SDB and cognitive performance using cross-sectional designs have provided mixed results[7,44–46], but longitudinal studies show that SDB is more clearly associated with conversion to Alzheimer's clinical syndrome of MCI and dementia, and with cognitive decline over time[6–8]. We thus hypothesize that older adults presenting with SDB show silent brain alterations, including enhanced amyloid deposition, which could explain why they are more at risk of developing Alzheimer's clinical syndrome.

The main strengths of the present study are the multimodal assessment of brain integrity, allowing to reveal the overlap of brain alterations in participants with SDB, and the detailed cognitive assessment, on a large sample of cognitively unimpaired older individuals. However, the present study also has some limitations. First, the cross-sectional design of the analyses does not allow to ascertain that SDB-related silent brain changes will progress to neurodegenerative processes and cognitive deficits, but longitudinal studies would allow validating this hypothesis. Second, following the recommended criteria of the American Academy of Sleep Medicine, SDB was found

to be highly prevalent in our sample, with 75.6% of the participants classified as SDB+. This raises potential concerns about the single use of the AHI to quantify SDB severity, especially when considering that the majority of SDB+ participants did not show any symptoms of daytime sleepiness (with 14/96 SDB+ participants presenting an ESS score≥9) or self-reported sleep difficulties (with 41/96 SDB+ participants having a PSQI score>5). Moreover, the AHI in itself is a measure presenting several limitations, such as equally considering apneas and hypopneas although the severity of the two events is different, especially regarding hypoxia severity[47].

Taken together, our data reveal that older individuals presenting with SDB show increased GM volume, perfusion, metabolism and amyloid burden in parieto-occipital regions, mainly converging in the posterior cingulate cortex and precuneus, typically altered in AD. Moreover, these brain changes were not associated with cognitive performance, cognitive complaint, subjective sleep quality or symptoms of excessive daytime sleepiness. This suggests that SDB could increase the susceptibility to AD at an asymptomatic stage. Thus, SDB seem to be a critical factor to consider in older individuals, even in the absence of cognitive or behavioural manifestations.

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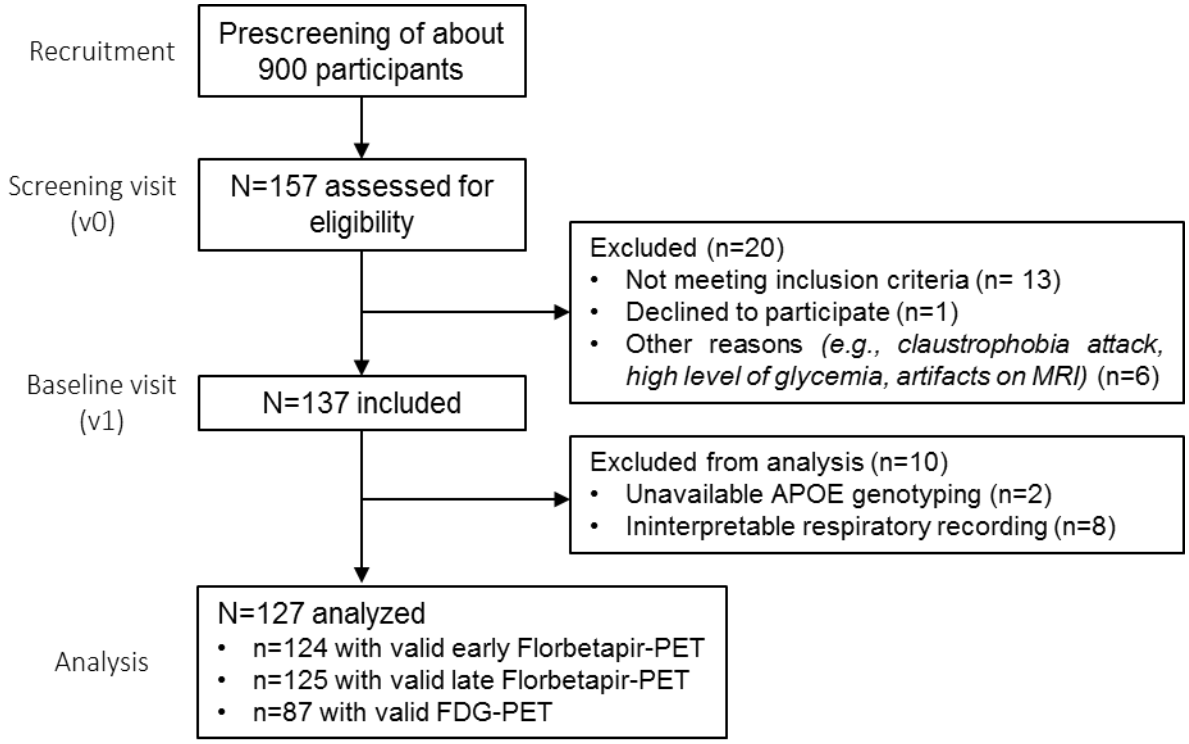
Figure 1: Flow diagram of the inclusion process.



Abbreviations: APOE, apolipoprotein E; FDG, ^{18}F-fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positons emission tomography.

Table 1: Participants characteristics and between-groups differences.

	SDB- (n=31)	SDB+ (n=96)	Between-group differences [1]
Demographics			
Age: years	69.19 (3.52)	69.00 (3.98)	p=0.81
Gender: number (%) of women	22 (70.97%)	70 (72.92%)	p=0.06
Education: years	13.45 (2.94)	12.90 (3.12)	p=0.38
GDS: total score	1.55 (1.89)	1.21 (1.70)	p=0.35
STAI-B: total score	36.13 (7.35)	34.05 (6.88)	p=0.15
Body mass index: kg/m²	24.77 (5.07)	26.73 (3.92)	**p=0.03**
Current sleep medication use: number (%) of users [2]	2 (6.45%)	10 (10.42%)	p=0.51
Florbetapir SUVr: mean value (SD; % positive) [3]	0.91 (0.13; 10%)	0.99 (0.23; 25%)	p=0.07
ApoE4: number (%) of carriers	9 (29.03%)	26 (27.08%)	p=0.83
Sleep			
PSQI: total score	4.38 (2.67)	5.17 (3.16)	p=0.22
ESS: total score	4.77 (3.04)	5.22 (3.45)	p=0.52
TST: min	358.63 (59.13)	362.81 (67.62)	p=0.76
Sleep efficiency: %	76.39 (10.24)	77.36 (9.89)	p=0.64
Sleep onset latency: min	18.73 (12.41)	21.12 (12.49)	p=0.36
Apnea-hypopnea index: number per hour	9.63 (3.91)	30.54 (13.26)	**p<0.001**
Fragmentation: composite score	-0.68 (0.41)	0.22 (0.81)	**p<0.001**
Respiratory arousals index: number per hour	7.15 (3.34)	25.28 (11.30)	**p<0.001**
Shifts to NREM-1: number per hour	5.81 (2.08)	8.39 (3.53)	**p=0.001**
Awakenings: number per hour	3.29 (1.11)	4.11 (1.72)	**p=0.02**
Hypoxia: composite score [4]	-0.44 (0.39)	0.15 (0.85)	**p<0.001**
Oxygen desaturation ≥3% index: number per hour	5.50 (3.95)	16.50 (11.21)	**p<0.001**
TST with oxygen saturation ≤90%: %	0.50 (1.08)	2.88 (9.69)	p=0.18
Minimal oxygen saturation: %	88.27 (3.82)	85.89 (5.06)	**p=0.02**
Cognition			
MMSE: total score	28.81 (1.08)	29.06 (1.04)	p=0.24
MDRS: total score	140.61 (2.89)	141.17 (2.64)	p=0.32
Processing speed: composite score	0.05 (0.85)	-0.02 (0.71)	p=0.66
Attention: composite score	-0.04 (0.66)	0.04 (0.64)	p=0.57
Executive functioning: composite score	0.12 (0.69)	-0.03 (0.66)	p=0.26
Working memory: composite score	0.04 (1.03)	-0.03 (0.85)	p=0.72
Episodic memory: composite score	0.16 (0.81)	-0.05 (0.69)	p=0.17
Cognitive Difficulties Scale: total score	33.84 (14.27)	34.18 (15.59)	p=0.92

Abbreviations: ESS, Epworth Sleepiness Scale; GDS, Geriatric Depression Scale; MDRS: Mattis Dementia Rating Scale; MMSE, Mini Mental State Examination; NREM-1: non-rapid eye movement sleep stage 1; ns, non-significant; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation; SDB, sleep-disordered breathing; STAI-B, State-Trait Inventory form B; SUVr, Standard Uptake Value ratio; TST, Total Sleep Time.

Results are expressed as mean (SD), unless otherwise specified.

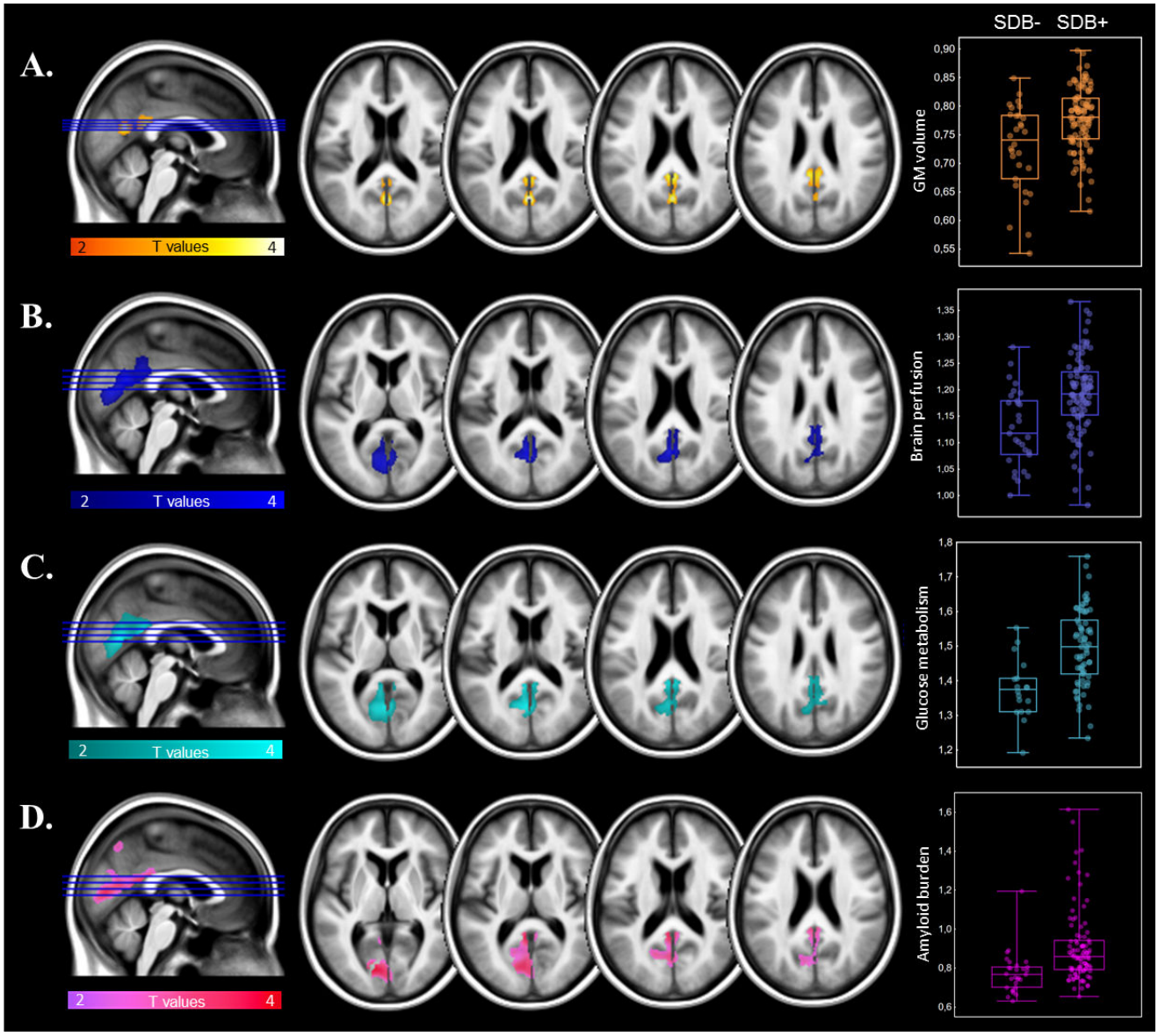
[1] Between-group differences were assessed using Student t-tests for continuous variables, and chi-square statistics for categorical variables. Statistical significance was set to $p<0.05$.

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

[3] n=30 controls with valid Florbetapir-PET scan. The threshold for amyloid positivity was defined as >0.99, and corresponded to the 99.9^{th} percentile of the neocortical SUVr distribution among 45 healthy young individuals, aged <40 years.

[4] n=30 SDB- and 88 SDB+ participants with valid data related to oxygen saturation.

Figure 2: Neuroimaging profile of SDB+ participants.

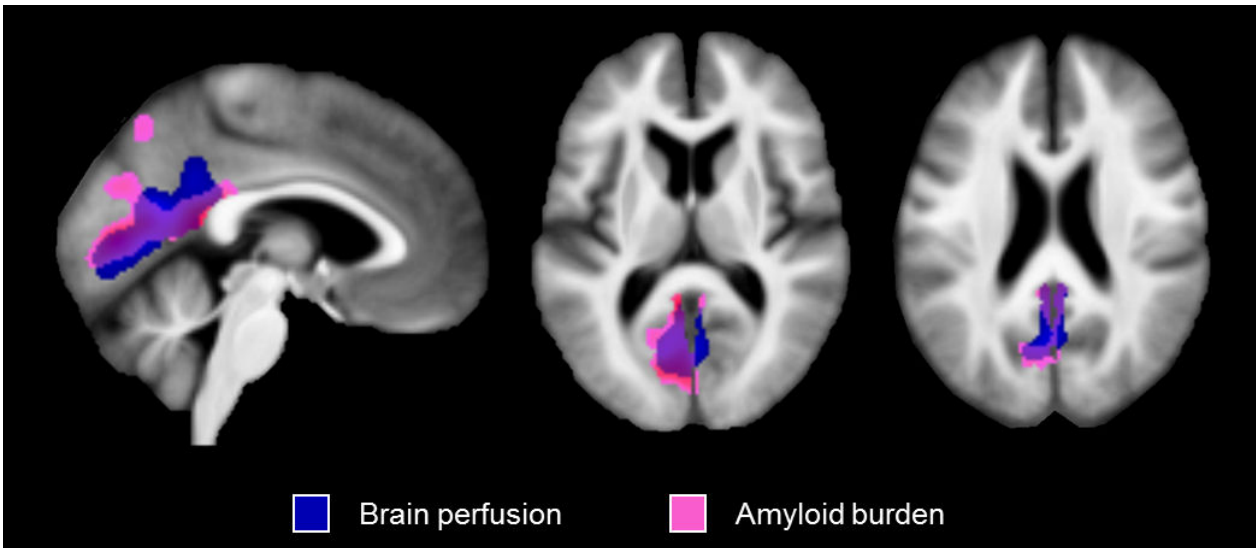


Abbreviations: APOE, apolipoprotein E; GM, gray matter; SDB, sleep-disordered breathing.

Results of voxel-wise between-groups comparisons showing patterns of **(A)** GM hypertrophy, **(B)** hyperperfusion, **(C)** hypermetabolism, and **(D)** increased amyloid burden in SDB+ participants. Analyses were adjusted for age, gender, education, body mass index, sleep medication use, and

ApoE4 status. Results were obtained at a $p<0.005$ (uncorrected) threshold, and only clusters surviving a FWE cluster-level correction are reported.

Figure 3: Overlap of SDB-related brain alterations.



Abbreviations: FWE, family-wise error; GM, gray matter.

Representation of the overlap between SDB-related patterns of hyperperfusion (blue) and amyloid burden (pink), obtained at a $p<0.005$ (uncorrected) threshold combined with a FWE cluster-level correction.

Table 2: Significant forward stepwise regressions predicting SDB-related changes.

Dependent variable	Predictors	β coefficient	R^2	p-value
Amyloid burden	First step: Hypoxia composite	0,278	0,077	0,002
	Second step: ApoE4 status	0,183	0,111	0,001
	Full model		*0,171*	*0,003*
GM volume	First step: BMI	-0,230	0,053	0,012
	Second step: AHI	0,200	0,092	0,004
	Full model		*0,143*	*0,015*

Abbreviations: AHI, apnea-hypopnea index; APOE, apolipoprotein E; BMI, body mass index; GM, gray matter.

Supplementary Material

Supplementary methods

Neuroimaging procedure

Neuropsychological scores

Supplementary Tables

Supplementary Table 1: Detailed statistics of significant neuroimaging clusters.

Supplementary Table 2: Results of partial correlations analyses between SDB parameters and brain alterations with cognitive and behavioural scores.

Supplementary Methods

Neuroimaging procedure

All participants were scanned at the Cyceron Center (Caen, France) on the same MRI (Philips Achieva 3.0T scanner) and PET (Discovery RX VCT 64 PET-CT scanner, General Electric Healthcare) cameras. During the MRI session, subjects were equipped with earplugs and their head was stabilized with foam pads in order to minimize head motion.

7.1.1. Structural MRI

A high-resolution T1-weighted anatomical image was acquired using a 3D fast-field echo sequence (3D-T1-FFE sagittal, repetition time =7.1 ms, echo time = 3.3 ms, flip angle = 6°, 180 slices with no gap, slice thickness = 1mm, field of view = 256x256 mm^2, in-plane resolution= 1x1x1 mm^3). T1-weighted images were segmented using FLAIR images (3D-IR sagittal, TR/TE/TI = 4800/272/1650 ms ; flip angle = 40°; 180 slices with no gap; slice thickness = 1 mm; field of view = 250x250 mm^2; in-plane resolution = 0.98x0.98 mm^2), spatially normalized to the Montreal Neurological Institute (MNI) template, modulated using the SPM12 segmentation procedure (http://www.fil.ion.ucl.ac.uk) and smoothed with an 8 mm full-width at half-maximum (FWHM) Gaussian filter. Images were then masked to exclude non-grey matter voxels from the analyses.

7.1.2. PET imaging

Florbetapir- and FDG-PET scans were acquired in two separate sessions with a resolution of 3.76 × 3.76 × 4.9 mm^3 (field of view = 157 mm). Forty-seven planes were obtained with a voxel size of

$1.95 \times 1.95 \times 3.27$ mm^3. A transmission scan was performed for attenuation correction before the PET acquisition.

For the Florbetapir-PET scan, each participant underwent a 10 min PET scan beginning at the intravenous injection of ~4MBq/Kg of Florbetapir, and a 10 min PET scan beginning 50 min after the intravenous injection. Early Florbetapir-PET, reflecting brain perfusion, was reconstructed from 1 to 6 min. Late-Florbetapir acquisition reflected brain amyloid burden.

For the FDG-PET scan, participants (n=87) were fasted for at least 6 hours before scanning. After a 30-min resting period in a quiet and dark environment, 180 MBq of ^{18}F-fluorodeoxyglucose were intravenously injected as a bolus. A 10-min PET acquisition scan began 50 min after injection.

PET images were coregistered on their corresponding anatomical MRI, voxel-wise corrected for partial volume effects using the three-compartmental voxel-wise Müller-Gärtner method, and were then normalized to the MNI template using deformation parameters derived from the anatomical MRI. Resulting images were scaled using cerebellar grey matter as a reference. A smoothing kernel of 10 mm Gaussian filter was applied and images were masked to exclude non-grey matter voxels from the analyses. PVE-corrected normalized and scaled Florbetapir-PET images were also used to extract the individual global cortical amyloid standard uptake value ratio (SUVr) using a predetermined neocortical mask including the entire grey matter, except the cerebellum, occipital and sensory motor cortices, hippocampi, amygdala and basal nuclei (La Joie 2013). The threshold for amyloid positivity was defined as >0.99, and corresponded to the 99.9th percentile of the neocortical SUVr distribution among 45 healthy young individuals, aged <40 years.

Reference:

La Joie R, Perrotin A, de La Sayette V, Egret S, Doeuvre L, Belliard S, et al. Hippocampal subfield volumetry in mild cognitive impairment, Alzheimer's disease and semantic dementia. NeuroImage Clin 2013;3:155-62. doi:10.1016/j.nicl.2013.08.007.

Neuropsychological scores

To obtain robust proxies of cognitive abilities and minimize the issue of multiple statistical testing, composite scores were used for each cognitive domain, instead of multiple (sub)tests. For that purpose, performance on various cognitive tests were z-transformed and averaged as follows. Please note that before averaging, Z-scores derived from reaction times and percentages/number of error were reversed so that increasing values always indicated better performance.

- **Processing speed**
  - Time to perform the Trail Making test (TMT) part A.
  - Time to complete the word card from the Stroop test (reading condition).
  - Time to complete the color card from the Stroop test (naming condition).
- **Attention**
  - Attention sub-score from the Mattis Dementia Rating Scale.
  - Number of correct items at the D2R test.
  - Percentage of errors at the D2R test.
- **Executive functions**
  - TMT test (time difference between TMT part B and part A, divided by the time to perform part A).
  - Stroop test (time difference between the interference and naming conditions).
  - Verbal fluency (number of words beginning with ‘‘p’’ in 2 min).
- **Working memory**
  - Digit span forward from the WAIS IV.
  - Digit span backward from the WAIS IV.

- Digit span forward + backward total raw note from the WAIS IV.

- **Episodic memory**
  - Memory subscore from the Mattis Dementia Rating Scale.
  - Sum of the five free recalls from the learning trials of the California Verbal Learning Test (CVLT).
  - Short-term free recall from the CVLT.
  - Long-term free recall from the CVLT.
  - Long-term free recall from the Logical Memory Story test from the WMS IV.

Abbreviations: CVLT, California Verbal Learning Test; TMT, Trail Making Test; WAIS, Wechsler Adult Intelligence Scale; WMS, Weschler Memory Scale.

References:

Beth A Ober, Dean C. Delis, Joel H. Kramer, Edith Kaplan, Beth A. Ober (2000) California Verbal Learning Test® - Second Edition (CVLT® -II)

R. Brickencamp and E. Zilmer (1969) Manuel de Bruxelles: Editest Hogrefe Publishing Corp. 38 Chauncy Street, Suite 1002, Boston, MA 02111

Godefroy, O. et le Grefex. (2008). Fonctions exécutives et pathologies neurologiques et psychiatriques: Evaluation en pratique clinique. Marseille: Solal.

Mattis S. (1976) Mental status examination for organic mental syndrome in the elderly patient, in Bellack R, Karasu B (eds): Geriatric Psychiatry, New York, Grune & Stratton,pp77-121.

Strauss, E., Sherman, E.M.S., & Spreen, O. (2006). A compendium of neuropsychological tests: administration, norms, and commentary. Oxford: Oxford University Press. p. 301. ISBN 0-19-515957-8.

Wechsler, D, (2010) Pearson, Wechler Adult Intelligence Scale (WAIS) IV, Pearson Education, Inc, www.pearsonclinical.co.uk

Supplementary Tables

Supplementary Table 1: Detailed statistics of significant neuroimaging clusters.

Brain areas	Cluster extent		MNI coordinates			T-value	$p_{FWE\text{-}corrected}$	Effect size (Cohen's d)
	Nb of voxels	mm^3	x	y	z			
MRI								
B precuneus, posterior cingulate	829	2 798	0	-63	20	4.12	0.038	0.75
Early Florbetapir-PET								
L calcarine, L lingual, B precuneus, B posterior and middle cingulate	3 946	13 318	-6	-76	6	4.62	0.001	0.86
FDG-PET								
B calcarine, B lingual, B precuneus, B posterior cingulate	4 295	14 496	-3	-68	12	4.63	0.001	1.04
Late Florbetapir-PET								
L calcarine, L precuneus, L posterior cingulate, L cuneus	4 699	15 859	-10	-78	6	4.51	0.037	0.83

Abbreviations: B, bilateral; FDG, ^{18}F-fluorodeoxyglucose, L, left; MNI, Montreal Neurological Institute; MRI: magnetic resonance imaging.

Results were obtained at a $p<0.005$ (uncorrected) threshold and only clusters surviving a FWE cluster-level correction are reported.

Supplementary Table 2: Results of partial correlations analyses between SDB parameters and brain alterations with cognitive and behavioural scores.

Cognitive and behavioral variables	SDB parameters			Brain alterations			
	AHI (n=127)	Fragmentation composite (n=127)	Hypoxia composite (n=118)	Perfusion (n=124)	Metabolism (n=87)	Amyloid burden (n=125)	GM volume (n=127)
Mattis Dementia Rating Scale (global score)	r=0.830 p=0.384	r=0,062 p=0,513	r=0,003 p=0,976	r=0,016 p=0,862	r=0,031 p=0,784	r=0,072 p=0,436	r=-0,095 p=0,302
Attention composite score	r=0.059 p=0.536	r=0,067 p=0,485	r=0,024 p=0,803	r=0,162 p=0,080	r=-0,013 p=0,911	r=0,072 p=0,436	r=0,058 p=0,529
Processing speed composite score	r=-0.015 p=0.876	r=0,003 p=0,978	r=0,031 p=0,748	r=0,041 p=0,656	r=0,045 p=0,689	r=0,019 p=0,842	r=-0,045 p=0,629
Working memory composite score	r=-0.011 p=0.910	r=-0,029 p=0,761	r=-0,005 p=0,960	r=-0,007 p=0,937	r=0,035 p=0,758	r=-0,113 p=0,222	r=-0,024 p=0,797
Executive functions composite score	r=-0.064 p=0.506	r=-0,073 p=0,447	r=-0,162 p=0,088	r=0,077 p=0,410	r=0,105 p=0,351	r=-0,088 p=0,341	r=-0,012 p=0,896
Episodic memory composite score	r=-0.090 p=0.348	r=-0,124 p=0,195	r=-0,167 p=0,078	r=-0,050 p=0,589	r=-0,077 p=0,495	r=-0,185 p=0,044	r=-0,116 p=0,206
Cognitive Difficulties Scale (global score)	r=0.061 p=0.525	r=0,039 p=0,687	r=0,089 p=0,351	r=0,067 p=0,469	r=-0,029 p=0,800	r=-0,060 p=0,518	r=0,122 p=0,184
Pittsburgh Sleep Quality Index (global score)	r=0.139 p=0.144	r=0,027 p=0,781	r=-0,034 p=0,726	r=0,112 p=0,226	r=0,068 p=0,549	r=0,047 p=0,614	r=0,216 p=0,018
Epworth sleepiness scale (global score)	r=-0.038 p=0.690	r=-0,030 p=0,754	r=-0,029 p=0,759	r=0,128 p=0,169	r=0,079 p=0,486	r=0,049 p=0,595	r=0,060 p=0,517

Abbreviations: AHI, apnea-hypopnea index; ApoE, apolipoprotein E; GM, gray matter; SDB, sleep-disordered breathing.

Partial correlations were adjusted for age, gender, education, body mass index, sleep medication use and ApoE4 status. R values correspond to partial correlation coefficients, and results were considered significant at $p<0.0008$, after applying a Bonferroni correction for multiple testing ($p=0.05/63$).

4. DISCUSSION GENERALE

4.1. SYNTHESE DES RESULTATS

L'objectif général de cette thèse était de contribuer à caractériser les liens entre les modifications objectives du sommeil dans le vieillissement, les altérations cérébrales structurales, fonctionnelles et moléculaires, et les performances cognitives. Nous avons utilisé une approche de neuroimagerie multimodale, permettant de révéler différents types d'atteintes et d'explorer les mécanismes sous-jacents potentiels. Les résultats des trois études menées au cours de cette thèse sont synthétisés en **Figure 16** ci-dessous.

En résumé, nos travaux ont permis de montrer que :

- Chez les sujets âgés sains, la fragmentation des premiers cycles de sommeil, où le SL prédomine, est associée à une diminution du métabolisme fronto-hippocampique et contribue à la diminution des performances cognitives. Cependant, ces associations n'étaient plus évidentes chez les patients SCD et MCI, présentant des déficits cognitifs subjectifs et/ou objectifs.
- La diminution de la puissance spectrale du rythme delta en SL est associée à la diminution du volume de substance grise et de la perfusion au niveau des aires fronto-cingulaires, tandis que la diminution de la puissance spectrale du rythme theta en SP est associée à une atrophie diffuse et une augmentation de la charge amyloïde néocorticale, et une hyperperfusion fronto-pariétale.
- La présence d'un SAOS est associée à une hypertrophie, une hyperperfusion, un hypermétabolisme et une augmentation de la charge amyloïde principalement au niveau du cortex cingulaire postérieur et du précunéus, sans lien avec les performances cognitives.

Ainsi, de manière générale, nous observons que les modifications objectives du sommeil liées à l'âge, consistant en une altération des ondes lentes, une fragmentation du sommeil, et la présence d'épisodes hypoxiques associées à un SAOS, sont liées à des altérations cérébrales chez les sujets âgés sains, dans des régions sensibles aux processus physiopathologiques de la MA. En revanche, les liens avec la cognition restent subtils, certaines altérations étant même asymptomatiques.

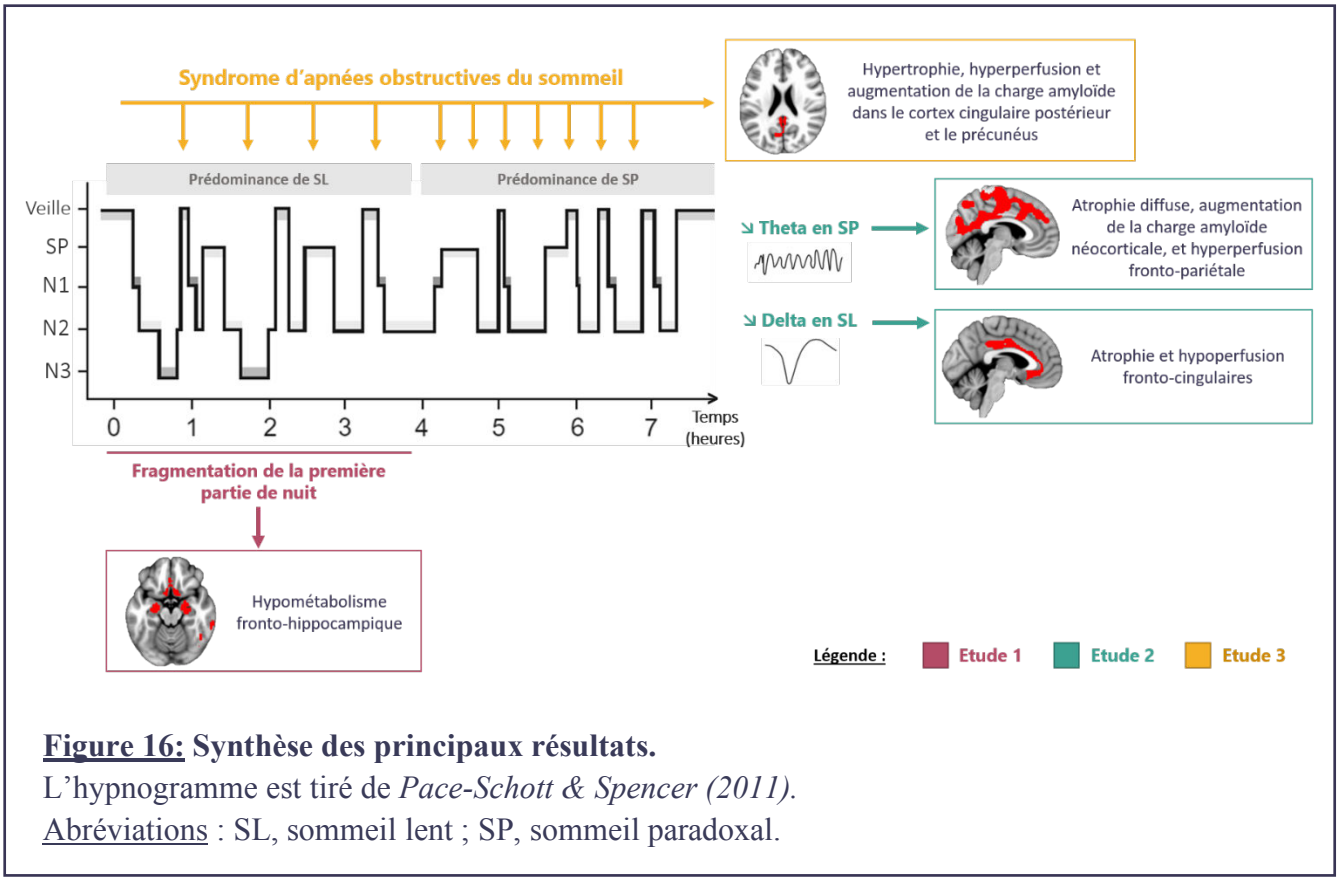


Figure 16: Synthèse des principaux résultats.
L'hypnogramme est tiré de *Pace-Schott & Spencer (2011).*
Abréviations : SL, sommeil lent ; SP, sommeil paradoxal.

4.2. TOPOGRAPHIE DES LIENS ENTRE SOMMEIL ET INTEGRITE CEREBRALE

Les résultats de cette thèse montrent que les altérations cérébrales associées aux modifications du SL, du SP et à la présence d'un SAOS concernent principalement les aires frontales, cingulaires, pariétales (incluant le cortex cingulaire postérieur et le précunéus), et l'hippocampe. De manière intéressante, ces zones appartiennent toutes au réseau du mode par défaut (DMN, pour *Default Mode Network*) (Buckner et al., 2008; Raichle et al., 2001). Ce réseau est notamment impliqué dans les processus d'introspection et de référence à soi, la mémoire épisodique et le fonctionnement exécutif (Buckner et al., 2008; Mevel et al., 2010). Il est composé de régions « hubs » situées au carrefour de l'information, présentant une activité métabolique particulièrement élevée par rapport aux autres régions du cerveau. Il est l'un des réseaux les plus précocément atteints dans la MA, et les régions qui le composent sont sensibles aux mécanismes de la pathologie, présentant un hypométabolisme et des dépôts amyloïdes particulièrement importants (Buckner et al., 2009; Drzezga et al., 2011; Greicius et al., 2004). De manière intéressante, il a été montré que l'hyperactivité neuronale favoriserait la production de peptide Aβ (Bero et al., 2011; Cirrito et al., 2005), ce qui pourrait exacerber l'accumulation des dépôts amyloïdes (Buckner et al., 2005; Pascoal et al., 2019; Vlassenko et al., 2010). A plus long terme, cela fragiliserait les régions concernées, entraînant l'apparition d'un hypométabolisme et leur atrophie (Buckner et al., 2005; Pascoal et al., 2019).

Nos travaux, appuyés par ceux d'autres équipes, montrent que ces zones cérébrales sont étroitement associées à la qualité de sommeil. En effet, le DMN se désactive lors des stades de sommeil profond

(Horovitz et al., 2009; Sämann et al., 2011), et les zones métaboliquement les plus actives à l'éveil présentent alors les niveaux d'activité à ondes lentes les plus élevés (Huber et al., 2004), sous-tendant la fonction de restauration du sommeil. Ainsi, les régions du DMN semblent constituer des substrats cérébraux communs à la fois à génération des rythmes du sommeil, ainsi qu'aux processus physiopathologiques de la MA. Il a été proposé que les modifications du sommeil liées à l'âge, en lien avec une augmentation de l'activité neuronale (Nir et al., 2011; Tabuchi et al., 2015), pourraient favoriser la propagation stéréotypée des pathologies amyloïde et tau au sein de réseaux prédéterminés, augmentant à terme le risque de développer une MA.

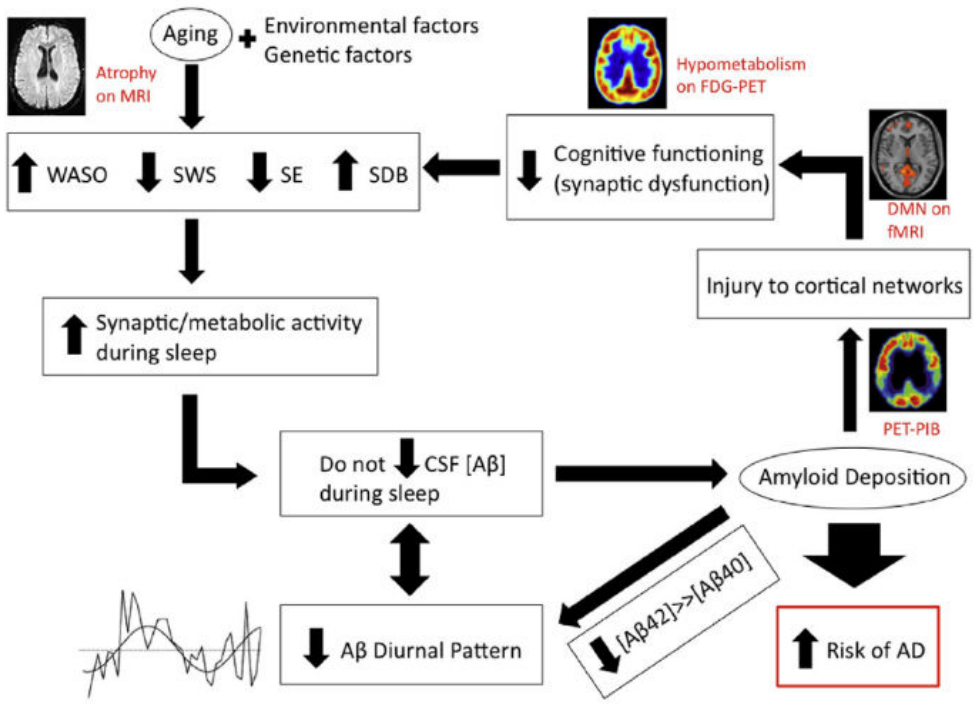


Figure 17: Modèle hypothétique des liens entre le sommeil et les mécanismes physiopathologiques de la maladie d'Alzheimer. *D'après Lucey & Bateman (2014).*
Abréviations : CSF, liquide cérébro-spinal; DMN, réseau du mode par défaut; SE, efficacité de sommeil; SWS, sommeil à ondes lentes; SDB, syndrome d'apnées du sommeil; WASO, durée des éveils nocturnes.

D'un point de vue topographique, nos travaux semblent en accord avec le modèle proposé par Lucey & Bateman en 2014 (voir la **Figure 17** ci-dessous). Selon ce modèle, les troubles du sommeil favoriseraient la propagation des dépôts amyloïdes dans les régions du DMN, provoquant à terme leur hypométabolisme et des dysfonctions cognitives.

4.3. SPECIFICITE DES ASSOCIATIONS : SL *VERSUS* SP

L'une des particularités de ce travail de thèse a été de focaliser chacune des études réalisées sur des aspects distincts mais complémentaires de la qualité du sommeil dans le vieillissement, dans le but de révéler d'éventuelles caractéristiques spécifiques à chacun d'entre-eux.

Ainsi, nos résultats mettent en évidence que chez les sujets âgés, l'altération des premiers cycles de sommeil et de l'activité à ondes lentes est associée à un hypométabolisme, une hypoperfusion et/ou une diminution du volume de substance grise, principalement au niveau des aires fronto-cingulaires et hippocampiques. Ces zones cérébrales sont classiquement touchées par les effets du vieillissement (Kalpouzos et al., 2009; Lockhart and DeCarli, 2014), et affectées précocément par les processus physiopathologiques de la MA (de Flores et al., 2015a; Villemagne and Chételat, 2016). Bien que nous développerons ce point ultérieurement (voir le paragraphe 4.4 ci-dessous), plusieurs éléments semblent suggérer que chez les sujets âgés sains, ces modifications cérébrales liées à l'âge entraînent une réduction de la qualité du SL, sous-tendant elle-même une diminution des performances cognitives (Mander *et al.*, 2013; Dube *et al.*, 2015; Latreille *et al.*, 2019, et voir les analyses de médiation réalisées dans la première étude de cette thèse). En effet, les aires fronto-cingulaires et l'hippocampe sont connues pour être impliquées dans la physiologie du SL, et

notamment pour sous-tendre la génération des ondes lentes et des fuseaux de sommeil (Massimini et al., 2004; Murphy et al., 2009; Schabus et al., 2007). De plus, elles sont impliquées dans le processus de consolidation mnésique dépendant du sommeil (Buzsáki, 1996; Harand et al., 2012; Takashima et al., 2006), et dans le fonctionnement exécutif et mnésique de manière plus large (Eichenbaum, 2017; Stuss, 2011). Ainsi, leur altération, en lien avec un sommeil moins réparateur, pourrait favoriser à terme le déclin cognitif. Toutefois, contrairement à ce que nous attendions, nous n'avons pas observé de lien entre la qualité du SLP et la pathologie amyloïde dans notre cohorte. Cette absence de lien pourrait s'expliquer par la nature et la temporalité des mesures de la pathologie amyloïde utilisées. En effet, les mesures en TEP sont moins dynamiques que les niveaux de peptide Aβ dosés dans le LCS, potentiellement plus enclins à révéler des associations directes.

En revanche, à défaut d'être fortement associée à la qualité du SLP, nous montrons que la pathologie amyloïde est significativement liée à la présence d'un SAOS et à l'altération de la microstructure du SP. Il est d'ailleurs important de mentionner que les apnées du sommeil sont souvent particulièrement sévères en SP, de par les caractéristiques physiologiques de ce stade de sommeil, et notamment de son atonie musculaire caractéristique, favorisant les dépressions respiratoires (Varga and Mokhlesi, 2019). Ainsi, la présence d'un SAOS pourrait être un facteur non négligeable participant à la fragilisation de ce stade de sommeil. De manière intéressante, si la proportion de SP reste relativement stable chez les sujets âgés (Ohayon et al., 2004), elle est en revanche significativement réduite chez les patients MA (Petit et al., 2004). De plus, plusieurs études longitudinales récentes montrent que l'altération du SP est prédictive du déclin cognitif (Pase et al., 2017; Song et al., 2015). Ainsi, les liens entre l'altération de la microstructure du SP

et la pathologie amyloïde semblent renforcer l'idée selon laquelle l'altération du SP pourrait constituer un marqueur précoce d'appartenance au continuum Alzheimer.

De manière intéressante, nous observons que l'augmentation de la charge amyloïde, en lien avec la sévérité du SAOS et les altérations de la microstructure du SP, s'accompagne de phénomènes d'hyperperfusion et/ou hypermétabolisme. Cette observation est particulièrement évidente dans la troisième étude portant sur le SAOS, où ces modifications cérébrales sont colocalisées au niveau du cortex cingulaire postérieur et du précunéus, suggérant l'existence de mécanismes sous-jacents communs aux deux phénomènes. Ces résultats semblent renforcer l'hypothèse selon laquelle l'hyperactivité neuronale, potentiellement en réaction à des processus neuroinflammatoires réactionnels, serait un mécanisme causal sous-tendant les liens entre une mauvaise qualité de sommeil et l'augmentation des dépôts amyloïdes. De plus, l'hyperperfusion et l'hypermétabolisme accompagnant l'augmentation de charge amyloïde semblent constituer des phénomènes aigus, qui pourraient précéder l'apparition d'un hypométabolisme et d'une atrophie (Oh et al., 2016).

4.4. TEMPORALITE ET DYNAMIQUE DES LIENS ENTRE SOMMEIL, INTEGRITE CEREBRALE ET COGNITIVE

L'observation selon laquelle les mécanismes du sommeil et les régions touchées par les processus physiopathologiques de la MA présentent des similitudes d'un point de vue topographique soulève la question de la causalité et de la temporalité des liens entre les modifications du sommeil, et les altérations cérébrales et cognitives liées à l'âge ou aux effets de la pathologie.

Comme abordé dans la partie introductive de cette thèse, l'hypothèse actuelle dominante est que ces associations seraient bidirectionnelles : les effets du vieillissement et la présence de la pathologie dans des régions impliquées dans les mécanismes du sommeil entraîneraient des troubles du sommeil, tandis que les problèmes de sommeil pourraient exacerber le développement des pathologies amyloïde et tau, créant ainsi un cercle vicieux augmentant le risque de déclin cognitif (Ju *et al.*, 2014; Lucey and Bateman, 2014 ; **Figure 17**). Cependant, la compréhension de la temporalité et de la directionnalité de ces associations au cours de la vie et des différents stades de progression de la pathologie reste aujourd'hui partielle, manquant d'arguments expérimentaux afin d'appuyer de manière forte cette hypothèse.

Les travaux menés dans le cadre de cette thèse permettent d'apporter de premiers éléments de réponse. En effet, les analyses de médiation réalisées dans la première étude de cette thèse montrent que la fragmentation des premiers cycles de sommeil médie la relation entre l'hypométabolisme fronto-hippocampique et la diminution des performances cognitives. Ainsi, ces résultats montrent que les altérations cérébrales liées à l'âge ou à la présence de la pathologie provoquent des modifications de la qualité du sommeil lent, ce qui a un impact délétère sur les performances cognitives. Ces résultats vont dans le sens de ceux retrouvés par d'autres équipes ayant montré que les modifications du sommeil résultent des altérations cérébrales chez les personnes âgées (Dube et al., 2015; Latreille et al., 2019; Mander et al., 2013). Cependant, ces observations s'appuient sur des analyses de médiations réalisées sur la base de données transversales, et n'excluent pas l'existence potentielle du lien inverse, selon lequel les troubles du sommeil pourraient être un facteur aggravant les altérations cérébrales. En effet, nous pouvons formuler l'hypothèse selon laquelle ce lien inverse serait principalement observable chez les sujets jeunes ou d'âge

intermédiaire, c'est-à-dire être majoritairement mesurables en amont des effets du vieillissement sur l'intégrité cérébrale. Ainsi, les études longitudinales pourraient permettre de clarifier la temporalité et la dynamique des associations entre sommeil, intégrité cérébrale et cognitive, qui comme nous venons de le discuter, pourraient varier selon les périodes de vie considérées et l'avancée dans la pathologie.

Les résultats de cette thèse suggèrent toutefois que les liens entre sommeil et intégrité cérébrale existent de façon précoce, et pourraient même précéder l'apparition des premières manifestations cliniques de la MA. En effet, nous montrons dans la première étude de thèse que les déficits cognitifs des patients SCD et MCI ne sont pas liés à la fragmentation des premiers cycles de sommeil. De plus, les résultats de la troisième étude montrent même que la présence d'un SAOS non traité est associée à des modifications cérébrales asymptomatiques, chez les sujets âgés cognitivement sains, sans lien significatif avec les performances attentionnelles, exécutives, de mémoire de travail ou de mémoire épisodique, mesurées lors d'une évaluation neuropsychologique classique. Cependant, les régions concernées (i.e., le cortex préfrontal ventromédian, l'hippocampe, le cortex cingulaire postérieur et le précunéus) étant impliquées dans le fonctionnement cognitif (Cavanna and Trimble, 2006; Eichenbaum, 2017; Leech and Sharp, 2014; Stuss, 2011), et touchées précocément par les mécanismes physiopathologiques de la MA (Braak and Braak, 1991; de Flores et al., 2015a; Thal et al., 2002; Villemagne and Chételat, 2016), leur fragilisation en lien avec les problèmes de sommeil pourrait contribuer au déclin cognitif, à plus long terme. Le maintien de performances cognitives dans les normes, malgré les associations délétères entre certaines altérations du sommeil et la pathologie amyloïde notamment, suggère l'existence d'une fenêtre temporelle chez les sujets âgés sains durant laquelle des mécanismes de

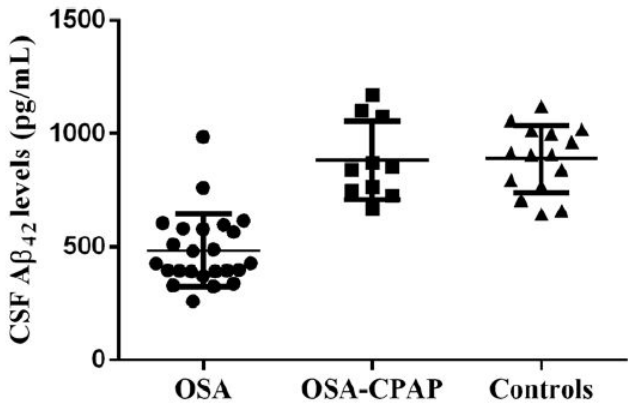
compensation se mettent en place. Ainsi, le maintien d'une qualité de sommeil optimale pourrait être l'un des mécanismes participant à la résilience face à la pathologie (Parrino and Vaudano, 2018). En effet, si nous montrons que certains troubles du sommeil sont associés à des altérations cérébrales asymptomatiques, ces résultats sont valables à l'échelle du groupe, mais n'excluent pas des variations inter-individuelles notamment si l'on compare des sujets présentant une haute ou une basse réserve cognitive. En effet, nous pouvons supposer que des personnes présentant une haute réserve cognitive résisteraient mieux aux effets du vieillissement, et présenteraient une qualité de sommeil plus préservée, permettant de maintenir un bon fonctionnement cognitif. En revanche, les personnes présentant une faible réserve cognitive pourraient être plus susceptibles d'exprimer des déficits cognitifs associés, même subtils.

4.5. IMPLICATIONS CLINIQUES

Nous avons montré que la qualité du sommeil est un facteur significativement associé aux altérations cérébrales dans le vieillissement, certaines étant liées à une diminution des performances cognitives (restant toutefois dans les normes pour l'âge et le niveau d'éducation), d'autres étant asymptomatiques. Ainsi, le sommeil pourrait être un facteur participant à la résilience face aux premières altérations neuropathologiques de la MA, notamment la présence des dépôts amyloïdes, avant l'apparition des premiers déficits cognitifs. En ce sens, dépister les pathologies du sommeil chez les personnes âgées, et les traiter afin de maintenir une qualité de sommeil optimale pourrait pemettre de compenser les premiers effets de la pathologie et de ralentir le déclin cognitif.

De manière intéressante, nous montrons que le SAOS est associé à des altérations cérébrales asymptomatiques au niveau du cortex cingulaire postérieur et du précunéus, incluant une augmentation de la charge amyloïde. De plus, il pourrait être à l'origine, au moins en partie, de la fragmentation des premiers cycles de sommeil étudiée dans la première étude de cette thèse. Plusieurs éléments suggèrent que le traitement du SAOS par pression positive continue (PPC) pourrait représenter une piste thérapeutique intéressante afin de maintenir une qualité de sommeil optimale chez les personnes âgées. En effet, il a été montré que le traitement du SAOS par PPC permet de réduire les symptômes de somnolence diurne (McMillan et al., 2014), d'améliorer les performances cognitives (Bucks et al., 2013; Davies and Harrington, 2016; Ferini-Strambi et al., 2013; Olaithe and Bucks, 2013), principalement au niveau exécutif. Le traitement par PPC a également été associé à une normalisation de certaines altérations cérébrales, même si peu d'études ont été réalisées à ce jour, et que les effets de la PPC sur les altérations cérébrales associées au SAOS restent mal connus (Ferini-Strambi et al., 2013).

Plusieurs études récentes se sont intéressées aux modifications des niveaux de peptide Aβ dans le LCS de participants présentant un SAOS, suite à un traitement par PPC. Ainsi, les patients SCD présentant un SAOS non traité possèdent des niveaux d'Aβ42 dans le LCS plus faibles, reflétant une accumulation plus importante au niveau cérébral (Liguori et al., 2017b). En revanche, les patients traités par PPC depuis plus d'un an avec une bonne compliance au traitement présentent des niveaux d'Aβ42 comparables aux contrôles (voir la **Figure 18** ci-dessous) (Liguori et al., 2017b). Il est à noter que dans cette étude, les niveaux de pathologie tau ne différaient pas entre les groupes.



<u>Figure 18:</u> Niveaux de peptide Aβ42 dans le LCS de patients SCD présentant un SAOS non traité *(gauche)***, traité par PPC** *(centre)* **ou ne présentant pas de SAOS** *(droite)*.

D'après Liguori et al., (2017b).

Une étude de cas longitudinale (Liguori et al., 2017a) réalisée par la même équipe a révélé qu'un patient SCD présentant un SAOS possédait en baseline des niveaux pathologiques de peptide Aβ42 (avec des ratios t-tau/Aβ42 et Aβ42/Aβ40 suggestifs d'une MA), sans toutefois présenter d'anomalie au niveau des dosages de protéines t-tau, p-tau, des orexines, de l'IRM structurale, ni du métabolisme en TEP-FDG. De manière intéressante, après un an de traitement par PPC, ce patient a présenté une normalisation des niveaux de peptide Aβ42, des ratios t-tau/Aβ42 et Aβ42/Aβ40, de sa plainte cognitive, et une amélioration de la qualité de sommeil (avec une augmentation de l'efficacité, de la continuité du sommeil, et des stades N3 et SP en PSG). Cette étude de cas est la première à s'intéresser à l'effet du traitement par PPC sur les biomarqueurs de la MA en utilisant un design longitudinal, mais mérite d'être répliquée sur de larges échantillons de volontaires sains et de patients SCD ou MCI. Enfin, une dernière étude récente (Ju et al., 2019) a montré que le traitement par PPC permettrait d'améliorer la qualité du sommeil lent profond, et qu'une meilleure activité à ondes lentes consécutive au traitement était elle-même corrélée à une diminution des niveaux de peptide Aβ.

L'ensemble de ces études suggère donc que le traitement par PPC du SAOS est une piste thérapeutique prometteuse, pouvant avoir un impact positif sur la pathologie amyloïde. Cependant, les effets du traitement par PPC sur la charge amyloïde globale mesurée en TEP, ainsi que sur un éventuel ralentissement du taux d'accumulation de la pathologie au cours du temps n'ont jamais été explorés. De plus, il ne semble pas y avoir d'effet direct sur la pathologie tau.

En parallèle, un certain nombre d'interventions non pharmacologiques semblent également constituer des pistes intéressantes afin d'améliorer la qualité du sommeil dans le vieillissement, de manière directe et/ou via une réduction des facteurs associés à une moins bonne qualité de sommeil chez les sujets âgés, comme l'anxiété et la dépression. Parmi elles, la pratique de la méditation, permettant de développer des stratégies de régulation attentionnelle et émotionnelle, semble une piste prometteuse afin d'améliorer la qualité de vie des personnes âgées (voir la **Figure 19** ci-dessous). De manière intéressante, les corrélats cérébraux de la méditation pleine conscience incluent des régions altérées dans le vieillissement, touchées précocément par les mécanismes physiopathologiques de la MA, et impliquées dans la génération et le maintien des rythmes du sommeil, dont le cortex préfrontal, les aires cingulaires antérieures et postérieures, et l'insula (voir la **Figure 19** et la revue de Tang *et al.*, 2015). Ainsi, la pratique de la méditation permettrait de réduire le stress, l'anxiété, la dépression, et certains problèmes de sommeil (Black et al., 2015; Chen et al., 2012; Chételat et al., 2018; Innes and Selfe, 2014). Une étude récente a par exemple démontré que suite à un entrainement à la méditation, on observe une augmentation de la puissance des oscillations de basse fréquence (1 à 12 Hz, surtout centrés autour du rythme theta) au cours du SL, surtout au niveau des dérivations préfrontales et pariétales (Dentico et al., 2016). Cependant,

de plus amples recherches sont nécessaires afin de préciser les effets à long-terme d'un entraînement à la méditation sur la qualité du sommeil, l'intégrité cérébrale et le risque de démence.

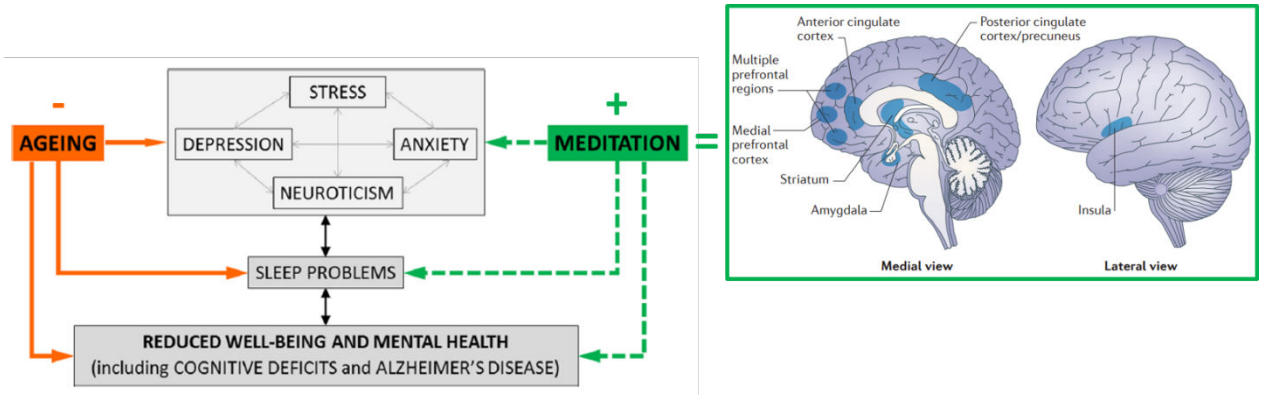


Figure 19: Corrélats cognitivo-comportementaux et cérébraux de la méditation.

La méditation aurait un impact positif sur les facteurs psycho-affectifs affectant négativement la qualité du sommeil, et permettrait ainsi d'améliorer la qualité de vie des personnes âgées, et de réduire le déclin cognitif (gauche). Les corrélats cérébraux de la méditation de pleine conscience sont représentés à droite.
Figure adaptée de Chételat et al., 2018 *(gauche)* et Tang et al., 2015 *(droite)*.

4.6. LIMITES ET PERSPECTIVES DE RECHERCHE

Au cours de ce travail de thèse, notre objectif a été de contribuer à approfondir la compréhension des liens entre les principales modifications objectives du sommeil dans le vieillissement, les altérations cérébrales structurales, fonctionnelles et moléculaires, ainsi que les performances cognitives. Si nos résultats permettent de confirmer qu'une mauvaise qualité de sommeil, mesurée de façon objective, est associée à des altérations cérébrales dans des régions touchées précocément

au cours du vieillissement et par les processus physiopathologiques de la MA, plusieurs limites doivent être mentionnées.

Tout d'abord, nous avons observé des liens significatifs entre la qualité objective du sommeil et l'intégrité cérébrale, mais nous n'avons pas ou peu mis en évidence d'associations avec les performanes cognitives, notamment mnésiques, malgré l'implication de régions cérébrales sous-tendant la mémoire épisodique. Si nous interprétons cette observation comme le signe que les liens entre le sommeil et l'intégrité cérébrale sont précoces, et précèdent l'apparition des déficits cognitifs, cette hypothèse doit être renforcée par des analyses complémentaires. En effet, nous avons créé des scores composites pour chaque domaine cognitif, à partir d'une évaluation neuropsychologique. Si ce type de score a l'avantage de représenter de façon robuste les fonctions cognitives et de conserver une bonne puissance statistique, en minimisant la multiplication des scores utilisés dans les analyses, ils ne sont pas construits pour être particulièrement sensibles à la qualité de sommeil. En effet, des tâches de consolidation mnésique dépendantes du sommeil seraient probablement plus enclines à révéler des liens avec les performances de mémoire épisodique (Mander et al., 2013, 2015). Toutefois, nous pouvons également mentionner que les scores composites issus d'épreuves neuropsychologiques classiques se rapprochent davantage des scores disponibles et utilisés en pratique clinique, en comparaison d'épreuves plus expérimentales.

De plus, si nous avons utilisé des mesures de l'intégrité structurale et fonctionnelle de la substance grise (i.e., volume, perfusion, et métabolisme de la substance grise), ainsi que de la pathologie amyloide, il sera important de compléter ces investigations en utilisant d'autres modalités de neuroimagerie. En effet, nous ne disposions pas de mesure de la pathologie tau, désormais

nécessaire afin de comprendre les mécanismes sous-tendant les liens entre une mauvaise qualité de sommeil et le risque de MA dans leur ensemble, mais aussi de mieux caractériser les populations étudiées, à la lumière des nouvelles recommandations du NIA-AA pour la recherche (Jack et al., 2018a). Des études en connectivité fonctionnelle permettront également de mettre en évidence d'éventuelles anomalies au sein du DMN.

Enfin, l'une des principales limites de ce travail de recherche réside dans son caractère transversal. En effet, si nos travaux permettent d'apporter de premiers éléments de réponse et de formuler des hypothèses concernant la directionalité et la temporalité des associations entre la qualité du sommeil, l'intégrité cérébrale et cognitive, ils doivent impérativement être complétés d'études longitudinales. Les études futures utilisant les données issues du suivi à 18 mois des participants du protocole Age-Well permettront de déterminer si les altérations cérébrales « silencieuses » et asymptomatiques que nous observons notamment dans l'étude 3, s'aggravent au cours du temps et/ou sont associées à un déclin objectif des performances cognitives. De plus, il serait également intéressant d'étudier la qualité du sommeil objective des personnes d'âge intermédiaire, afin de voir si l'installation de certaines anomalies du sommeil lors de cette période conditionne le développement de la pathologie amyloïde dans le vieillissement.

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6. ANNEXES

6.1. TABLEAU RECAPITULATIF DES LIENS ENTRE SOMMEIL ET COGNITION DANS LE VIEILLISSEMENT.

Paramètre de sommeil	Méthode de mesure	Fonctionnement cognitif global [1] *(Longitudinal : déclin cognitif, risque de démence)*	Attention et vitesse de traitement [2]	Mémoire de travail [3]	Fonctions exécutives [4]	Mémoire déclarative [5]
Qualité globale	Subjective	Chang-Quan 2012, Gildner 2014, Nebes 2009, Saint Martin 2012 ***Longitudinal : Shi 2018, Bubu 2017***	Saint Martin 2012	Almondes 2016, Nebes 2009	Almondes 2016, Nebes 2009 *Longitudinal : Blackwell 2014*	Tsapanou 2017
Latence d'endormissement	Subjective	Chang-Quan 2012, Tworoger 2006 *Longitudinal : Suh 2018*	Schmutte 2007	Cavuoto 2016, Schmutte 2007		Schmutte 2007
	Objective	Blackwell 2006, Luik 2015 *Longitudinal: Diem 2016, Yaffe 2007*			Luik 2015 *Longitudinal : Yaffe 2007*	Cavuoto 2016, Luik 2015
Efficacité de sommeil	Subjective	Chang-Quan 2012 *Longitudinal : Niu 2016*				
	Objective	Blackwell 2006 *Longitudinal : Diem 2016, Yaffe 2007*	Lambiase 2014, Miyata 2013	Miyata 2013	*Longitudinal : Blackwell 2014, Yaffe 2007*	
Courte durée de sommeil	Subjective	**Lo 2016** ***Longitudinal : Liang 2018, Virta 2013***		**Lo 2016**	**Lo 2016**	**Lo 2016**
Longue durée de sommeil	Subjective	**Lo 2016** ***Longitudinal : Kim 2016, Liang 2018; Virta 2013***		**Lo 2016**	**Lo 2016**	**Lo 2016**
	Objective	Blackwell 2011			Spira 2017	Cavuoto 2016
Fragmentation du sommeil et nombre de réveils nocturnes	Subjective	Tworoger 2006 *Longitudinal : Johar 2016*				
	Objective	*Longitudinal : Lim 2013*			Wilckens 2014 *Longitudinal : Blackwell 2014*	Wilckens 2014
Durée des éveils nocturnes	Subjective			Cavuoto 2016		
	Objective	Blackwell 2006, 2011 *Longitudinal : Yaffe 2007*			Spira 2017 *Longitudinal : Blackwell 2014, Yaffe 2007*	Cavuoto 2016, Spira 2017
Somnolence diurne excessive	Subjective	Ohayon & Vecchierini 2002 *Longitudinal : Foley 2001, Gabelle 2017, Jaussent 2012, Merlino 2010, Nakakubo 2018*	Tsapanou 2016 (transversal et *longitudinal)*		Ramos 2016 (transversal et *longitudinal)*	
Durée des siestes	Objective	Blackwell 2006, Keage 2012 (associations inverses) *Longitudinal : Yaffe 2007*				
Altérations circadiennes	Objective	Cochrane 2012 *Longitudinal : Rogers-Soeder 2018, Tranah 2011*	Luik 2015, Oosterman 2009		Luik 2015, Oosterman 2009, *Longitudinal : Walsh 2014*	Oosterman 2009
Stade N1	Objective	Blackwell 2011 *Longitudinal : Song 2015*			*Longitudinal : Song 2015*	
Stade N2 et fuseaux de sommeil	Objective	Taillard 2019 (transversal et *longitudinal*)	Lafortune 2014		Lafortune 2014 *Longitudinal : Taillard 2019*	Lafortune 2014, Mander 2014, Seeck-Hirschner 2012
Stade N3 et activité à ondes lentes	Objective	Taillard 2019			Anderson & Horne 2003, Lafortune 2014	Mander 2013, 2015
Sommeil paradoxal	Objective	Blackwell 2011 *Longitudinal : Pase 2017, Song 2015*				Lafortune 2014
Apnées du sommeil	Objective	***Longitudinal : Leng 2017, Zhu 2017***	**Bucks 2013, Olaithe 2018, Stranks & Crowe 2016**	**Bucks 2013, Stranks & Crowe 2016**	**Olaithe 2018, Stranks & Crowe 2016**	**Bucks 2013, Olaithe 2018, Stranks & Crowe 2016**

Abréviations : CERAD: Consortium to Establish a Registry for Alzheimer's disease, CDS: Cognitive Difficulties Scale, CPT: Conners' Continuous Performance, CVLT: California Verbal Learning Test, HVLT-R: Hopkins Verbal Learning Test Revised, MCI: Mild Cognitive Impairment, MMSE: Mini Mental State Examination, RAVLT: Rey Auditory Verbal Learning Test, RBANS: Repeatable Battery for the Assessment of Neuropsychological Status, SRT: Selective Reminding Task, REM: Rapid Eye Movement, TICS: Telephone Interview of Cognitive Status, TMT : Trail Making Test, WAIS: Wechsler Adult Intelligence Scale.

Les méta-analyses sont indiquées en gras dans le tableau. Lorsqu'une méta-analyse était disponible, les autres études montrant le même type d'associations n'ont pas été mentionnées dans le tableau. Les mesures subjectives de sommeil ont été recueillies par le biais de questionnaires ou d'entretiens cliniques, tandis que les mesures objectives regroupent les données issues d'enregistrements d'actimétrie ou de polysomnographie.

1 Le fonctionnement cognitif global a été mesuré grâce au MMSE dans toutes les études, sauf dans *Ohayon et al., 2002* (CDS), *Nebes et al., 2009* (RBANS), *Taillard et al., 2019* (risque de posséder un SCD ou MCI), *Gildner et al., 2014* et *Luik et al., 2015* (scores composites). Le déclin cognitif a été quantifié par le déclin au score du MMSE *(Yaffe et al., 2007 ; Jaussent et al., 2012 ; Keage et al., 2012 ; Song et al., 2015 ; Niu et al., 2016 ; Gabelle et al., 2017 ; Taillard et al., 2019)*, l'incidence du MCI et/ou de la démence *(Suh et al., 2018 ; Diem et al., 2016 ; Foley et al., 2001 ; Merlino et al., 2010 ; Bubu et al., 2017)*, le déclin au score de la TICS *(Johar et al., 2016)* ou le déclin de scores composites globaux *(Lim et al., 2013)*.

2 Les performances attentionnelles et de vitesse de traitement au temps de réalisation de la partie A du TMT *(Saint-Martin et al., 2012 ; Tsapanou et al., 2016)*, ou aux performances au subtest « Codes » de la WAIS *(Schmutte et al., 2007 ; Lambiase et al., 2014 ; Luik et al., 2015)*, au test du 0-back *(Miyata et al., 2013)*, au CPT *(Lafortune et al., 2014)*, ou à des scores composites *(Oosterman et al., 2009)*.

3 Les performances de mémoire de travail ont été évaluées par le test de n-back *(Nebes et al., 2009 ; Miyata et al., 2013 ; Cavuoto et al., 2016)*, les empans envers de la WAIS *(Schmutte et al., 2007 ; de Almondes et al., 2016)* ou les performances à la SRT *(Schmutte et al., 2007)*.

4 Les fonctions exécutives ont été évaluées grâce à la partie B du TMT *(Nebes et al., 2009 ; Spira et al., 2017)*, la Batterie Rapide d'Efficience Frontale *(de Almondes et al., 2016)*, les fluences

verbales *(Anderson & Horne 2003 ; Lafortune et al., 2014 ; Luik et al., 2015 ; Spira et al., 2017)*, le temps d'interférence au test de Stroop *(Luik et al., 2015)*, le test de la Tour de Londres *(Anderson & Horne 2003)* ou des scores composites *(Oosterman et al., 2009 ; Wilckens et al., 2014 ; Ramos et al., 2016)*. Le déclin des fonctions exécutives a été quantifié par la diminution des performances à la partie B du TMT dans toutes les études, excepté dans *Ramos et al., 2016* et *Walsh et al., 2014* (déclin à un score composite).

5 La mémoire déclarative à long-terme a été mesurée par les scores de rappel libre différé aux tâches d'apprentissage de liste de mots du HVLT-R *(Cavuoto et al., 2016)*, du CVLT *(Spira et al., 2017)*, du RAVLT *(Luik et al., 2015)*, de la CERAD *(Wilckens et al., 2014)*, le rappel à la Figure de Rey *(Seeck-Hirschner et al., 2012)*, les performances aux subtests « Vocabulaire » et « Information » de la WAIS *(Schmutte et al., 2007)*, ou des scores composites *(Oosterman et al., 2009 ; Lafortune et al., 2014 ; Tsapanou et al., 2017)*.

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6.2. TABLEAU RECAPITULATIF DES LIENS ENTRE SOMMEIL ET NEUROIMAGERIE DANS LE VIEILLISSEMENT.

Paramètre de sommeil		Volume de substance grise	Perfusion ou métabolisme cérébral [1]	Charge Amyloïde [2]	Pathologie Tau [3]
Qualité globale subjective		Frontal (Sexton 2014), hippocampe (Alperin 2018, Liu 2018), thalamus (Liu 2018), cortex pariétal et amygdale (Alperin 2018) *Longitudinal : cortex frontal, temporal, pariétal (Sexton 2014)*		Niveau global (Sprecher 2017), cortex fronto-pariétal (Sprecher 2017) *Longitudinal : niveau global (Fjell 2018)*	Niveau global (Sprecher 2017) *Longitudinal : niveau global (Fjell 2018).*
Privation de sommeil			Cortex frontal (Wu 2006, Zhou 2019), thalamus, striatum (Wu 2006), fusiforme, hippocampe/parahippocampe (Zhou 2019)	Niveau global (Ooms 2014)	Niveau global (Holth 2019)
Somnolence diurne excessive		CPF ventro-médian (Killgore 2012) *Longitudinal : cortex temporal (Carvalho 2017)*		Cortex fronto-pariétal (Sprecher 2015) *Longitudinal : niveau global (Spira 2018), cortex cingulaire antérieur, postérieur et précuneus (Carvalho 2018)*	Niveau global (Sprecher 2017)
Siestes				Niveau global (Ju 2013)	Niveau global (Lucey 2019)
Latence d'endormissement				Niveau global (latence subjective : Brown 2016 et objective : Ettore 2019), cortex frontal (latence subjective: Branger 2016).	
Courte durée de sommeil (subjective)		Atrophie globale (Lo 2014), cortex occipital (Spira 2016). *Longitudinal : cortex frontal (Spira 2016)*		Niveau global et précunéus (Spira 2013)	
Longue durée de sommeil (subjective)		Atrophie globale (Westwood 2017) *Longitudinal : cortex frontal (Spira 2016)*			
Efficacité de sommeil (objective)				Niveau global (Ju 2013, Molano 2017, Ettore 2019)	Niveau global (Ju 2017)
Réveils nocturnes ou précoces (subjective)		COF (Stoffers 2012, réveils précoces), insula (Branger 2016, réveils nocturnes)			
Réveils et Fragmentation (objective)		Cortex frontal (Lim 2016)		Niveau global (Wilckens 2018, Lucey 2019, Ettore 2019)	Niveau global (Lim 2013)
Sommeil lent profond (activité à ondes lentes)		Cortex frontal (Mander 2013, Dubé 2015, Latreille 2019), cortex pariétal et insula (Dubé 2015)	CPF dorsolatéral (Wilckens 2016)	Niveau global (Ju 2017, Varga 2016, Winer 2019), CPF (Mander 2015).	Niveau global (Lucey 2019), lobe temporal médial (Winer 2019 : couplage fuseaux/OL)
Fuseaux de sommeil					Niveau global (Kam 2019), lobe temporal médial (Winer 2019 : couplage fuseaux/OL)
Sommeil paradoxal				Niveau global (diminution de la latence d'apparition du REM : Lucey 2019)	
SAOS	↘ *volume, perfusion, métabolisme.*	**Hippocampe/parahippocampe (Weng 2014, Huang 2019, Tahmasian 2016), cortex temporo-pariétal (Weng 2014, Shi 2017), cortex frontal (Shi 2017, Huang 2019), insula (Tahmasian 2016)**	Cortex pariéto-ocipital (Yaouhi 2009, Baril 2015, Joo 2007, Kim 2017), cortex frontal (Yaouhi 2009, Innes 2015, Kim 2017, Shiota 2014, Nie 2017), cortex temporal, hippocampe, parahippocampe (Innes 2015, Kim 2017, Joo 2017, Nie 2017), thalamus (Innes 2015)		
	↗ *volume, perfusion, métabolisme, Aβ, tau.*	CPF (Baril 2017), cortex pariéto-occipital (Baril 2017, Cross 2018), hippocampe (Cross 2018, Rosenzweig 2013)	Insula, ganglions de la base, zones limbiques (Baril 2015), cortex frontal (Nie 2017)	Niveau global (Elias 2018, Osorio 2014, Bu 2015, Liguori 2017), CCP/Précuneus et cortex temporal (Yun 2017). *Longitudinal : niveau global (Sharma 2018, Bubu 2019).*	Niveau global (Ju 2016, Osorio 2014, Bu 2015, Liguori 2017, Motamedi 2018). *Longitudinal : niveau global (Bubu 2019)*

Abréviations : ASL : Arterial Spin Labeling, FDG : ^{18}F-fluorodeoxyglucose, LCS: Liquide Cérébro-Spinal, SPECT: Single Photon Emission Computed Tomography, TEP: Tomographie par Emission de Positons.

Les méta-analyses sont indiquées en gras. Lorsqu'une méta-analyse était disponible, les autres études mettant en évidence le même type d'associations n'ont pas été mentionnées.

1 Les études ont mesuré la perfusion cérébrale par le biais de séquences ASL *(Innes et al., 2015 ; Nie et al., 2017 ; Zhou et al., 2019)* ou par SPECT *(Joo et al., 2007 ; Shiota et al., 2014 ; Baril et al., 2015 ; Kim et al., 2017)*, et le métabolisme cérébral du glucose par TEP-FDG *(Wu et al., 2006 ; Yaouhi et al., 2009 ; Wilckens 2016)*.

2 Les niveaux de pathologie amyloïde sont mesurés dans le LCS *(Ju et al., 2013 ; Ooms et al., 2014 ; Osorio et al., 2014 ; Varga et al., 2016 ; Liguori et al., 2017 ; Sprecher et al., 2017 ; Molano et al., 2017 ; Ju et al., 2017 ; Fjell et al., 2018 ; Sharma et al., 2018 ; Bubu et al., 2019)*, le sang *(Bu et al., 2015)* ou en TEP *(Spira et al., 2013; Mander et al., 2015; Sprecher et al., 2015; Branger et al., 2016; Brown et al., 2016; Yun et al., 2017; Elias et al., 2018; Wilckens et al., 2018; Spira et al., 2018; Carvalho et al., 2018; Lucey et al., 2019; Ettore et al., 2019; Winer et al., 2019; Bubu et al., 2019)*.

3 Les niveaux de pathologie tau sont mesurés dans le LCS *(Osorio et al., 2014 ; Ju et al., 2016 ; Liguori et al., 2017 ; Sprecher et al., 2017 ; Ju et al., 2017 ; Fjell et al., 2018 ; Bubu et al., 2019 ; Ju et al., 2019 ; Holth et al., 2019 ; Kam et al., 2019)*, le sang *(Bu et al., 2015 ; Motamedi et al., 2018)*, en TEP *(Lucey et al., 2019 ; Winer et al., 2019)*, ou à l'autopsie *(Lim et al., 2013)*.

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6.3. PROTOCOLE AGE-WELL (POISNEL *ET AL.*, ALZHEIMERS DEMENT (NY) 2018)

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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.

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

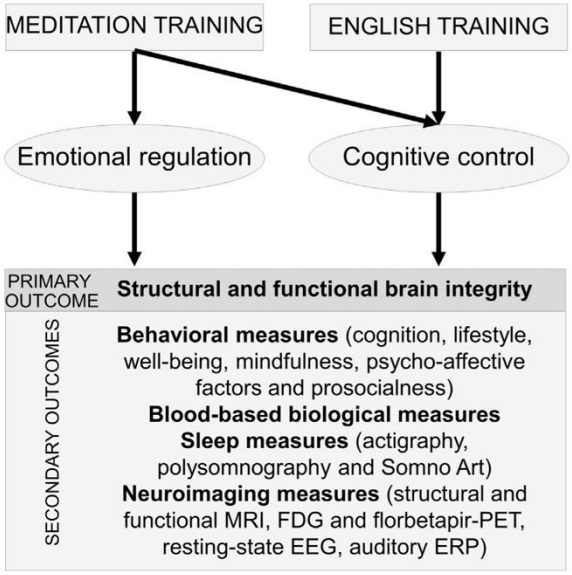

Fig. 1. Hypothetical model of the expected effects and mechanisms of the meditation and foreign language training interventions included in the Age-Well RCT. Meditation training is thought to promote both emotional regulation/positive affect and cognitive control. Foreign language training is expected 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

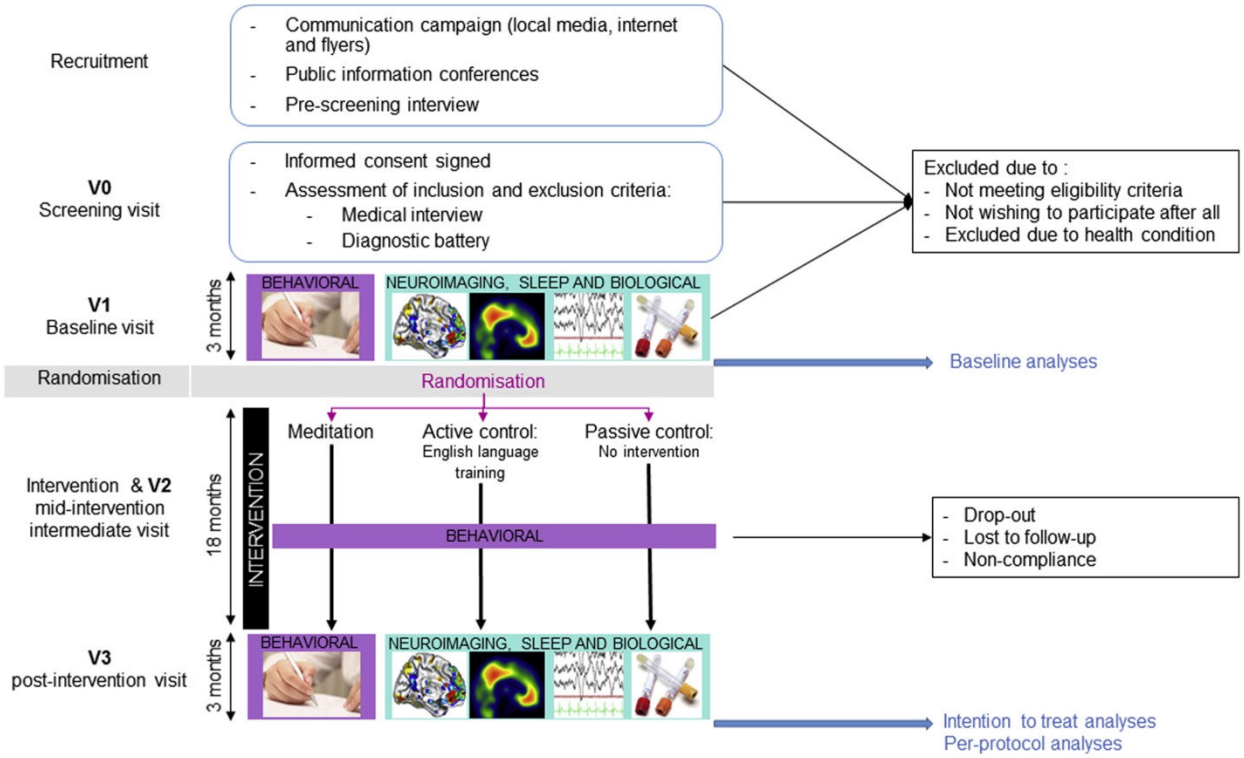

Fig. 2. Flow chart of the Age-Well RCT participants. The different steps are detailed in the text. The boxes at V1 and V3 depict the types of measurements that are collected. Abbreviation: RCT, randomized controlled trial.

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

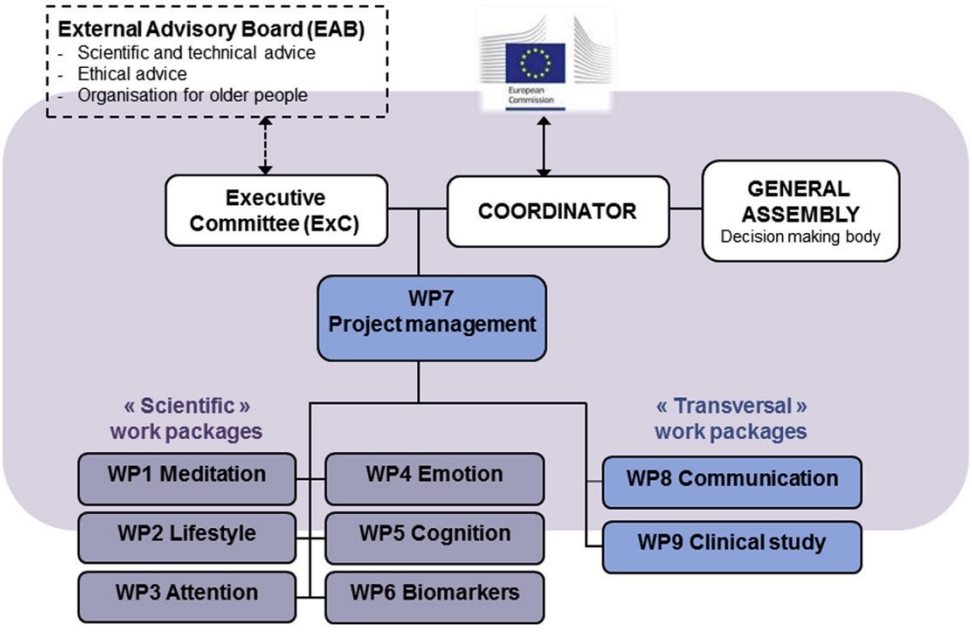

Fig. 3. Management structure of Medit-Ageing.

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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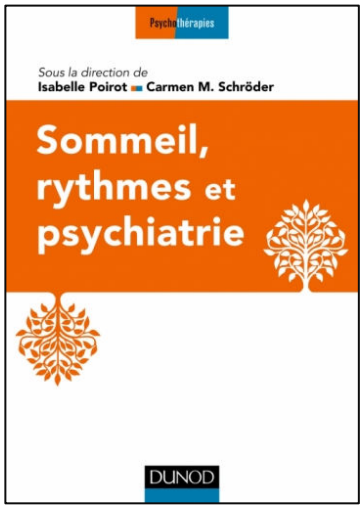
6.4. CHAPITRE « DEMENCES ET SOMMEIL » (ANDRE ET AL., 2016)

Ce chapitre fait partie du rapport « Sommeil, Rythmes et Psychiatrie » paru aux Editions Dunod en 2016.



Démences et sommeil

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Les patients atteints de maladies neurodégénératives se plaignent très fréquemment de troubles du sommeil. Ceux-ci altèrent la qualité de vie des patients et de leur entourage, et peuvent conduire à l'institutionnalisation des malades. L'objectif de ce chapitre est de décrire les altérations du sommeil observées dans plusieurs maladies neurodégénératives. Ainsi, nous nous intéresserons aux deux principales démences avec synucléinopathies, à savoir la démence parkinsonienne, et la démence à corps de Lewy, puis nous envisagerons la maladie d'Alzheimer et la maladie de Huntington.

1. La démence Parkinsonienne

Il s'agit d'une démence à prédominance sous-corticale qui survient au cours de l'évolution à long terme d'une maladie de Parkinson. Selon les résultats d'une méta-analyse (Aarsland 2005) et d'une cohorte de suivi (Sydney multicenter study, Hely *et al.*, 2008), la survenue de démence au cours de la maladie de Parkinson semble être quasi-inévitable avec une prévalence de 30% à 10 ans, 50% à 15 ans et 80% à 20 ans d'évolution. Le syndrome dysexecutif, les troubles attentionnels et le déficit mnésique d'allure sous corticale prédominent généralement le tableau cognitif et sont à l'origine d'une perte d'autonomie.

Les troubles du sommeil sont un symptôme fréquent chez les patients atteints de maladie de Parkinson, et incluent l'insomnie, des parasomnies telles que le trouble du comportement en sommeil paradoxal (TCSP) ou les mouvements périodiques des jambes, l'hypersomnie ainsi qu'une somnolence diurne excessive. Ceux-ci sont liés à l'atteinte du système dopaminergique, impliqué dans le contrôle du cycle de veille-sommeil et les mécanismes du sommeil paradoxal, ainsi qu'à l'accumulation de corps de Lewy au niveau du tronc cérébral et de l'hypothalamus.

L'architecture du sommeil est modifiée chez les patients parkinsoniens. Ainsi, le sommeil est plus fragmenté, avec des réveils fréquents. La proportion de stade N1 augmente tandis que celle de sommeil paradoxal diminue. De plus, le taux de sommeil paradoxal sans atonie musculaire augmente (Petit *et al.*, 2004 pour revue). Sur l'EEG, on observe un ralentissement des rythmes chez un tiers des patients dans les régions temporo-occipitales et frontales. Des analyses plus fines des tracés EEG révèlent que le nombre et la densité des fuseaux de sommeil, caractéristiques du stade 2 de sommeil lent, diminuent. En revanche, leur durée et leur amplitude augmentent (Christensen *et al.*, 2015). Une étude longitudinale, menée sur 68 patients parkinsoniens pour une période de suivi de 4 ans et demi, a montré que les patients présentant une altération de la densité, de l'amplitude et de la fréquence des fuseaux de sommeil dans les régions corticales postérieures lors de l'évaluation initiale sont plus susceptibles de développer une démence à l'issue du suivi (Latreille *et al.*, 2015). Ainsi, l'altération des fuseaux de sommeil pourrait être un marqueur précoce du déclin cognitif.

L'insomnie est également très fréquente chez les patients parkinsoniens, touchant entre 37 à 81% des patients, soit une proportion 2 à 3 fois supérieure à la population saine de même âge. Elle se

caractérise par des réveils nocturnes longs (plus d'un tiers de la nuit passé éveillé) et fréquents (2 à 5 par nuit chez 39% des patients), ou un éveil matinal précoce (chez près d'un patient sur quatre ; Tandberg *et al.*, 1998). L'insomnie peut être causée par la présence de troubles moteurs nocturnes (akinésie nocturne, dystonies, tremblements...), dont la fréquence augmente avec l'avancée de la pathologie et la dose des traitements dopaminergiques. Elle peut également être causée par des douleurs nocturnes (pour s'étirer, se retourner, se lever...). Enfin, une dépression coexistante serait un facteur de risque majeur et fréquent d'insomnie chez les patients atteints de maladie de Parkinson, provoquant des difficultés d'endormissement et de maintien du sommeil. Les traitements médicamenteux, en particulier les agonistes dopaminergiques, présenteraient également un effet « insomniant », et favoriseraient la fragmentation du sommeil ainsi que la diminution de l'efficacité de sommeil.

Les troubles du comportement en sommeil paradoxal (TCSP), sont très fréquents dans la maladie de Parkinson et correspondent à une extériorisation des rêves, couplée à une activité motrice excessive. Les TCSP sont le résultat d'une absence de frein moteur donc d'atonie musculaire lors du sommeil paradoxal, conduisant à l'apparition de comportements complexes lors du sommeil (cris, rires, coups...), qui peuvent représenter un danger pour le patient ou son conjoint (Gagnon *et al.*, 2002). Ils sont présents chez 30 à 60% des patients, et le diagnostic peut être évoqué lors de l'interrogatoire du patient ou du conjoint, et peut être confirmé par une vidéo-polysomnographie. Cet examen permet d'observer en particulier une augmentation de la quantité de sommeil paradoxal sans atonie musculaire et la présence de mouvements complexes des bras et des jambes, et des comportements anormaux voire violents lors du sommeil. Les études longitudinales ont montré que la présence de TCSP serait prédictive de l'émergence des maladies neurodégénératives (Iranzo

et al., 2006, 2014), car il anticiperait les symptômes moteurs, les hallucinations ou la démence de plusieurs années. En effet, il a été montré que plus de 80% des cas de TCSP idiopathique évolueront en synucléinopathie (Schenck *et al.*, 2013), en majorité la maladie de Parkinson ou la démence à corps de Lewy (Postuma *et al.*, 2009).

Enfin, les patients se plaignent fréquemment de somnolence diurne et d'hypersomnie. La somnolence diurne excessive (SDE) s'évalue au moyen de l'Echelle de Somnolence d'Epworth pour laquelle un score supérieur à 10 est synonyme de somnolence anormale. La SDE touche 15 à 50% des patients (Tan *et al.*, 2002), et peut culminer en attaques de sommeil chez 1 à 14% des patients (Ondo *et al.*, 2001), notamment lors de la conduite chez les patients parkinsoniens encore autonomes ce qui est une source d'accidents et constitue un risque de chutes élevé avec fractures chez tous les patients. Bien que la SDE soit peu souvent évoquée comme une plainte par les patients eux-mêmes, elle est très souvent rapportée par l'entourage proche. L'évaluation de la SDE peut être réalisée sans difficulté par l'observation du patient par la famille ou par les soignants en institution. L'auto-questionnaire de somnolence Epworth n'est pas adapté pour évaluer la SDE de ces patients, en raison de ses items qui ne sont pas cohérents avec les conditions de vie, d'autonomie et l'état cognitif dans ce type de pathologie.

La somnolence peut précéder la maladie de Parkinson de plusieurs années, mais elle s'aggrave souvent après l'introduction d'un traitement dopaminergique (Monaca *et al.*, 2006). La cause la plus classique de cette SDE est le manque de sommeil dû aux troubles moteurs nocturnes, mais sa sévérité est aussi associée à l'hypersomnie. La perte neuronale, notamment des neurones à hypocrétine (Fronczek *et al.*, 2012 ; Thannickal *et al.*, 2007), et la présence de corps de Lewy au

niveau des systèmes d'éveils, sont un mécanisme possible de la somnolence diurne excessive et de l'hypersomnie.

2. Démence à corps de Lewy

La démence à corps de Lewy représente environ un quart des cas de démence chez le sujet âgé, et est la seconde cause de démence la plus fréquente après la maladie d'Alzheimer. Elle se caractérise par des fluctuations de l'état cognitif (notamment de l'attention et de la vigilance), des hallucinations visuelles et des symptômes parkinsoniens. D'un point de vue physiopathologique, on retrouve la présence diffuse de corps de Lewy au niveau du tronc cérébral, puis leur propagation progressive des structures limbiques vers le néocortex associée à la présence de plaques amyloïdes. Les troubles du sommeil sont particulièrement fréquents dans la démence à corps de Lewy, concernant environ 70 % des patients. On retrouve toutes les anomalies de sommeil présentes dans la maladie de Parkinson. En revanche, le trouble du comportement en sommeil paradoxal est retrouvé de façon quasi constante chez ces patients, au point de permettre une distinction clinique entre la démence à corps de Lewy et la maladie d'Alzheimer, avant tout bilan neuropsychologique (Boeve *et al.*, 1998 ; Arnulf, 2012 pour revue). Comme pour la maladie de Parkinson, la présence de TCSP est un symptôme évocateur d'une démence à corps de Lewy, qui précèderait les symptômes cognitifs et moteurs parfois de plusieurs années (Claassen *et al.*, 2010 ; McKeith *et al.*, 2005).

Cependant, les troubles du sommeil dans la démence à corps de Lewy ont été beaucoup moins étudiés que dans la maladie d'Alzheimer ou la maladie de Parkinson. Les études systématiques en polysomnographie menées chez les patients atteints de démence à corps de Lewy afin d'explorer

l'architecture du sommeil et les altérations de sommeil autres que le TCSP sont peu nombreuses. Les quelques études menées révèlent toutefois que le sommeil paradoxal est quasiment constamment sans atonie musculaire, avec une fréquence importante de mouvements périodiques des jambes, et que les rythmes de base en EEG sont ralentis chez ces patients (Terzaghi *et al.*, 2013 ; Bonnani *et al.*, 2008 ; Fantini *et al.*, 2003).

3. Maladie d'Alzheimer

Les altérations du sommeil sont décrites très précocement dans la maladie d'Alzheimer. Ainsi, Beaulieu-Bonneau et Hudon (2009) rapportent, dans une méta-analyse de 18 études réalisées auprès de patients atteints de Mild Cognitive Impairment (MCI), que 14 à 59% de ces patients se plaignent de leur sommeil. Ces troubles peuvent être observés plusieurs années avant le diagnostic de maladie d'Alzheimer chez des sujets porteurs asymptomatiques de l'allèle APOE ε4, principal facteur de risque de maladie d'Alzheimer (Hita-Yañez *et al*., 2012), et sont dus à l'atteinte précoce de régions cérébrales et de voies impliqués dans la régulation des états de veille et de sommeil (Braak & Braak, 1991).

Contrairement aux troubles de mémoire qui sont qualitativement différents de ce qui est observé dans le vieillissement normal, certaines modifications du sommeil dans la maladie d'Alzheimer sont comparables ou sont une exagération de ce qui est observé physiologiquement chez le sujet âgé sain (Petit *et al*., 2004). On observe ainsi une fragmentation du sommeil, une diminution de l'efficacité de sommeil, une réduction importante de la quantité de sommeil lent profond en lien avec la sévérité de la démence et une somnolence diurne. Des analyses plus fines révèlent également des modifications du nombre, de l'amplitude ou de la densité des fuseaux et des

complexes K. Certains troubles sont, en revanche, spécifiques de la pathologie. Ainsi, l'atteinte du sommeil paradoxal est un élément caractéristique de la maladie d'Alzheimer. Toutefois, cette atteinte surviendrait à un stade relativement avancé de la démence (Montplaisir *et al*., 1995 ; mais voir également Gagnon *et al*., 2006 pour une étude mettant en évidence des quantités équivalentes de sommeil paradoxal chez des patients Alzheimer, dont les scores au MMS étaient compris entre 12 et 26, et des sujets témoins) et se traduit par un allongement de la latence d'apparition, une réduction de la durée moyenne des épisodes (Montplaisir *et al*., 1995) ainsi qu'une fragmentation de ce stade de sommeil (Onen & Onen, 2003). Les autres paramètres (densité des mouvements oculaires rapides, nombre d'épisodes et atonie musculaire) ne seraient pas modifiés (Montplaisir *et al*., 1995 ; Petit *et al*., 2004 pour revue). Cependant, cette atteinte du sommeil pourrait s'observer de manière bien plus précoce, chez les patients atteints de MCI (Hita-Yañez *et al*., 2012) et serait plus marquée chez les porteurs de l'allèle APOE ε4. Les patients présentent également une altération générale des rythmes circadiens (Motohashi *et al*., 2000) et un phénomène d'agitation vespérale, également appelé *sundowning*, qui se caractérise par une tendance à s'agiter et à déambuler à la tombée du jour, avec des signes d'anxiété, des troubles émotionnels, une pensée et un discours désorganisés.

Enfin, le syndrome d'apnées du sommeil est fréquemment associé à la maladie d'Alzheimer, aggravant potentiellement les déficits cognitifs (Beebe *et al*., 2003). Une étude récemment publiée (Osorio *et al*., 2015), a rapporté que parmi les individus présentant un déclin cognitif modéré ou une maladie d'Alzheimer, la présence d'un syndrome d'apnées obstructives du sommeil non traité avançait de 13 ans l'apparition des premiers signes de déficit de mémoire (à 77 ans au lieu de 90 ans). En revanche, le traitement de cette pathologie par une ventilation en pression positive

continue la nuit, permet de faire disparaitre cet effet délétère, en réduisant le risque de maladie d'Alzheimer et de perte de mémoire au même niveau des individus sans troubles du sommeil.
Plusieurs études ont montré que ces troubles du sommeil sont corrélés aux déficits cognitifs (Bonanni *et al*., 2005), en particulier avec les scores de mémoire épisodique et autobiographique (Rauchs *et al*., 2008, 2013 ; Westerberg *et al*., 2010, 2012 ; Hot *et al*., 2011).

Des données récentes suggèrent que les troubles du sommeil pourraient également constituer des symptômes précurseurs de la maladie d'Alzheimer et exacerber le processus neuropathologique conduisant à la formation des dépôts amyloïdes. Ainsi, Kang *et al*. (2009) ont montré, dans une étude chez un modèle murin de maladie d'Alzheimer, qu'une privation aigüe de sommeil augmente de 25% les niveaux de protéine amyloïde (Aβ) dans le liquide cérébral interstitiel. Des résultats similaires ont été obtenus après infusion d'orexine (peptide stimulant l'état d'éveil). De plus, une restriction chronique du temps de sommeil (4 heures par nuit) pendant 21 jours, augmentait également les niveaux de dépôts amyloïdes dans différentes régions cérébrales. Chez le rongeur et chez l'Homme, les niveaux d'Aβ augmentent significativement pendant les phases d'éveil et diminuent durant le sommeil (Kang *et al*., 2009 ; Roh *et al.*, 2012 ; Huang *et al.*, 2012) et sont négativement corrélés au temps passé en sommeil NREM (Kang *et al*., 2009).
Récemment, Ju *et al.* (2013) ont mené une étude, chez des sujets sains de plus de 45 ans auprès desquels étaient réalisés un enregistrement actimétrique pendant deux semaines et un dosage du peptide Aβ(1-42) dans le liquide céphalorachidien. Ces auteurs ont montré que les sujets présentant une forte probabilité de dépôts amyloïdes (soit des taux d'Aβ < 500 pg/mL) avaient un sommeil de moins bonne qualité, attestée par une efficacité de sommeil moindre (80.4 versus 83.7 %), comparés aux individus sans dépôts amyloïdes, après correction pour l'âge, le sexe et le statut

APOE ε4. En revanche, le temps total de sommeil, estimé par actimétrie, ne différait pas entre les deux groupes. Enfin, Spira et collaborateurs ont montré qu'un sommeil de qualité médiocre ou de durée insuffisante (≤ 6 heures) était associé à une augmentation de la charge amyloïde (évaluée en Tomographie par Emission de Positons (TEP) et du radioligand PiB) chez des sujets âgés sains (Spira *et al*., 2013). Dans une autre étude très préliminaire incluant des polysomnographies réalisées chez 5 patients MCI, ces mêmes auteurs suggèrent que les troubles respiratoires au cours du sommeil (notamment l'index de désaturation en oxygène et l'index d'apnées-hypopnées), et non la quantité des différents stades de sommeil, seraient corrélés à la charge amyloïde (Spira *et al*., 2014).

Plusieurs auteurs ont tenté d'expliquer les interactions réciproques entre sommeil et MA (Ju *et al.*, 2013, 2014 ; Lucey *et al*., 2014). Ils émettent l'hypothèse que l'accumulation de peptide Aβ altère le cycle veille-sommeil et, réciproquement, qu'un sommeil de qualité médiocre augmente le risque d'agrégation de ce peptide. Cette boucle de rétrocontrôle positif ainsi que les facteurs susceptibles d'influer les liens entre sommeil et maladie d'Alzheimer sont illustrés en **Figure 1**. Ainsi, le syndrome d'apnées du sommeil, fréquemment associé à la maladie d'Alzheimer, pourrait favoriser la formation des dépôts d'Aβ en augmentant le stress hypoxique et l'inflammation ou bien en fragmentant le sommeil et augmentant les périodes d'éveil. La diminution des activités physiques et cognitives aurait également un lien bidirectionnel avec le cycle veille-sommeil et la pathologie amyloïde et pourrait renforcer la boucle de rétrocontrôle entre sommeil de médiocre qualité et maladie d'Alzheimer.

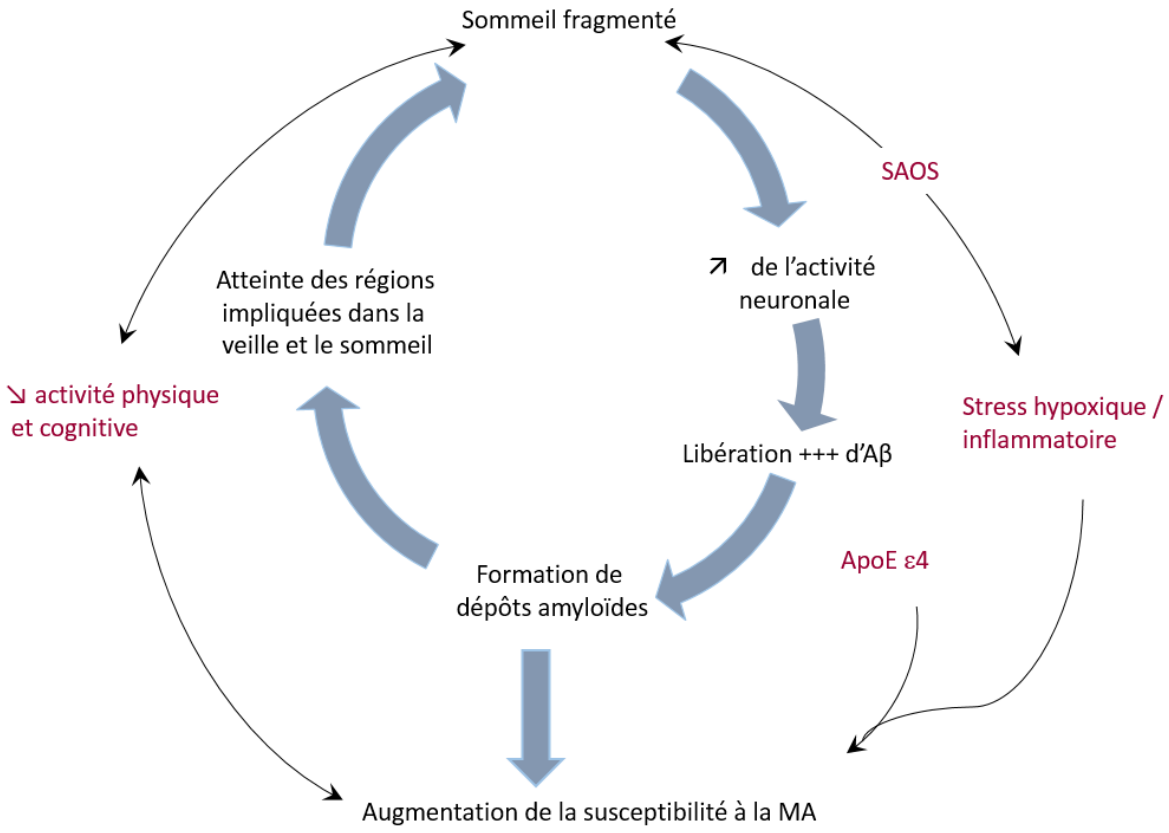

Figure 1 : Modèle des interactions entre qualité de sommeil et dépôts amyloïdes dans la MA. D'après Ju *et al*. (2013).

4. Maladie de Huntington

Les patients atteints de maladie de Huntington présentent des anomalies du rythme circadien qui n'ont été décrites qu'assez récemment (Morton *et al.*, 2005), et reproduites chez des modèles animaux (Fisher *et al.*, 2013 ; Morton, 2013 pour revue). Celles-ci seraient dues à l'atrophie et la neurodégénérescence touchant les neurones hypocrétinergiques (Roos *et al.*, 2007 ; Petersen *et al.*, 2006), ainsi qu'à une dysfonction du noyau supra-chiasmatique (van Wamelen *et al.*, 2013). Par ailleurs, des travaux menés sur un modèle murin de cette pathologie ont montré que l'architecture

du sommeil se modifie également (Kantor *et al.*, 2013), mais les études en polysomnographie chez l'homme restent peu nombreuses, principalement à cause des difficultés méthodologiques inhérentes à la pathologie, notamment les mouvements choréiques. Sur le plan de la macrostructure du sommeil, ces études montrent que les patients présentent une augmentation de la latence d'endormissement, une efficacité de sommeil réduite, une augmentation de la fragmentation de sommeil avec des réveils nocturnes fréquents et plus longs – pendant lesquels les mouvements choréiques sont amplifiés – et une réduction du sommeil lent profond (Hansotia *et al*., 1985 ; Wiegand *et al*., 1991a ; Petit *et al.*, 2004 pour revue). Le sommeil paradoxal apparaît plus tardivement et sa durée est raccourcie (Aziz *et al*., 2010). Ces anomalies peuvent être observées chez les sujets porteurs du gène muté, mais encore asymptomatiques sur les plans moteur et cognitif (Arnulf, 2012), et corrèlent avec la sévérité des troubles cognitifs (Aziz *et al.*, 2010).

Des anomalies ont également été retrouvées au niveau des enregistrements EEG, notamment au niveau du rythme alpha (Scott *et al.*, 1972), et seraient détectables dès le stade pré-symptomatique de la maladie (Hunter *et al.*, 2010). Contrairement aux patients atteints d'autres maladies neurodégénératives, les patients souffrant de maladie de Huntington ont une densité de fuseaux de sommeil plus élevée que les sujets contrôles (Emser *et al*., 1988 ; Wiegand *et al*., 1991b), pouvant refléter un signe de dysfonctionnement du thalamus (Morton, 2013). Les troubles du sommeil seraient par ailleurs corrélés au degré d'atrophie du noyau caudé et à la sévérité des symptômes cliniques (Wiegand *et al*., 1991a).

Des données récentes indiquent que des mouvements périodiques des membres inférieurs seraient observés très fréquemment chez les patients (Piano *et al*., 2015). En revanche, seule une minorité

de patients présenteraient des troubles respiratoires (Cuturic *et al*., 2009) et des troubles du comportement en sommeil paradoxal (Piano *et al.*, 2015), au moins dans les premiers stades de la maladie.

En pratique clinique, l'évaluation des troubles du sommeil de ces patients présentant une démence peut être aidée par le SDI (Sleep Disorders Inventory) qui permet de repérer les manifestations nocturnes du patient et la gêne occasionnée sur l'aidant au domicile (Tractenberg 2003, Onen & Onen, 2008a, 2010). Enfin, le test ONSI (Observation-based Nocturnal Sleep Inventory, Onen *et al.,* 2008b) permet de réaliser un dépistage du syndrome d'apnées du sommeil chez les patients hospitalisés ou en institution.

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6.5. COLLABORATION A DES ETUDES PUBLIEES DANS DES REVUES INTERNATIONALES

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Relationships between sleep quality and brain volume, metabolism, and amyloid deposition in late adulthood

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ABSTRACT

Recent studies in mouse models of Alzheimer's disease (AD) and in humans suggest that sleep disruption and amyloid-beta (Aβ) accumulation are interrelated, and may, thus, exacerbate each other. We investigated the association between self-reported sleep variables and neuroimaging data in 51 healthy older adults. Participants completed a questionnaire assessing sleep quality and quantity and underwent positron emission tomography scans using [^{18}F]florbetapir and [^{18}F]fluorodeoxyglucose and an magnetic resonance imaging scan to measure Aβ burden, hypometabolism, and atrophy, respectively. Longer sleep latency was associated with greater Aβ burden in prefrontal areas. Moreover, the number of nocturnal awakenings was negatively correlated with gray matter volume in the insular region. In asymptomatic middle-aged and older adults, lower self-reported sleep quality was associated with greater Aβ burden and lower volume in brain areas relevant in aging and AD, but not with glucose metabolism. These results highlight the potential relevance of preserving sleep quality in older adults and suggest that sleep may be a factor to screen for in individuals at risk for AD.

1. Introduction

Sleep-wake disturbances are frequent in Alzheimer's disease (AD; Montplaisir et al., 1995; Peter-Derex et al., 2015; Petit et al., 2004). They reduce patients' quality of life, increase caregivers' physical and psychological burdens, and frequently motivate institutionalization. Sleep disruptions are described early in the course of the disease, in patients with mild cognitive impairment (MCI), a clinical stage considered to be prodromal AD (Beaulieu-Bonneau and Hudon, 2009) and have been found to be related to memory impairment (Bonanni et al., 2005; Hot et al., 2011; Rauchs et al., 2008, 2013; Westerberg et al., 2010, 2012). Recent evidence suggests that sleep alterations may also constitute a risk factor for AD and hasten amyloid-beta (Aβ) pathology. Thus, in a pioneering study in a mouse model of AD, Kang et al. (2009) reported that acute sleep deprivation or orexin (a peptide promoting wakefulness) infusion increased Aβ levels in brain interstitial fluid. In addition, chronic sleep restriction (4 hours of sleep per night) for 21 days significantly increased Aβ deposition in multiple brain areas. Both animal and human studies have reported diurnal physiological fluctuations in Aβ levels in cerebrospinal fluid (CSF), increasing during wakefulness and decreasing during sleep, especially non-rapid eye movement sleep (Bateman et al., 2007; Kang et al., 2009). These normal fluctuations in Aβ are disrupted in mouse models of AD (Roh et al., 2012) and in individuals with Aβ deposition (Huang et al., 2012), and may contribute to AD. However, research in humans is still in its infancy. Ju et al. (2013) reported worse sleep efficiency, measured using actigraphic recordings over a 2-week period, in participants with abnormal CSF $A\beta_{1-42}$ than in those with normal CSF $A\beta_{1-42}$ levels, even though there was no difference in total sleep time between the groups. So far, there have been only neuroimaging studies using [^{11}C] PiB (Pittsburgh compound B) positron emission tomography (PET). These suggested that healthy older adults with shorter self-reported

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sleep duration (Spira et al., 2013) or who report less adequate sleep, more sleep problems, or increased somnolence (Sprecher et al., 2015) have a greater Aβ burden in AD-sensitive brain regions, particularly the precuneus, cingulate gyrus, and frontal areas. In addition, several studies have revealed the effects of sleep disorders such as insomnia or sleep apnea on brain structure and metabolism (Altena et al., 2010; Macey et al., 2002; Nofzinger et al., 2004).

The aim of the present study was to further investigate the association between sleep and Aβ burden in healthy adults. Using a questionnaire developed in our laboratory, we assessed sleep quality over the previous 5 years, a period during which Aβ deposition might occur covertly, to determine whether long lasting sleeping difficulties have an impact on Aβ load. Sleep variables were first correlated with florbetapir-PET data reflecting in vivo Aβ deposition in gray matter (GM), adopting a voxel-wise approach. The originality of our study lays in the fact that we also addressed the potential association between sleep parameters and two other hallmarks of AD, namely GM metabolism measured with fluorodeoxyglucose (FDG)-PET and GM volume measured with structural T1 magnetic resonance imaging (MRI). We hypothesized that sleep quality would be related to Aβ deposition, as well as to GM volume and metabolism, in brain areas sensitive to aging and AD, such as the precuneus and prefrontal areas.

2. Materials and methods

2.1. Participants

Participants were recruited from the Multimodal Imaging of Early-Stage Alzheimer's Disease study conducted in Caen, France (see Table 1 for demographic data). They were all volunteers aged >40 years, right-handed, with at least 7 years of education, native French speakers, living at home, and without any memory complaints. They had no contraindications to MRI and no history or evidence of major neurologic or psychiatric disorders. A neuropsychological assessment including the mini-mental state examination (Folstein et al., 1975) and Mattis dementia rating scale (Mattis, 1976), as well as tests assessing verbal and visual episodic memory, semantic memory, language, executive functions, visuospatial functions, and praxis, confirmed the absence of signs of cognitive decline.

Table 1
Participants' characteristics

Characteristics	Data[a]
Age in years	64.1 (10.6)
No. women (%)	28 (54.9)
Education level in years	12.4 (3.7)
BMI, kg/m^2	24.5 (2.9)
MMSE	28.9 (0.9)
MDRS (total score)	141.8 (2.5)
MDRS (memory subscore)	24.5 (0.9)
No. (%) participants on sleep medication[b]	4 (7.8)
No. (%) ApoE4 positive	14 (27)
MADRS	1.2 (2.1)
STAI (trait version)	36.6 (10.4)
Florbetapir SUVr	0.95 (0.1)
No. (%) florbetapir positive[c]	7 (13.7)

Key: ApoE, apolipoprotein E; BMI, body mass index; MADRS, Montgomery-Åsberg depression rating scale; MDRS, Mattis dementia rating scale; MMSE, mini-mental state examination; SD, standard deviation; STAI, State Trait Anxiety Inventory; SUVr, standardized uptake value ratio.

[a] For 51 participants. Unless otherwise indicated, data are expressed as means (SD).

[b] Excluding phytotherapy, homeopathy, and occasional use (<1/wk).

[c] Positive florbetapir SUVr was defined as >0.991, based on mean SUVr + 2 SDs in a group of healthy individuals aged <40 years.

All participants completed a sleep questionnaire and underwent the structural MRI and florbetapir-PET scans, but 1 volunteer could not undergo the FDG-PET scan owing to diabetes diagnosed after his inclusion. There was a mean interval of 2.8 ± 3.3 months between the sleep assessment and the neuroimaging scans. The FDG- and florbetapir-PET scans were acquired in two different sessions, separated by a mean interval of 1 ± 1.2 months. The FDG scan was performed first for 37 participants, but given the dynamics of Aβ deposition, which is a protracted process, the interval between the 2 PET scans is unlikely to have affected our results (Villemagne et al., 2013).

Participants also completed the Montgomery-Åsberg depression rating scale (Montgomery and Åsberg, 1979) and the trait version of the State-Trait Anxiety Inventory (Spielberger and Sydenham, 1994).

The IMAP study was approved by a regional ethics committee (CPP Nord-Ouest III) and registered with http://clinicaltrials.gov (no. NCT01638949). All participants gave their written informed consent to the study before the investigation.

2.2. Subjective sleep data

All participants completed a sleep questionnaire developed in the laboratory and derived from the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). However, although the PSQI assesses sleep quality and disturbances over a 1-month interval, our questionnaire covered a far longer period (previous 5 years; see Appendix A). Although assessing sleep quality over this period maybe less precise, it has the advantage of preventing the sleep data from being influenced by temporary phenomena such as personal events (bereavement and stress) or seasonal variations (Honma et al., 1992; Kim and Dimsdale, 2007; Monk et al., 2008). More specifically, participants were asked about their mean sleep duration, difficulties falling asleep estimated by sleep latency (considered as normal if ≤15 minutes), and number of nocturnal awakenings. Although the sleep latency and mean sleep duration items were similar to those in the PSQI, because of the lengthy period we were exploring, our questionnaire did not allow us to compute an index of sleep efficiency. We requested a numerical response for the number of nocturnal awakenings to improve response accuracy. Sleep quality was estimated on a 6-point scale ranging from very poor to very good (see Appendix A), and we also assessed the regularity of the sleep-wake cycle on a 4-point scale ranging from very variable to very regular, as some data indicate that high across-night variability in sleep quality may be associated with poorer memory functioning (Westerberg et al., 2010). We also asked participants about the duration, frequency, and timing of their naps, as it has been suggested that frequent, lengthy, and unplanned daytime naps in older adults have a potentially negative impact on nocturnal sleep and may be associated with cognitive impairment (Ficca et al., 2010). Finally, we also asked whether sleep quality had improved or deteriorated over the previous 5 years and, as in the original PSQI questionnaire, assessed the impact of sleep disturbances on daily functioning and the use of sleep medication.

Qualitative measures were recorded on numerical scales of 1–6 for sleep quality and 1–4 for variability in the sleep-wake cycle.

To limit the number of analyses we computed, and given that there was insufficient variability in the responses to some questions, we focused our statistical analyses on sleep latency, duration, and quality, and on the number of nocturnal awakenings.

2.3. Acquisition of imaging data

2.3.1. MRI data

For each participant, a high-resolution T1-weighted anatomic image was acquired on a 3T Philips Achieva MRI scanner using a

three-dimensional fast-field echo sequence (sagittal; repetition time = 20 ms, echo time = 4.6 ms, flip angle = 20, 180 slices with no gap, slice thickness = 1 mm, field of view = 256 × 256 mm^2, in-plane resolution = 1 × 1 mm^2).

2.3.2. PET data

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

2.3.2.1. FDG-PET

Participants were fasted for at least 6 hours before scanning. After a 30-minute resting period in a quiet and dark environment, ~180 MBq of FDG were intravenously injected as a bolus. A 10-minute PET acquisition scan began 50 minutes after injection.

2.3.2.2. Florbetapir-PET

Each participant underwent a 20-minute PET scan, beginning 50 minutes after intravenous injection of ~4 MBq/kg of florbetapir.

2.4. MRI data processing and analyses

The MRI data were segmented, spatially normalized to Montreal Neurological Institute (MNI) space, modulated to correct for nonlinear warping effects, and smoothed with a 10-mm full width at half maximum Gaussian kernel using the VBM5 toolbox implemented in SPM5 software (www.fil.ion.ucl.ac.uk). Images were masked to exclude non-GM voxels from the analyses.

2.5. PET data processing and analyses

FDG- and florbetapir-PET data were first corrected for partial volume effects (PMOD Technologies Ltd, Adliswil, Switzerland), coregistered onto their corresponding MRI, and then spatially normalized using the deformation parameters derived from the MRI procedure. The resulting images then underwent quantitative scaling, using cerebellar GM as a reference, to obtain standardized uptake value ratio (SUVr) images, and finally smoothed using a 12-mm full width at half maximum Gaussian kernel and masked to exclude non-GM voxels from the analyses.

2.6. Apolipoprotein E genotyping

Participants' apolipoprotein (APOE) genotype was identified from genomic DNA extracted from frozen leukocytes by restriction isotyping, using polymerase chain reaction amplification followed by Hha1 digestion (Hixson and Vernier, 1990). Participants with 1 or more copies of the ε4 allele were deemed to be ApoE ε4 carriers. All others were classified as ApoE ε4 noncarriers.

2.7. Statistical analyses

We performed multiple regression analyses to assess the associations between the sleep variables yielded by the sleep questionnaire and our neuroimaging data (florbetapir-PET, FDG-PET, and MRI), adopting a whole-brain voxel-wise approach. Images were analyzed with SPM5 using the multiple regression design. As age (Ohayon et al., 2004), ApoE ε4 status (Hita-Yañez et al., 2012; Osorio et al., 2014), anxiety (Spira et al., 2009), depression (Murphy and Peterson, 2015), and body mass index (BMI; Wheaton et al., 2011) can significantly alter sleep quality, these factors were used as covariates in the analyses. Results were considered as significant at $p < 0.001$, with a minimum cluster size (k) of 100 voxels to control for false positives. Pearson correlation coefficients and plots were obtained by extracting signal values from the main cluster obtained in the SPM whole-brain voxel-wise analyses, then correlating them with the relevant sleep variable using Statistica software (StatSoft, Tulsa, OK, USA).

3. Results

3.1. Participants' characteristics

A total of 51 cognitively healthy participants (mean age ± standard deviation = 64.1 ± 10.1 years, range = 41–84) took part in this study. Seven of these participants (14%) had a positive florbetapir-PET scan and 14 (27%) were ApoE ε4 carriers. BMI was within the normal range (between 18.5 and 24.99) for 30 participants, but 19 were overweight and 2 were obese.

Montgomery-Åsberg depression rating scale scores revealed that none of the participants had any signs of depression, except for 1 who had a score of 12, indicating mild depressive symptoms. Finally, 43 participants had low-to-mild anxiety levels, and 8 exhibited moderate-to-high anxiety, as assessed using the trait version of the State-Trait Anxiety Inventory.

3.2. Self-reported sleep variables

Self-reported sleep variables indicated that sleep quality was rated as quite good by participants (see Table 2). Mean sleep latency was within the normal range observed for this age group (Ohayon et al., 2004), but with considerable interindividual variability. Mean sleep time was around 7 hours per night. Sleep also appeared to be quite regular across nights, with a limited number of nocturnal awakenings.

3.3. Associations between self-reported sleep characteristics with amyloid load, GM volume, and metabolism

Multiple regression analyses revealed that mean sleep latency was positively correlated with Aβ deposition, as estimated by florbetapir-PET, in prefrontal areas that included the anterior cingulate cortex ($N = 51$, $p < 0.001$; Fig. 1A, Table 3). This result remained significant, albeit less spatially extended, after controlling for age, ApoE ε4 status, BMI, anxiety, and depression scores ($N = 51$, $p < 0.001$; Fig. 1B, Table 3). Pearson's correlation tests computed between SUVr (extracted from the main cluster) and sleep latency were $r = 0.54$, $p = 4 \times 10^{-5}$ for the first analysis without any covariate and $r = 0.54$, $p = 3.6 \times 10^{-5}$ for the analysis controlling for age, ApoE ε4 status, BMI, anxiety, and depression scores (Fig. 2). The correlation remained significant when only participants >60 years were considered ($N = 35$, $r = 0.57$, $p = 3 \times 10^{-4}$ for the analysis with no covariate and $r = 0.6$, $p = 1 \times 10^{-4}$ for the analysis including the 5 covariates), and after controlling for sleep medication use ($r = 0.49$,

Table 2
Self-reported sleep variables across the previous 5 years

Sleep variable	Data
Sleep quality	4.3 (1.2)
Mean sleep latency in min	19.7 (18.3)
Mean sleep time in min	417.7 (60.2)
Regularity	2.9 (0.7)
Mean number of awakenings per night	1.7 (1.1)

Data are expressed as means (SD). Sleep quality was assessed on a 6-point scale, and regularity of the sleep-wake cycle on a 4-point one.
Key: SD, standard deviation.

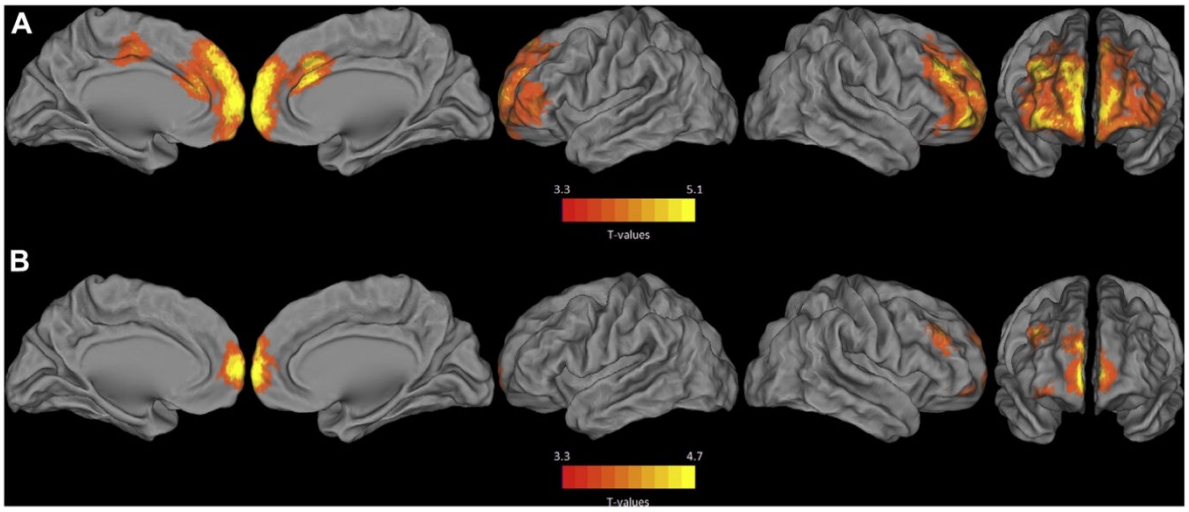

Fig. 1. Regression analysis between sleep latency and Aβ deposition (measured by florbetapir-PET) in healthy individuals with no covariate (A) and when age, anxiety and depression scores, BMI, and ApoE ε4 status were entered as covariates (B). Results are displayed at $p < 0.001$ with a minimum cluster size of 100 voxels. Color scales are adapted to the range of significance for each correlation. Pearson's correlation coefficients were computed between the SUVr (extracted from the main cluster) and sleep latency. Abbreviations: Aβ, amyloid-beta; ApoE, apolipoprotein E; BMI, body mass index; PET, positron emission tomography; SUVr, standardized uptake value ratio.

$N = 51$, $p = 3 \times 10^{-4}$ for the analysis with no covariate and $r = 0.47$, $p = 5 \times 10^{-4}$ after adjusting for the 5 covariates).

None of the other sleep variables (sleep duration, number of awakenings, and subjective sleep quality) was associated with Aβ deposition.

Similar analyses were conducted with the FDG-PET and MRI data. The number of nocturnal awakenings was negatively correlated with GM volume in the bilateral insula and inferior frontal gyri ($N = 50$, $p < 0.001$; Fig. 3A, Table 4). This result remained significant, albeit less spatially extended, after controlling for age, ApoE ε4 status, BMI, anxiety, and depression scores ($N = 50$, $p < 0.001$; Fig. 3B, Table 4). Pearson's correlation coefficients computed between GM volume (extracted from the main cluster) and the number of nocturnal awakenings were $r = -0.56$, $p = 2.5 \times 10^{-5}$, $N = 50$ (as 1 participant did not answer this question) for the first analysis without any covariate and $r = -0.57$, $p = 1.6 \times 10^{-5}$ for the analysis controlling for age, ApoE ε4 status, BMI, anxiety, and depression scores (Fig. 4). The correlation remained significant when only participants >60 years were considered ($r = -0.62$, $N = 34$, $p = 9 \times 10^{-5}$ for the analysis with no covariate and $r = -0.56$, $p = 6 \times 10^{-4}$ when adjusting for the 5 covariates), and after controlling for sleep medication use ($r = -0.59$, $n = 50$, $p = 7 \times 10^{-6}$ without any covariate and $r = -0.58$, $p = 1 \times 10^{-5}$ in the adjusted model).

For all the reported analyses, r coefficients were >0.5, indicating large effect sizes.

None of the other sleep variables (sleep latency, sleep duration, and sleep quality) were associated with GM volume. In addition, none of the sleep variables we considered were associated with brain metabolism.

Note that standardized beta coefficients were also evaluated for all statistical analyses performed and were found to be equal to r coefficients.

Table 3
Brain areas in which amyloid load was significantly correlated with sleep latency

Brain region	Cluster size (voxels)	MNI coordinates (mm)			T value
		x	y	z	
a. Analysis without covariate					
L superior, middle, medial frontal gyri, L rectus gyrus	2132	−8	56	8	5.11
L anterior cingulate gyrus					
R superior, middle, medial frontal gyri, R rectus gyrus	3208	36	32	30	4.82
R anterior cingulate gyrus					
L, R anterior cingulate gyrus	323	6	22	32	4.28
R middle cingulate gyrus					
L middle cingulate gyrus	124	−6	16	44	4.21
L supplementary motor area					
L middle and inferior frontal gyri	169	−46	38	4	3.88
b. Analysis including age, BMI, anxiety, depression, and ApoE4 status as covariates					
L superior and medial frontal gyri	225	−6	56	8	4.65
L anterior cingulate gyrus					
R middle and inferior frontal gyri	114	36	32	32	4.07
R superior and medial frontal gyri	269	4	58	10	4.00
R anterior cingulate gyrus					
R superior, middle and inferior frontal gyri	110	42	52	−14	3.67

Key: ApoE, apolipoprotein E; BMI, body mass index; L, left; R, right.

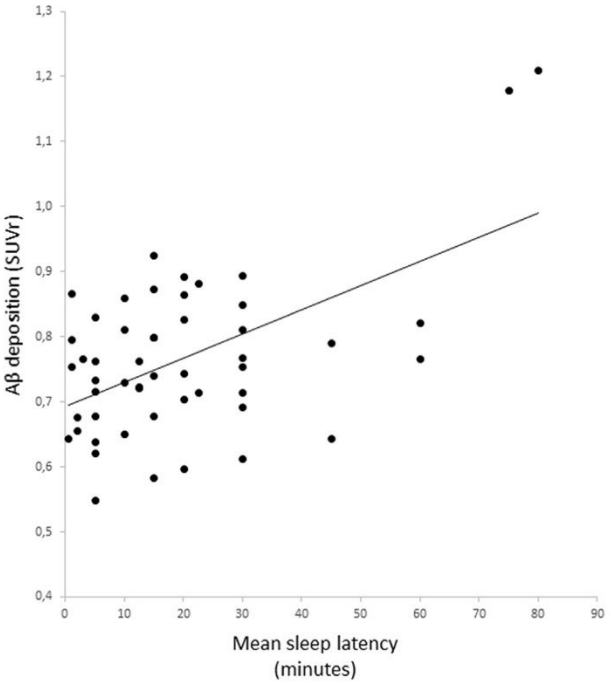

Fig. 2. Plot illustrating the correlation between Aβ deposition and sleep latency, controlling for the effects of age, BMI, anxiety and depression scores, and ApoE ε4 status. Abbreviations: Aβ, amyloid-beta; ApoE, apolipoprotein E; BMI, body mass index; SUVr, standardized uptake value ratio.

4. Discussion

Using multimodal neuroimaging (florbetapir-PET, FDG-PET, and structural MRI), we examined the associations between self-reported sleep variables and AD biomarkers (Aβ burden, GM metabolism, and GM volume) in healthy older individuals. Our data revealed that poor sleep quality, as reflected by longer sleep latency or the number of nocturnal awakenings, was associated with greater Aβ burden and lower volume in frontal areas.

Our results are consistent with two PET studies that found associations between self-reported sleep quality and Aβ burden (Spira et al., 2013; Sprecher et al., 2015). They are also in line with another study based on actigraphic recordings and CSF Aβ measurements, which revealed differences in sleep efficiency between participants with abnormal CSF Aβ levels and those with normal levels (Ju et al., 2013). Overall, these data show that poor sleep quality, reflected by increased sleep latency, decreased sleep efficiency, or reduced total sleep time, is associated with a greater Aβ burden.

Voxel-wise regression analyses revealed an association between sleep disturbances and Aβ deposition in prefrontal areas, in line with Sprecher et al. (2015). Spira et al. (2013), however, reported associations between sleep duration and mean Aβ burden not just in the cortex but also in the precuneus. Although the locations differed in these two studies, the precuneus and prefrontal cortex are both known to be affected by Aβ deposition at an early stage in AD (Thal et al., 2002). The specific location of Aβ deposition has been shown to be poorly related to symptomatology (Lehmann et al., 2013; Rabinovici et al., 2008), so methodological differences (e.g., partial volume effect correction in our study, but not in Spira et al., 2013) can probably explain why one area might be more significant than the other.

In one recent study, poor sleep quality was associated with reduced GM volume in the frontal cortex and an increased rate of atrophy within frontal, temporal, and parietal regions (Sexton et al., 2014). These areas are particularly vulnerable to age- and AD-related changes and may be responsible for the multiple cognitive deficits that coexist with poor sleep. Our data revealed a negative correlation between the number of nocturnal awakenings and GM volume in the insular region. Although this result was rather unexpected, several studies have related sleep to the insula. Sleep slow waves mainly originate from the left frontoinsular area and cingulate gyrus and then propagate to posterior areas (Murphy et al., 2009). In addition, activation of the insula has been reported during the occurrence of sleep spindles—key features of sleep stage 2 (Schabus et al., 2007) that are regarded as an index of sleep stability (Dang-Vu et al., 2010; Kim et al., 2012). Finally, Koenigs et al. (2010) reported that focal brain damage to the frontoinsular region is associated with subjective reports of insomnia. Thus, atrophy of the left insula could alter the generation and propagation of slow waves but also sleep spindles, resulting in difficulty initiating or maintaining sleep.

Our study did not allow us to address the causality of the relationship between sleep, Aβ burden, and brain atrophy. Previous research has highlighted bidirectional relationships between sleep and Aβ pathology. Amyloid plaques are thought to arise in brain areas and pathways controlling the sleep-wake cycle, leading to sleep disturbances (Braak and Braak, 1991; Mander et al., 2015). Conversely, poor sleep quality may increase Aβ aggregation (Kang et al., 2009) and the risk of AD (Ju et al., 2014; Lim et al., 2013). In addition, sleep has been described as the brain's housekeeper (Underwood, 2013), with reference to a study showing that sleep increases the clearance of potentially neurotoxic waste products, such as Aβ peptides (Xie et al., 2013). Sleep has also been associated with increased expression of genes related to myelin formation (Bellesi et al., 2013). Poor sleep quality may, therefore, have a direct impact on brain structure. Conversely, atrophy can also induce sleep disturbances. Mander et al. (2013) reported that age-related atrophy of prefrontal areas mediates a decrease in non-rapid eye movement slow-wave activity (electroencephalography spectral power in the delta frequency band). Our results provide additional evidence for a link between sleep quality and AD biomarkers, but further investigations involving the long-term follow-up of participants are needed to better understand the mechanisms and causality of this link.

Our analyses did not reveal any association between sleep variables and brain metabolism. Future studies will allow us to investigate this question further, notably with larger samples and using objective sleep measures. Our multimodal approach did, however, allow us to demonstrate that poor self-reported sleep quality tends to have a greater impact on brain volume (determined by structural MRI) and Aβ deposition (measured with florbetapir-PET) than on glucose metabolism (estimated by FDG-PET). The results we observed were independent of ApoE ε4 status. However, there is evidence that ApoE ε4 carriers have more pronounced sleep disturbances (Hita-Yañez et al., 2012). Modifiable lifestyle factors may also have a greater impact on AD biomarkers in ApoE ε4 carriers (Arenaza-Urquijo et al., 2015; Wirth et al., 2014). Further studies are, therefore, needed to better understand the effect of the interaction between sleep and ApoE ε4 on AD biomarkers.

Our findings are in line with growing evidence from cognitively normal older adults that modifiable lifestyle factors may have an impact on AD biomarkers. Although greater engagement in cognitive or physical activities has been related to lower Aβ deposition (Landau et al., 2012; Liang et al., 2010) and increased brain volume (Arenaza-Urquijo et al., 2013; Valenzuela et al., 2008), our study

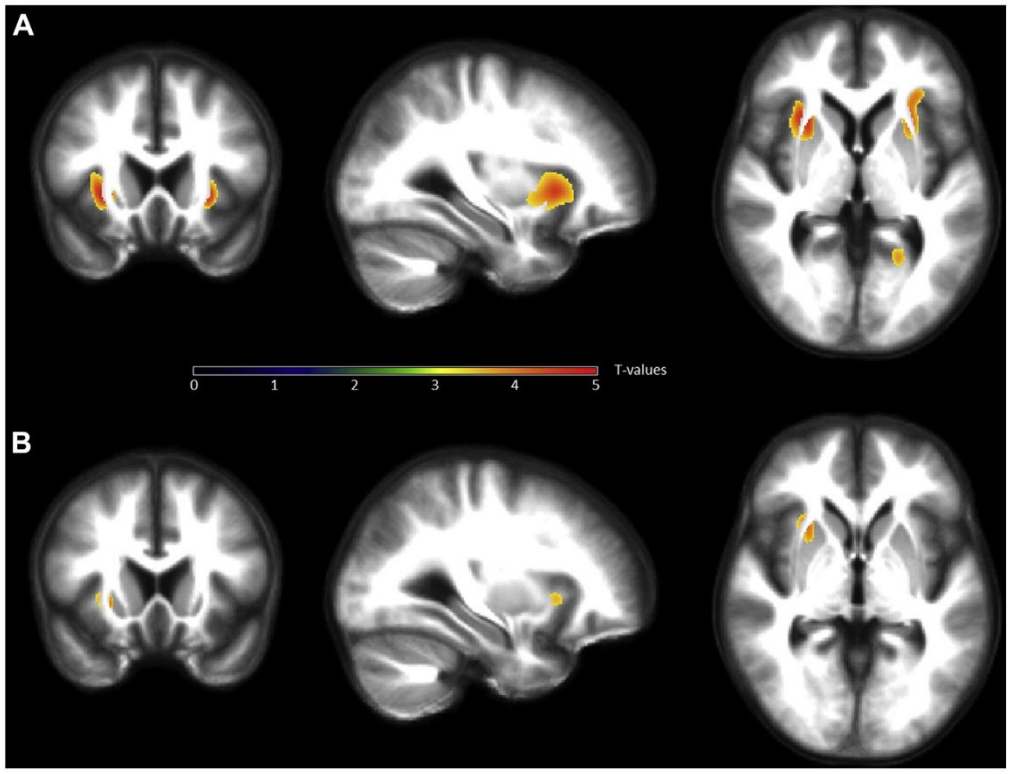

Fig. 3. Regression analysis between the number of nocturnal awakenings and lower gray-matter volume in healthy individuals with no covariate (A), and when age, anxiety and depression scores, BMI and ApoE ε4 status were entered as covariates (B) Results are displayed at $p < 0.001$ with a minimum cluster size of 100 voxels. Pearson's correlation coefficients were computed between gray-matter volume (extracted from the main cluster) and the number of nocturnal awakenings. Abbreviations: ApoE, apolipoprotein E; BMI, body mass index.

shows that poor sleep quality has a negative effect on both Aβ deposition and GM volume. As recently proposed, both protective (e.g., engagement in cognitive and physical activities) and risk (e.g., sleep disturbances) factors may actively contribute to increased/depleted reserve (cognitive debt hypothesis; Marchant and Howard, 2015). Thus, our findings suggest that sleep could also be a critical factor to consider in older adults and might help to fully understand the effects of lifestyle factors on the brain.

Our study had several strengths, including multimodal neuroimaging (FDG- and florbetapir-PET, structural MRI) combined with an assessment of sleep quality and disturbances over the previous 5 years, a period during which the formation of Aβ deposits may occur covertly, without any sign of cognitive decline. Questionnaires have the advantage of being easy to use in clinical practice and reflect the respondents' subjective feelings, discomfort, or dissatisfaction with their sleep. However, subjective and objective measures of sleep are weakly correlated (Van Den Berg et al., 2008; Williams et al., 2013), and self-reported sleep variables can be influenced by lower cognitive functioning (Van Den Berg et al., 2008). Hita-Yañez et al. (2012) compared overnight polysomnography recordings and self-reported sleep measures in healthy older individuals and patients with MCI. They showed that the patients, but not the healthy controls, overestimated their sleep latency, suggesting that sleep latency obtained by means of

Table 4
Brain areas in which lower gray matter volume was significantly correlated with the number of nocturnal awakenings

Brain region	Cluster size (voxels)	MNI coordinates (mm)			T value
		x	y	z	
a. Analysis without covariate					
R putamen, insula, inferior frontal gyrus R olfactory and rectus gyri	3104	26	16	−2	5.00
L insula, putamen, superior and inferior frontal gyri L olfactory gyrus	2012	−26	13	−4	4.53
L middle and inferior temporal gyri	567	−61	−31	−12	4.30
L calcarine, lingual gyrus, precuneus	295	−21	−56	1	3.79
L lingual and fusiform gyrus	159	−22	−78	−10	3.61
b. Analysis including age, BMI, anxiety, depression and ApoE4 status as covariates					
R putamen	328	26	16	−2	4.04
R putamen, insula	110	29	20	−2	3.75

Key: ApoE, apolipoprotein E; BMI, body mass index; L, left; R, right.

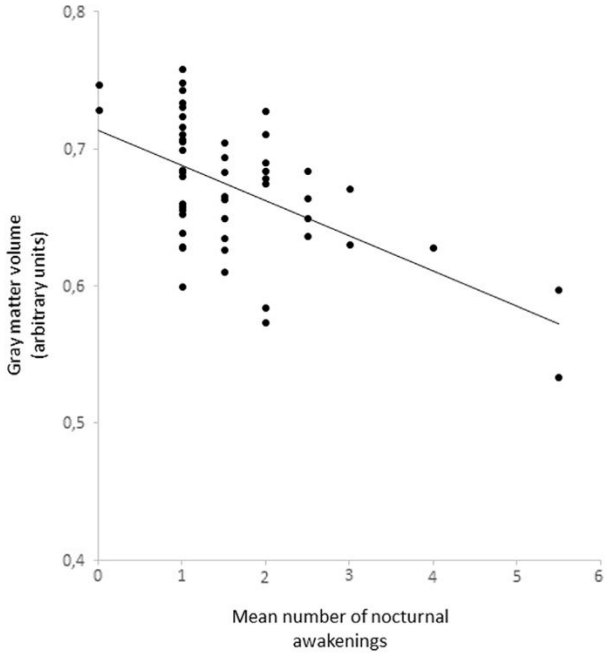

Fig. 4. Plot illustrating the correlation between gray matter volume and the mean number of awakenings, controlling for the effects of age, BMI, anxiety and depression scores, and ApoE ε4 status. Abbreviations: ApoE, apolipoprotein E; BMI, body mass index.

questionnaires can be used as a reliable marker of sleep disturbances in healthy older adults. Nevertheless, gathering objective data on sleep quality with actigraphy or polysomnography would complement the approach we used here and provide a means of examining the consistency of results yielded by our subjective sleep assessment. This was recently done in a preliminary study of 5 patients with MCI (Spira et al., 2014). No association was reported between Aβ burden and nonrespiratory sleep variables measured with polysomnography, although higher apnea-hypopnea and oxygen desaturation indices were both associated with greater amyloid load. Thus, the negative impact of sleep on Aβ deposition may mainly be driven by respiratory events and not by changes in sleep architecture. These results are supported by two studies showing that sleep-disordered breathing is associated with an earlier onset of cognitive decline and with AD CSF biomarkers in cognitively normal older individuals (Osorio et al., 2014, 2015). On the whole, these data further indicate that using questionnaires to detect individuals with poor sleep quality or who complain of sleep disturbances may be particularly relevant in clinical practice and is easier and less expensive than polysomnography. However, particular attention must be paid in questionnaires to assess the risk of sleep-disordered breathing.

To conclude, our results indicate that poor sleep quality in older, asymptomatic individuals is associated with greater Aβ burden and lower brain volume in brain areas known to be sensitive to aging and AD processes. Sleep may, therefore, play a role in protecting against age- and AD-related brain changes. This study highlights the potential relevance of preserving sleep quality in older adults and suggests that sleep may also be a critical factor to explore in individuals at risk for AD. Future studies, combining objective and subjective measures of sleep, will need to determine the temporal sequence of events and the usefulness of sleep promotion strategies to deter or slow disease progression.

Disclosure statement

All authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2016.02.009.

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Reduced age-associated brain changes in expert meditators: a multimodal neuroimaging pilot study

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Aging is associated with progressive cerebral volume and glucose metabolism decreases. Conditions such as stress and sleep difficulties exacerbate these changes and are risk factors for Alzheimer's disease. Meditation practice, aiming towards stress reduction and emotion regulation, can downregulate these adverse factors. In this pilot study, we explored the possibility that lifelong meditation practice might reduce age-related brain changes by comparing structural MRI and FDG-PET data in 6 elderly expert meditators versus 67 elderly controls. We found increased gray matter volume and/or FDG metabolism in elderly expert meditators compared to controls in the bilateral ventromedial prefrontal and anterior cingulate cortex, insula, temporo-parietal junction, and posterior cingulate cortex /precuneus. Most of these regions were also those exhibiting the strongest effects of age when assessed in a cohort of 186 controls aged 20 to 87 years. Moreover, complementary analyses showed that these changes were still observed when adjusting for lifestyle factors or using a smaller group of controls matched for education. Pending replication in a larger cohort of elderly expert meditators and longitudinal studies, these findings suggest that meditation practice could reduce age-associated structural and functional brain changes.

Aging is associated with a number of changes in the brain that, collectively, contribute to the decline in cognitive function observed in older adults. Neuroimaging studies have allowed us to track age-related macroscopic, structural, functional and molecular brain changes. They have shown substantial decreases with age in cerebral volume and glucose metabolism[1,2]. These changes are not homogeneous throughout the brain as they predominate in the frontal cortex and are also often reported in the anterior cingulate cortex, insula, sensorimotor, and perisylvian regions[1–3]. Other parietal and temporal brain regions, including the hippocampus, seem to be involved as well, yet findings are less consistent across studies. Age-related decreases in brain structure and function are known to be associated with decline in cognitive performance, especially in executive functions and episodic memory[2,4]. Age is also associated with a significant increase in β-amyloid (Aβ) deposition, as measured with positron emission tomography (TEP) using different amyloid radiotracers[5,6]. Decreased gray matter (GM) brain volume (especially in the hippocampus and temporal neocortex), and glucose metabolism (in the posterior cingulate cortex and temporo-parietal region), and the presence of Aβ deposition, are known to be associated with increased risk for dementia, and particularly for Alzheimer's disease (AD).

It is increasingly acknowledged that several lifestyle factors modulate brain aging and the development of dementia; around a third of AD cases may be attributable to potentially modifiable risk factors[7]. These findings are of considerable interest as they suggest that a modification in these lifestyle factors might allow for the

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	Healthy controls			Elderly expert meditators
	Whole sample	Elderly controls	Education-matched Aβneg elderly subgroup	
Sample size	186	67	31	6
Age mean ± SD (range)	49.1 ± 18.7 (20–85)	64.8 ± 6.4 (55–75)	64.5 ± 6.9 (55–75)	64.8 ± 3.2 (61–70)
Education mean ± SD (range)	13.1 ± 3.2 (7–20)	12.1 ± 3.7* (7–20)	15.1 ± 2.6 (12–20)	16.2 ± 2.7 (12–20)
N females/males	97/89	38/29	20/11	3/3
MMSE mean ± SD (range)	—	29.1 ± 1.0 (26–30)	29.2 ± 1.0 (26–30)	29.5 ± 0.8 (28–30)

Table 1. Demographics Mann-Whitney U-tests and chi2 statistics were performed to compare elderly expert meditators to the elderly control group (*Significant difference from the elderly expert meditators, $p < 0.05$). MMSE: mini mental state examination. SD: standard deviation.

promotion of healthy brain aging, prevent or delay AD, and reduce AD risks. Thus, higher levels of cognitive and physical activity have been shown to be associated with higher brain volume and metabolism, lower cerebral Aβ deposition, and lower risk for cognitive decline and dementia in cognitively normal elderly[8–11]. Similarly, psycho-affective factors such as depression, stress and anxiety – and sleep difficulties often associated with these conditions – have also been identified as risk factors for AD, having a negative impact on brain structure and function, and reducing the mental health and well-being of the aging population. Moreover, stress has a detrimental effect on hippocampal integrity[12], sleep disorders foster AD-related pathological processes[13], and depressive symptoms in older persons are associated with an increase in dementia risk[14].

Mental training for stress reduction and emotion regulation through meditation practice has the potential to downregulate various adverse factors[15,16], and thus could positively affect neurological conditions, and promote mental health and wellbeing in the aging population[17]. While meditation research is still in its infancy especially in elderly populations, there is emerging evidence that meditation practice improves cognition, mainly attention, but also memory, which are the most sensitive to aging and AD[18]. It has also been shown to reduce stress, anxiety, depression, insomnia, feelings of loneliness and social exclusion[17,19], and cardiovascular risk factors in older adults[20]. A previous study showed reduced age-effects on the volume of the putamen in meditators compared to controls aged 25 to 45 years[21]. Moreover, the effects of meditation on brain structure and function have consistently been reported in young and middle-aged adults, especially in frontal and limbic structures, as well as the insula[22,23].Interestingly, these structures are known to be particularly sensitive to aging and AD. Yet, only one research team investigated this question in the context of an elderly population, assessing brain volume in expert meditators and controls aged between 24 and 77 years. They showed that the regression line between GM volume and age was steeper in controls than in meditators, particularly in frontal and temporal brain regions[24,25]. No study to date has explored changes in glucose metabolism associated with long-term meditation practice in young or elderly participants.

The present pilot study aimed at providing an overall picture of structural and functional brain changes in elderly expert meditators by measuring cerebral volume and glucose metabolism with MRI and FDG-PET scans. As a secondary objective, we investigated whether the brain regions exhibiting meditation-expertise-related effects were sensitive to aging and whether the elderly expert meditators differed from matched controls in this aging process. Additionally, complementary analyses were conducted to assess changes in cognition, lifestyle, and self-perceived sleep quality in the expert meditators, as well as to explore the hippocampal substructures in more detail. 192 participants were included in this study, including six expert meditators aged 60–70 years, and 186 controls aged 20–87 years. The whole control group was used to map age-related brain changes, while a group of 67 elderly controls (those aged 55–75) was used for direct comparison to the elderly expert meditators.

Results

The elderly expert meditators did not differ in age, sex ratio, nor MMSE scores in comparison to the elderly control group, yet showed significantly higher years of education (Table 1). Among the participants who had a Florbetapir-PET scan, 10/61 were classified as Aβ-positive (16%), while all 4 elderly expert meditators were classified as Aβ-negative (Supplementary Figure S1). Due to these differences in years of education and rate of Aβ-positive individuals, all neuroimaging comparisons were also performed using a subgroup of Aβ-negative elderly controls matched for education (see complementary analyses below).

Main analyses. Structural MRI and FDG-PET data of elderly expert meditators were transformed in w-score maps using the elderly control group as the reference and adjusting for age and education. The mean w-score maps of the elderly expert meditators showed that w-score values were mainly positive for GM volume (Fig. 1B), and almost only positive for FDG metabolism (Fig. 2B), indicating that the elderly expert meditators tended to have higher values compared to elderly controls. The highest mean w-scores were found in the insula, medial frontal and temporal cortical areas for both GM volume and FDG metabolism. More specifically, the z-scores were significantly higher than zero, the reference for the elderly controls, in three clusters for GM volume (Fig. 1C) and in three clusters for FDG metabolism (Fig. 2C), referred to as the clusters of interest in what follows. Thus, GM volume was significantly increased in the elderly expert meditators in the ventromedial prefrontal and anterior cingulate cortex bilaterally (MRI-cluster 1), and in the left (MRI-cluster 2) and right (MRI-cluster 3)

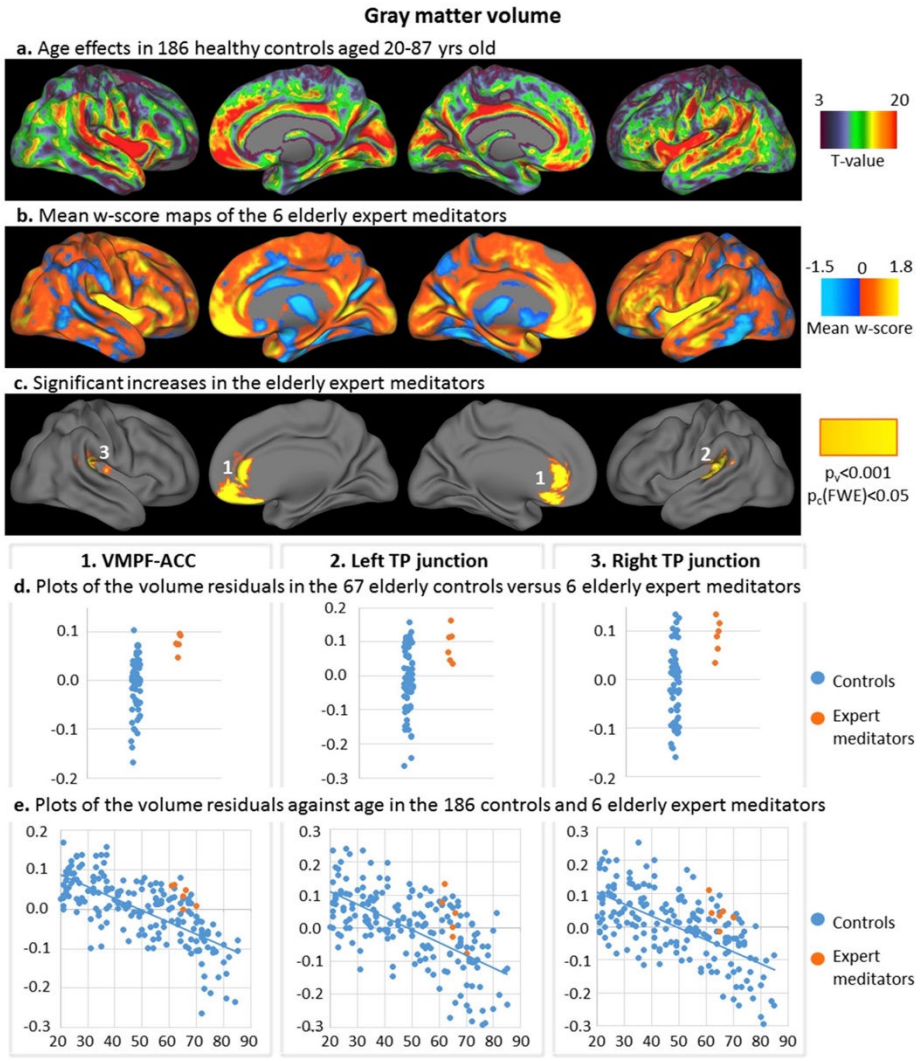

Figure 1. Results of the analyses on gray matter volume. T-values of the voxelwise regression analysis between the z-score maps of the 186 controls (corrected for education) and age were superimposed on brain surface views (**a**). Mean w-score values of the expert meditators corrected for age and education and using the elderly control group as the reference (**b**), and clusters of interest showing significantly higher values in the expert meditators (voxel-level $p < 0.001$ and FWE-corrected cluster-level $p < 0.05$) (**c**) were superimposed on brain surface views. Volume residuals in the 3 clusters of interest were plotted in the elderly expert meditators (orange) and in the controls (blue) of the elderly control group (**d**; residuals are corrected for age and education); of the entire control group against age (**e**; residuals are corrected for education). **VMPF-ACC**: ventromedial prefrontal and anterior cingulate cortex; **TP**: temporo-parietal.

medial temporo-parietal junction encompassing the transverse temporal gyrus, planum temporale, parietal operculum, and posterior extremity of the insula (long gyrus). FDG metabolism was significantly increased in the elderly expert meditators in the ventromedial prefrontal and anterior cingulate cortex bilaterally (FDG-cluster 1), in the right insula (mainly the anterior section i.e. the short gyrus), also encompassing the pars opercularis of the inferior frontal gyrus (FDG-cluster 2), and in the posterior cingulate cortex extending to the precuneus and cuneus (FDG-cluster 3). The plots of the individual values (Figs 1D and 2D) show that, for all regions, the values of the elderly expert meditators fall within the upper limit of those of the controls (or were still above the highest values of the controls for FDG-cluster 1). The reverse contrasts, that is the lower GM volume or FDG metabolism in the elderly expert meditators, did not reveal any significant results.

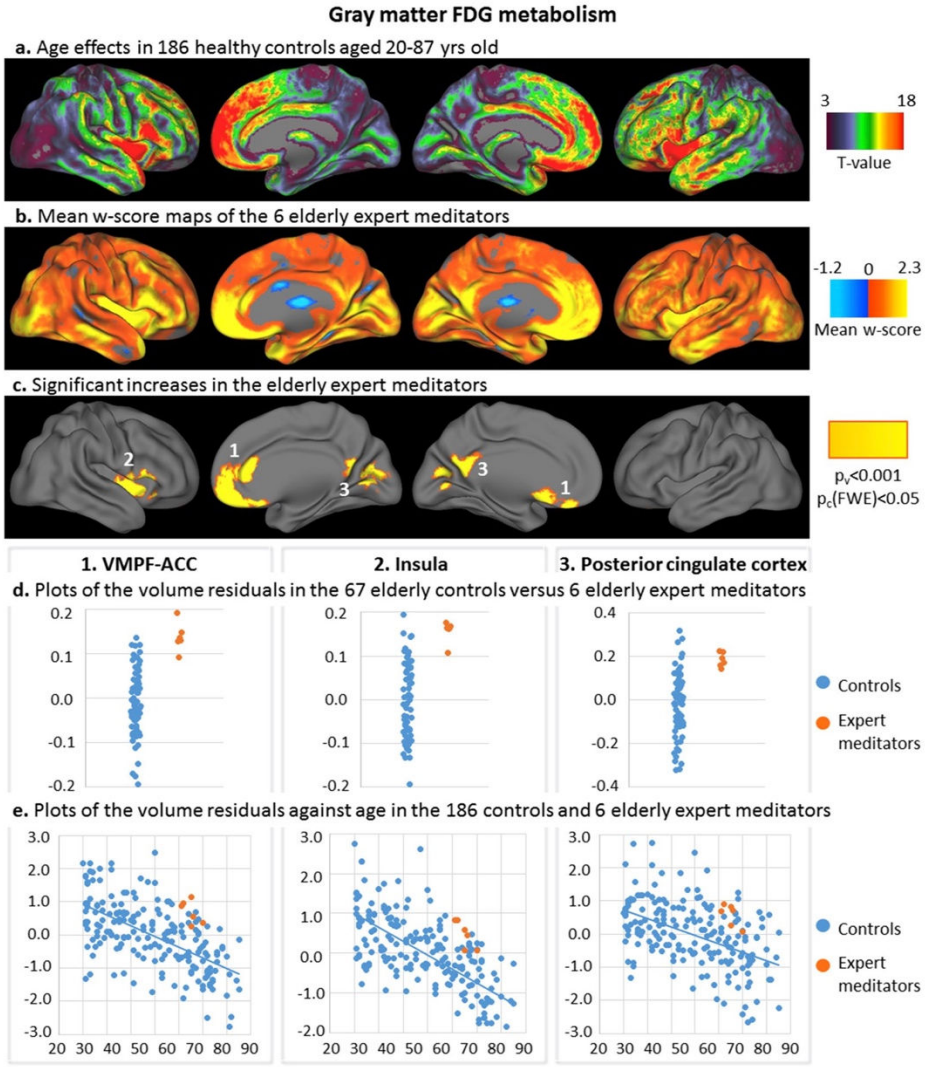

Figure 2. Results of the analyses on gray matter glucose metabolism. T-values of the voxelwise regression analysis between the z-score maps of the 186 controls (corrected for education) and age were superimposed on brain surface views (**a**). Mean w-score values of the expert meditators corrected for age and education and using the elderly control group as the reference (**b**), and clusters of interest showing significantly higher values in the expert meditators (voxel-level $p < 0.001$ and FWE-corrected cluster-level $p < 0.05$) (**c**) were superimposed on brain surface views. Glucose metabolism residuals in the 3 clusters of interest were plotted in the elderly expert meditators (orange) and in the controls (blue) of the elderly control group (**d**; residuals are corrected for age and education); of the entire control group against age (**e**; residuals are corrected for education). **VMPF-ACC**: ventromedial prefrontal and anterior cingulate cortex; **TP**: temporo-parietal.

In the 186 controls aged 20–87 years, age-related decreases in cortical GM volume and FDG metabolism were found predominantly in the bilateral insula, medial frontal, cingulate, and temporal neocortical areas (Figs 1A and 2A). Decreases in GM volume also included the cuneus and temporo-parietal junction, while age-related decreases in FDG metabolism predominated in anterior brain regions. Increased GM volume or FDG metabolism in elderly expert meditators concerned regions that were primarily affected by age, with the exception of the posterior cingulate cortex, which showed only moderate age-related FDG metabolism decreases (FDG-cluster 3). Regression plots showing GM volume and FDG metabolism as a function of age in the clusters of interest (Figs 1E and 2E) show that elderly expert meditators had higher volume and metabolism in the clusters of interest than expected for their age; all individual values of elderly expert meditators were above the slope of the regression with age in the controls. Interestingly, the voxels showing the strongest age-effects (25% highest t-values) on GM

	67 elderly controls	31 education-matched Aβneg elderly controls
MRI-cluster 1: VMPC-ACC	0.0003	0.00008
MRI-cluster 2: L TP junction	0.008	0.01
MRI-cluster 3: R TP junction	0.002	0.003
FDG-cluster 1: VMPC-ACC	0.0001	0.0003
FDG-cluster 2: R Insula	0.0003	0.0007
FDG-cluster 3: PCC	0.001	0.0009

Table 2. Between-group differences in gray matter volume and FDG metabolism in the clusters of interests (shown in Figs 1C and 2C) when comparing the 6 elderly expert meditators versus the 67 elderly controls or the 31 Aβ-negative elderly controls matched for education (p-values; Mann-Whitney U-tests). **VMPF:** ventromedial prefrontal cortex; **ACC**: anterior cingulate cortex; **TP**: temporo-parietal; **PCC:** posterior cingulate cortex; **L:** left; **R:** right.

volume and FDG metabolism overlapped 75% and 60% respectively of the MRI and FDG clusters showing an effect of meditation, i.e. the clusters of interest.

Complementary analyses. Results of complementary analyses on cognition and lifestyle are reported in the Supplementary Table S1. There was no significant difference in the cognitive performance between the elderly expert meditators and the elderly control group, but a marginal effect was observed for episodic memory, with a trend for higher performances in the elderly expert meditators. With regard to lifestyle, a significant difference was found for the leisure activity score before 30 years, and a trend was observed for all other measures in non-parametric statistics. However, in the ANOVA correcting for years of education, only the trend effect for diet remained as the expert meditators tended to have a greater adherence to the Mediterranean diet than did controls. As for sleep measures, a difference was found only for duration of awakenings, with expert meditators showing shorter duration than controls, the difference being significant in the non-parametric test and marginal in the ANOVA correcting for education. When assessing hippocampal subfield volumetry, the elderly expert meditators tended to have larger CA1 subfield volumes compared to controls (Supplementary Table S1). The projection on the 3D surface view of the hippocampus showed that meditation-expertise-related effects on the hippocampus were weak and mainly concerned the CA1 subfield (predominantly in the left hemisphere), and to a lesser degree the subiculum (on left and right inferior views; Supplementary Figure S2).

The differences in GM volumes and FDG metabolism in the clusters of interest between the elderly expert meditators and the elderly controls remained essentially the same when performing ANOVAs including education and all lifestyle measures as covariates (Supplementary Table S2), or when using a subgroup of 31 Aβ-negative elderly controls matched for education (Table 2).

Discussion

The main aim of this pilot study was to explore differences in GM volume and glucose metabolism in elderly expert meditators compared to elderly controls. We found higher volume and glucose metabolism in the anterior cingulate and ventro-medial prefrontal cortex, insula, temporo-parietal junction (for volume) and posterior cingulate cortex (for metabolism) in the elderly expert meditators. The findings need to be interpreted with caution given the small sample size of the elderly expert meditators. Yet, this study is the first to measure FDG-PET changes in meditators and it suggests that brain glucose metabolism is a sensitive measure for detecting changes associated with meditation practices. Meditation-expertise related metabolism changes included brain regions which spatially overlapped with the meditation-expertise related structural changes observed in our study (e.g. the anterior cingulate and ventro-medial prefrontal cortex), which were consistent with previous research on young and middle-aged meditators (e.g. the insula, see below). These effects were more marked than those found with structural MRI scans.

Our findings of increased brain volume and metabolism in elderly expert meditators and the topography of these findings are consistent with previous literature. Luders *et al.*[25] showed markedly less age-related brain atrophy in expert meditators aged between 24 and 77 years compared to controls in extended brain areas including those highlighted in this study. In elderly participants, expert meditators were thus expected to show larger brain volume than controls in (at least some of) these brain regions, and our results confirmed this expectation. Moreover, studies assessing brain structure in young and middle-age meditation practitioners have reported higher volume compared to non-meditators in the insula, frontal, anterior cingulate, inferior temporal cortex, hippocampus and putamen, as well as the temporo-parietal junction and posterior cingulate cortex - precuneus[16]. In a meta-analysis from 21 structural neuroimaging studies examining nearly 300 meditation practitioners, changes in the insula and anterior cingulate cortex were found to be among the most replicated findings in these studies[22]. The anterior insula and anterior cingulate cortex are highly interconnected and together form the salience network, an intrinsic large-scale network involved in interoceptive awareness, i.e. self-awareness of one's own body, respiration, heart rate, pain perception and emotional state[26,27]. The insula is also involved in emotional and empathic processing, high-level cognitive control, and attentional processes[28]; the anterior cingulate is particularly associated with self-regulation of attention and emotion[22,26,29]. Meditation-related changes of activity in these regions were also consistently reported in fMRI studies[16,22]. Thus, increased activity during mindfulness and/or compassion meditation in all or part of the salience network, anterior cingulate cortex and/or insula, was

notably found to be associated with breath awareness[30], heart rate[31], pain perception[32], emotional processing and empathy[33,34], and awareness of mind-wandering[35]. Our finding of increased anterior cingulate and insula volume/metabolism in elderly expert meditators is thus in line with the expected effects of meditation practice on brain structure and function based on these previous experiments.

The ventromedial prefrontal cortex is also consistently reported in structural neuroimaging studies on meditation practitioners, and is thought to underlie self-monitoring, affective theory of mind, and emotion regulation processes[16,22,36,37]. Although less frequently involved, the temporo-parietal junction and posterior cingulate cortex – precuneus were also found to show increased volume in young and middle-aged meditators compared to controls[38,39]. Altogether, these regions are parts of the default mode network (DMN) thought to be involved in self-referential processing, theory of mind, and mind wandering[40]. fMRI studies in meditators have shown decreased activity within the DMN, which has been interpreted as reflecting diminished self-referential processing and mind wandering[41]. By contrast, increased connectivity was found in meditators between DMN areas and anterior brain regions such as the anterior cingulate cortex, which was interpreted as reflecting increased cognitive control over the function of the DMN. Interestingly, lifelong elevated neuronal and metabolic activity within the DMN is thought to increase DMN hubs' vulnerability to aging and AD pathological processes[42]. It is thus possible that DMN structures are relatively preserved in elderly expert meditators because they have endured lifelong reduced DMN activity compared to controls. Higher volume and metabolism in DMN structures in elderly expert meditators might thus reflect both a direct effect of meditation practice on brain structures involved in self-monitoring, emotion regulation, and cognitive control, and a protective effect of DMN activity regulation, resulting in better maintenance or preservation of these structures. Also, several structures of the DMN, such as the hippocampus, posterior cingulate and ventromedial prefrontal cortex, are known to be involved in episodic memory processes[42,43]; the increased volume and/or FDG metabolism found in the elderly expert meditators might underlie the tendency for higher memory performances in our sample.

Regarding the hippocampus, morphometric differences have frequently been reported in meditators in this structure[22]. For instance, meditation practice was associated with increased left hippocampus volume in cognitively normal young and middle aged adults[38], with trends for reduced bilateral hippocampal atrophy in patients with mild cognitive impairment[44]. Moreover, lighter age effects[24] and larger volume[45] were found in the subiculum of meditators aged 24 to 77 years compared to controls. In the present study, we found only marginal effects in the hippocampus of elderly expert meditators, with higher volume observed mainly in the CA1 subfield and part of the subiculum using a lenient statistical threshold. Our findings are thus partly consistent– although the volume of the CA1 subfield *per se* has not been assessed in previous research. The weakness of the effects in the present study might be due to the limited sample size of the meditator group and/or indicates that long-term meditation effects are less marked in the hippocampus, at least in elderly meditators, compared to those found in other brain structures. It is interesting to note that, while age effects are known to predominate in the subiculum, the CA1 subfield is the most sensitive to AD, especially in early prodromal stages of the disease[46,47].

Importantly, all the brain regions where elderly expert meditators showed higher volume and higher FDG metabolism were specifically those that are particularly sensitive to aging and/or AD. Thus, as highlighted in the Figs 1A and 2A, age effects in a large group of 186 healthy controls were found to be maximal in the insula, medial prefrontal,and anterior cingulate cortex, consistent with previous findings[1–3]. On the other hand, earlier AD-related structural/ glucose metabolism changes are known to concern the hippocampus or posterior cingulate cortex and temporo-parietal junction respectively[48]. This is particularly interesting in a perspective of brain reserve, maintenance and prevention, as the effects in expert meditators specifically concerned brain areas sensitive to aging and AD[9,49]. It suggests that long-term meditation might help preserve the brain from the progressive deleterious effects of aging on brain volume and glucose metabolism, which in turn confers a brain reserve associated with a reduced risk of developing AD and/or a delay in the onset of the disease. Interestingly, previous studies in aging (or populations at-risk for AD) have shown increased volume and/or metabolism especially in the anterior cingulate cortex, but also in the medial prefrontal cortex, insula, and hippocampus in elderly with higher years of education, higher cognitive activity, or maintained cognitive functions[10,50,51].

Our complementary analyses showed that elderly expert meditators also tended to have a more active lifestyle, both early on, including higher education, and later in life, a higher adherence to a Mediterranean diet, and better sleep quality (i.e., shorter duration of awakenings during the night). Some of these differences reflect initial differences in the samples, especially for early-life measures such as education and leisure activities.While we could not fully account for possible cohort effects, (see limitation paragraph below), adjusting for years of education and lifestyle factors and using a subsample of Aβ-negative elderly controls matched for education only poorly influenced our findings, suggesting that they were not merely reflections of these differences. Beyond neuroimaging, part of the between-group differences highlighted in our complementary analyses, especially those assessing later life / current periods, might reflect an impact of expert meditation on behavioural measures, including lifestyle, diet, and sleep. This result is again particularly interesting in the context of aging and Alzheimer's disease, given the growing acknowledgment of the relevance of these factors (healthy diet, good sleep quality, more active lifestyle) for wellbeing and mental health, including decrease of AD risk in the aging population[7,8,10,52].

The present study has strengths and limitations. It is the first study to focus on elderly expert meditators, and the only study on meditation to include a measure of brain glucose metabolism. The large samples of controls who underwent the same examinations on the same scanners are also valuable as they allowed to refer to reliable normative data and to highlight aging effects across the entire adult lifespan. Despite the noise introduced by the heterogeneity in the styles of mindfulness or compassion meditation practiced in the various Buddhist traditions represented here (Zen, Dzogchen, Vipassana), we found brain regions commonly sensitive to meditation expertise. This finding suggests a generalizability of this effect beyond any particular tradition, but prevented us from identifying tradition-related effects. A larger sample of experts will be necessary to address this question. The main limitation of the present study is the small sample size of the elderly expert meditators (n = 6), which limited

the statistical analyses we could conduct and their statistical power, and thus the interpretation of the findings. For instance, we could not assess reliable correlation analyses between neuroimaging and behavioural measures within the expert meditators, and the lack of significant differences in cognitive measures might be due to the limited sample size. Inversely, small sample size could also conduct to inflated or spurious effects[22,53]. For instance, in studies assessing the impact of meditation on brain structures, the largest effect sizes were reported in studies with the smallest sample sizes, whereas more reasonable effect sizes were reported in well-powered, large sample size studies[22]. The cross-sectional nature of the study is also a limitation because of possible cohort effects. Only longitudinal studies would allow to test for a causal relationship between meditation and brain volume preservation in elderly populations. Overall, we think that this study provides encouraging findings to stimulate future research on meditation in the context of aging. Further studies with larger cohorts of elderly expert meditators and longitudinal studies assessing the effects of meditation on naïve elderly individuals are needed. Moreover, future research is needed to investigate the mechanisms underlying the effects of meditation, especially in the context of aging and AD.

Methods

Participants. A total of 192 participants were included in this study, including six expert meditators aged 60–70 years and 186 controls aged 20–87 years. The entire control group was used to map age-related brain changes, while a group of 67 elderly controls (those aged 55–75) was used for direct comparison to the elderly expert meditators (see Table 1 for demographics). All participants were involved in the *Imagerie Multimodale de la maladie d'Alzheimer à un stade Précoce* (IMAP+) Study (Caen, France), and part of the controls were included in previous publications from our laboratory[1,8,54,55]. All participants were screened for the absence of history and clinical evidence for major neurological or psychiatric disorder and performed in the normal range on all tests of the screening neuropsychological battery, including the mini mental state examination (MMSE[56]).

Consistent with prior research on expertise, elderly expert meditators had at least 10,000 h of formal lifelong meditation practice. Meditators were trained in Buddhist meditation practices from various traditions including Zen Korean Buddhism (1 person), Tibetan Buddhism (4) and Vipassana (3). They all practiced some kind of mindfulness-related, loving-kindness, and compassion meditations. We deliberately chose to include a variety of Buddhist traditions, which practice these two families of practice, to be able to generalize our finding above and beyond any particular style of mindfulness or compassion meditation in these traditions. The underlined assumption is that these various sub-genres of mindfulness and compassion meditation could commonly impact aspects of attention, emotion and stress regulation, and psychoaffective factors known to impact on brain aging, and overall on mental health and well being in aging. Elderly expert meditators had between 15,000 to 30,000 hours of meditation practice over the last 10 to 40 years, about half of which was carried out at retreats.

The IMAP+ Study was approved by a regional ethics committee (Comité de Protection des Personnes Nord-Ouest III) and is registered with http://clinicaltrials.gov (number NCT01638949). All participants gave written informed consent to the study prior to participation. All experiments were performed in accordance with relevant guidelines and regulations.

Imaging data acquisition. All participants underwent neuroimaging scans on the same MRI and PET scanners at the Cyceron Centre (Caen, France).

MRI data. MR scans were all acquired on a Philips Achieva (Eindhoven, The Netherlands) 3 T scanner. Subjects were equipped with earplugs and their heads were stabilized with foam pads to minimize head motion. T1-weighted structural images were obtained in all participants using a three-dimensional fast-field echo sequence (sagittal; repetition time = 0 ms; echo time = 4.6 ms; flip angle = 10°; 180 slices; slice thickness = 1 mm; field of view = 256 × 256 mm^2; matrix = 256 × 256). Moreover, a high resolution proton density (PD) weighted sequence was acquired perpendicularly to the long axis of the hippocampus (TR = 3500 ms; TE = 19 ms; flip angle = 90°; 13 slices; slice thickness = 2 mm; inter-slices gap = 2 mm; in-plane resolution = 0.375 × 0.375 mm^2, acquisition time = 7.4 min), in the 6 elderly expert meditators and in 53 of the 67 older controls. This last scan was used for hippocampal subfield manual delineation.

PET data. All participants had a FDG-PET scan within 2 months of the 3D-T1 MRI. Sixty-one of the elderly control group and 4 of the expert meditators also had a Florbetapir-PET scan to measure Aβ deposition. Both FDG- and Florbetapir-PET scans were acquired on a Discovery RX-VCT-64 PET-CT device (GE Healthcare) with a resolution of 3.76 × 3.76 × 4.9 mm (field of view = 157 mm). Forty-seven planes were obtained with a voxel size of 2.7 × 2.7 × 3.27 mm. A transmission scan was performed for attenuation correction before the PET acquisition. For FDG–PET scans, participants fasted for at least 6 hours before scanning and were at rest in a quiet and dark room during the 30 minutes preceding tracer injection. Intravenous injection of approximately 180 MBq of FDG was carried out 50 minutes before a 10-minute acquisition. Regarding the Florbetapir-PET scan, intravenous injection of approximately 4 MBq/kg of Florbetapir was carried out 50 minutes before a 20-minute acquisition.

Imaging data pre-processing. *T1-weighted MRI* were segmented, normalized, and modulated for nonlinear warping using the Segment function of the Statistical Parametric Mapping 12 (SPM12) software (Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Resulting local GM volume maps corrected for brain size were finally smoothed with a Gaussian kernel of 8 × 8 × 8 (x, y, z).

FDG and Florbetapir PET data were first corrected for partial volume effects (PVE, PMOD Technologies) using a 2-tissue compartment model. Resultant images (GM compartment only) were coregistered onto their corresponding MRI, and normalized using the deformation parameters derived from the MRI. Images were then scaled using the cerebellar GM as a reference. Normalized and scaled FDG-PET data were smoothed with a

Gaussian kernel of 10 × 10 × 10 (x, y, z). For Florbetapir-PET data, a global neocortical mean value was extracted from each individual using a predetermined mask, (including all regions but the cerebellum, hippocampus, amygdala and subcortical gray nuclei), and participants were classified as Aβ-positive or Aβ-negative based on Florbetapir-PET data acquired in a group of 41 healthy adults under 40 years old[54,57].

High resolution PD-weighted hippocampal acquisition. Hippocampal subfields were manually segmented on the high resolution Proton Density weighted scan according to a protocol detailed in previous publications[46,58]. Briefly, three hippocampal regions were delineated: (i) the subiculum; (ii) CornuAmmonis (CA) 1; and (iii) CA2, CA3, CA4, and the Dentate Gyrus (DG) pooled together in a unique region termed CA2/3/4/DG in what follows. Manual delineations were all performed by the same raters as in our previous publications showing high inter-rater reliability (ICC values between the two raters = 0.8 to 0.9). The volume of the whole hippocampus corresponded to the sum of the volumes of the three resulting hippocampal regions.

Neuropsychological tests and lifestyle and sleep questionnaires. Neuropsychological measures and questionnaire scores were selected among detailed assessments included in the IMAP+ study and are fully described in our previous publications[59,60]. Here we selected a few representative measures of cognition and self-reported assessment of lifestyle and sleep quality. We used one score for each of the following cognitive areas: verbal fluency (sum of category and letter fluency tasks), episodic memory (sum of the free recall of two 16-word lists from the ESR task[59]), short-term memory, and working memory (forward and backward digit span), processing speed and executive functions (Trail Making Test part A and inhibition score part B – part A, respectively). Moreover, we used scores derived from the Lifetime of experiences questionnaire (LEQ[61]) to assess complex mental activity early and later in life. Specifically, we derived two scores reflecting the frequency of participation in leisure activities before 30 and from 30 to 65 years, and a third score reflecting the highest level of occupation reached from 30–65 years. Adherence to Mediterranean diet was quantitatively assessed using the Mediterranean Adherence Screener (MEDAS, Schröder *et al.*, 2011). Finally, sleep was assessed using a questionnaire derived from the Pittsburgh Sleep Quality Index (PSQI[62]), assessing sleep quality and disturbances during the last five years. This questionnaire, previously used by our research group[52], allows to extract the following information: sleep quality, sleep latency and duration, as well as the number and duration of nocturnal awakenings.

Statistical analyses. *Main analyses.* Firstly, we aimed to assess whether the elderly expert meditators showed differences in GM volume and FDG metabolism compared to elderly controls. For this purpose, w-score maps were computed for each expert meditator and each imaging modality using the 67 elderly controls aged 55–75 as the reference and regressing out the effects of age and education as detailed elsewhere[63]. For each modality, individual w-score maps were averaged across the elderly expert meditators to provide whole-brain profiles of GM volume and FDG metabolism changes compared to matched controls. One-sample t-tests were then performed on the GM volume and FDG metabolism w-scores maps and differences from 0 were assessed using a threshold of p (voxel-level uncorrected) <0.001 with a cluster-level FWE-corrected $p < 0.05$ threshold. These latter analyses, for GM volume and FDG metabolism respectively, were conducted to identify the clusters of interest.

Secondly, we wished to assess whether the brain regions exhibiting meditation-expertise-related effects were sensitive to aging and whether the elderly expert meditators differed from matched controls in this aging process. For this purpose, i) we performed voxelwise regression analyses between age and GM volume or FDG metabolism, including education as a covariate, within the entire group of 186 controls aged 20 to 87 years; ii) we extracted, in the 186 controls aged 20 to 87 years, the values of GM volume and FDG metabolism in the clusters of interest. The effect of education were regressed out from these extracted values and the education-adjusted values were plotted against age across the 186 controls. The values of the elderly expert meditators, similarly corrected for education, were reported on these plots.

Complementary analyses. Firstly, group comparison analyses were conducted on measures of cognition, lifestyle, and sleep quality, (missing data indicated in Supplementary Table S1), using both non-parametric Mann-Whitney U-test and ANCOVAs to correct for education. Differences were considered as marginal when $p < 0.05$ and as significant when $p < 0.01$.

Secondly, to investigate possible changes in hippocampus substructures, two different approaches were used. First, the raw volumetric measures of the subiculum, CA1 and CA2/3/4/DG obtained from manual delineation were normalized by the total intracranial volume (derived from the segmentation of the T1-MRI with SPM12) to compensate for inter-individual variability in head size, and compared between groups using both non-parametric Mann-Whitney U-test and ANCOVAs to correct for education. To limit the number of statistical tests, and as there was no significant effect of laterality (left versus right), the analyses were performed on the bilateral (left plus right) measurements. Secondly, 3D-hippocampal surface projection was also performed as described in details elsewhere[64]. Briefly, the SPM-T map of the one-sample t-test performed on the GM volume w-scores maps of the elderly expert meditators was superimposed onto a 3D template surface representation of the right and left hippocampi using the publicly available "Anatomist/BrainVISA" software (http://www.brainvisa.info/).

Thirdly, if significant differences were found between elderly expert meditators and elderly controls in their lifestyle measures, we tested whether the differences in the neuroimaging measures were still significant when correcting for these lifestyle measures. ANCOVAs were performed on the extracted GM volume or FDG metabolism values within the clusters of interest comparing both groups and including education and the lifestyle measures as covariates.

Finally, a subgroup of the elderly controls was composed by excluding all elderly with less than 12 years of education–the minimum in the elderly expert meditators–and/or with an Aβ-positive Florbetapir PET scan (n = 31;

see demographic information in Table 1). Values of GM volume and FDG metabolism were extracted in the clusters of interest in the 6 elderly expert meditators and in the 31 Aβ-negative education group-matched elderly controls and Mann-Whitney U tests were used to compare both groups.

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

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Author Contributions

The study was conceived by G.C. and A.L. Data collection, data entry, and data processing was supervised by G.C., F.M., C.T., B.L., E.A.U., G.R., R.F., C.A., S.E., J.G., G;P., G.P., A.C., A.Q., B.D., J.G.B., M.R., A.L; G.C. had full access to all the study data and G.C. assumes responsibility for the data integrity and the accuracy of the data analysis. G.C. and A.L. wrote the first draft of the paper and have primary responsibility for the final content. All authors contributed to and approved the final manuscript.

Additional Information

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RESEARCH ARTICLE

Hippocampal subfields alterations in adolescents with post-traumatic stress disorder

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Abstract

Reexperiencing symptoms in adolescent Post-Traumatic Stress Disorder (PTSD) are characterized by the apparition of vivid intrusive images of the traumatic event. The emergence of these intrusions is thought to be related to a deficiency in context processing and could then be related to hippocampal alterations. The hippocampus is a complex structure which can be divided into several subfields, namely, the Cornu Ammonis (CA1, CA2, and CA3), the subiculum, and the dentate gyrus (DG). As each subfield presents different histological characteristics and functions, it appears more relevant to consider hippocampal subfields, instead of only assessing the whole hippocampus, to understand the neurobiology of PTSD. Hence, this study presents the first investigation of structural alterations within hippocampal subfields and their links to reexperiencing symptoms in adolescent PTSD. Hippocampal subfields were manually delineated on high-resolution MRI images in 15 adolescents (13–18 years old) with PTSD and 24 age-matched healthy controls. The volume of the region CA2-3/DG region was significantly smaller in the PTSD group compared to controls in both hemispheres. No other significant difference was found for other subfields. Moreover, the volume of the left CA2-3/DG was negatively correlated with the intrusion score (as measured by the Impact of Events Scale-Revised) in the PTSD group. To conclude, an alteration in the hippocampal subregion CA2-3/DG, known to resolve interferences between new and similar stored memories, could participate in the apparition of intrusive trauma memories in adolescents with PTSD.

KEYWORDS

adolescents, hippocampal subfields, MRI, post-traumatic stress disorder

1 | INTRODUCTION

Individuals who lived a traumatic experience are at risk of developing a post-traumatic stress disorder (PTSD). This psychiatric disorder is associated with reexperiencing symptoms, which are characterized by the intrusions of vivid and involuntary memories of the traumatic event. PTSD symptoms also encompass avoidance of trauma-reminders, excessive physiological arousal, and negative alteration in cognition and mood (American Psychiatric Association, 2013). Deficient context processing could be at the core of PTSD pathophysiology (Liberzon & Abelson, 2016). Processing contextual information is crucial to disambiguate cues associated with safety and threat and, consequently, adapt our behavior to the environment (Liberzon & Abelson, 2016; Maren, Phan, & Liberzon, 2013). Hence, deficient context processing could participate in the emergence of recurrent intrusive memories and the overgeneralization of fear responses in safe environments (Liberzon & Abelson, 2016). These intrusions could be related to an alteration of the hippocampal structure, known to be involved in contextual memory (Maren et al., 2013). Indeed, several neuroimaging studies reported smaller hippocampal volumes in adults suffering from PTSD compared to people who lived a traumatic experience without PTSD and compared to healthy controls (Logue et al., 2018; Pitman et al., 2012).

The hippocampus is a complex structure which can be divided into several subfields, namely, the Cornu Ammonis (CA1, CA2, and CA3), the subiculum, and the dentate gyrus (Duvernoy, 2005). These hippocampal subfields have distinct histological characteristics and present, thereby, differential vulnerability to pathological conditions such as Alzheimer's disease, schizophrenia, and major depression (Cao et al., 2017; de Flores et al., 2015; Ho et al., 2017; Tannous et al., 2018) and to other factors like stress (Gould, 2007). Furthermore, hippocampal subfields are involved in different memory processes. It has been shown that CA1 is involved in pattern completion (ability to recall a memory based on a partial cue; Carr, Rissman, & Wagner, 2010). The dentate gyrus (DG) plays a role in pattern separation (ability to diminish the similarity between two resembling memories) and CA3 is thought to be involved in both processes. Hence, investigating hippocampal subregions, instead of the hippocampus as a single entity, appears more appropriate for the understanding of the neurobiology of PTSD and the mechanisms underlying the reexperiencing symptoms.

Alterations within hippocampal subregions can be examined in volumetric studies using high-resolution Magnetic Resonance Imaging (MRI). Wang et al. (2010) manually segmented a part of the hippocampal body and found that only the CA3/DG volume was significantly smaller in veterans with PTSD compared to veterans without PTSD. Although they did not investigate subfield volumes of the entire hippocampus, they suggested that PTSD was not related to a global atrophy of the hippocampus but to alterations of these specific subfields (Wang et al., 2010). These results are in line with theoretical models which propose that reexperiencing symptoms could be related to a pattern separation dysfunction resulting from a reduced neurogenesis in the dentate gyrus (Besnard & Sahay, 2016; Liberzon & Abelson, 2016). To our knowledge, there is no existing investigation of hippocampal subfield alterations in adolescent PTSD. This could result from the consistent finding that the hippocampus is not impaired in children and adolescents with PTSD. Unlike work in adults, most pediatric neuroimaging studies do not report any significant difference in hippocampal volume in children and adolescents with PTSD compared to controls (Morey, Haswell, Hooper, & De Bellis, 2016; Woon & Hedges, 2008) (but see (Mutluer et al., 2017)). Nonetheless, these studies may have failed to detect any alteration because of the use of low-resolution structural MRI images or processing techniques not adapted to pediatric populations (Keding & Herringa, 2015). For instance, the automatic segmentation method Freesurfer is known to over-estimate hippocampal volumes in children (Schoemaker et al., 2016). In addition, even if there are no global changes detected on the hippocampus, it does not mean that there are no local effects on hippocampal subfields. For example, one study (Gogtay et al., 2006) showed that the volume of the whole hippocampus in 4 years old was similar to young adults, but recent volumetric studies revealed differential ongoing maturation of the hippocampal subfields during childhood and adolescence (Daugherty, Flinn, & Ofen, 2017; Lee, Ekstrom, & Ghetti, 2014). Hence, even if there is no alteration of the volume of the whole hippocampus, PTSD symptomatology in adolescents may be associated with alterations of specific hippocampal subfields.

This present study aims to examine the volume of the hippocampus as a whole and hippocampal subfields in adolescent PTSD. The hippocampus and its subfields were manually segmented on high-resolution 3 T MRI images and, then, their volumes were extracted. We predicted smaller volumes of the CA3 and DG subfields in adolescents with PTSD compared to controls. We also hypothesized that these alterations would be related to reexperiencing symptoms.

2 | METHODS AND MATERIALS

2.1 | Participants

Fifteen adolescents with PTSD, aged 13–18 years (13 females), were recruited through the departments of child and adolescent psychiatry of three French University Hospitals (Caen, Rennes, Rouen). PTSD adolescents received no psychotropic medication during the previous week and were free from other mental disorders including major depression. Twenty-five typically developing adolescents (12 females) with no history of trauma were recruited by prospecting in several junior high schools of the region (Normandy, France). One subject was excluded due to severe motion artifacts on the MRI data.

Hence, 15 PTSD patients and 24 controls were included in the analyses (see Table 1). Some participants for this study took part in a larger project investigating self-reference processing (Dégeilh et al., 2017). All were right-handed and French native speakers. None of them reported any prior or neurological or learning disabilities, head trauma, and MRI contra-indications. The study was approved by the local Ethics Committee (CPP Nord Ouest III). All adolescents and their parents signed informed consent after a comprehensive description of the study.

2.2 | Assessment

A board-certified child and adolescent psychiatrist interviewed and screened all participants. Psychiatric diagnoses were assessed using the Structured Clinical Interview-Clinician Version (SCID-CV) (First, Spitzer, Gibbon, & Williams, 1996; Lobbestael, Leurgans, & Arntz, 2011). PTSD severity was additionally examined with the French version of the Impact of Event Scale Revised (IES-R) (Brunet, St-Hilaire, Jehel, & King, 2003; Weiss & Marma, 1997). This scale assessed intrusions, hyperarousal, and avoidance symptoms. Major depression was categorically screened using the SCID-CV (First et al., 1996; Lobbestael et al., 2011) and dimensionally measured with the French version of the Children Depression Inventory (CDI; Dugas & Bouvard, 1996; Kovacs, 1981).

2.3 | Neuroimaging data acquisition

All participants were scanned with a 3 T Philips MRI scanner at the Cyceron Center (Caen, France). T1-weighted anatomical volumes were acquired using a three-dimensional fast-field echo sequence (3D-T1-FFE sagittal; Repetition Time (RT) = 20 ms; Echo Time (ET) = 4.6 ms; flip angle = 10°; 180 slices; slice thickness = 1 mm; field of view = 256 × 256 mm^2, in-plane resolution = 1 × 1 mm^2; acquisition time = 9 min 41 s). To segment the hippocampal subfields, a high-resolution proton density-weighted sequence was acquired perpendicularly to the long axis of the hippocampus (Repetition Time [RT] = 3,500 ms; Echo Time [ET] = 19 ms; flip angle = 90°; 13 slices; slice thickness = 2 mm; interslice

TABLE 1 Demographic and psychopathological measures, depicting means and standard deviations (SD), for adolescents with PTSD and healthy controls

	PTSD Mean ± *SD*	Controls Mean ± *SD*	t	*p* value
Number (F/M)	15 (13/2)	24 (12/12)	–	–
Age (months)	187.20 ± 18.46	196.92 ± 21.08	1.46	.151
IQ (WISC-IV)[a]	97.43 ± 19.48	109.04 ± 17.24	1.91	.064
Index trauma (n)	Sexual abuse (11) Witness of suicide (2) Car accident (1) Loss of loved one (1)	–	–	–
PTSD duration (months)	25.27 ± 24.58	–	–	–
Age of onset (years)	13.33 ± 1.72	–	–	–
IES-R				
Intrusion	20.40 ± 8.58	8.16 ± 7.29	4.76	<.001
Hyperarousal	13.60 ± 5.37	3.21 ± 4.83	6.26	<.001
Avoidance	18.07 ± 7.10	8.63 ± 6.99	4.07	<.001
CDI	19.73 ± 9.58	9.17 ± 4.85	4.57	<.001

[a] Missing data of one patient.

gap = 2 mm; in-plane resolution = 0.375 × 0.375 mm^2; acquisition time = 7 min 38 s).

2.4 | Manual segmentation of hippocampal subfields

Hippocampal subfields were manually demarcated following the procedure developed in our laboratory (Figure 1) (de Flores et al., 2015; La Joie et al., 2010). From the most anterior part of the hippocampus to the apparition of colliculi, the hippocampus was segmented into three areas: (1) Subiculum; (2) CA1; and (3) a region combining CA2, CA3, and the DG ("CA2-3/DG"). Because it is particularly difficult to differentiate the subfields in the tail of the hippocampus, the most posterior part of the hippocampus (posterior to the colliculi) was segmented into one single region called "tail." The volume of the whole hippocampus corresponded to the sum of the four segmented subregions (subiculum, CA1, CA2-3/DG, tail). Manual delineations were all performed by the same rater (CP), blind to any information concerning the participants. Then, a second rater (CA), also blind to the identity of the participants, visually checked and validated all the delineations. Before segmenting the data, CP was trained during several months by two expert raters (RDF and CA). The formation was validated by a high interrater reliability between CP and CA on an independent sample of 20 healthy subjects (Intraclass Correlation Coefficients: ICC (2;1) = 0.94, 0.91, and 0.91 for CA1, Subiculum, and CA2-3/DG, respectively).

2.5 | Statistical analyses

Statistical analyses were performed using Statistica 13 (Statsoft, Tulsa, OK). First, raw volumes were normalized to the total intracranial volume (TIV) in order to correct for head-size differences (de Flores et al., 2015; La Joie et al., 2010). TIV values were extracted from the T1-weighted images with the Computational Anatomy Toolbox (CAT12). To evaluate group differences, we performed general linear models (GLMs) with the TIV-adjusted volumes as dependent variables, diagnosis as independent variable, and sex as nuisance covariate. As several studies reported age-related differences in hippocampal subfields volumes across lifespan, we also considered controlling our analyses for age (Daugherty, Bender, Raz, & Ofen, 2016) despite this variable not differing significantly between our groups. To choose the best statistical model, with or without age as a covariate, we conducted F-tests and AICc (Akaike Information Criterion corrected for

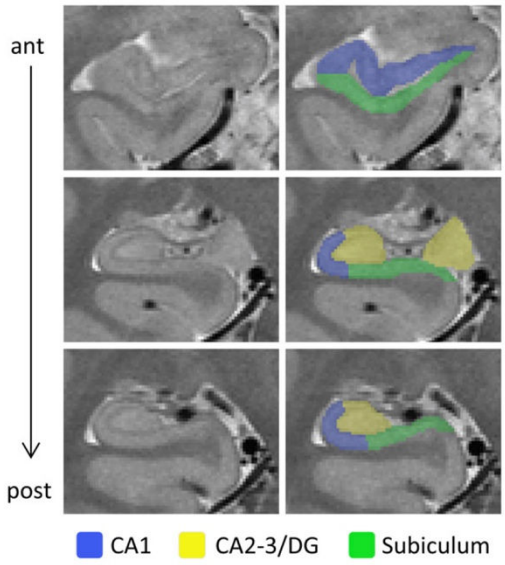

FIGURE 1 Example of segmentation of the hippocampus into the following subfields: CA1 (blue), CA2-3/DG (yellow), and subiculum (green). These hippocampal subregions were delineated on 9 slices on average. However, for the purpose and ease of illustration, segmentation is displayed on three representative slices along the anterior (ant) – posterior (post) axis of the hippocampus. For a complete slice-by-slice example of subfields segmentation, see (La Joie et al., 2010) [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 TIV-adjusted hippocampal volumes in adolescents with PTSD and healthy controls

	TIV-adjusted volumes (mm3)		Group			Sex		Age	
	PTSD	Controls	F	*p*	p_{FDR}	F	*p*	F	*p*
Hippocampus									
L	3,011 ± 413	3,511 ± 379	10.14	.003	0.008	1.301	.262	–	–
R	3,001 ± 373	3,573 ± 342	16.99	.0002	0.002	1.696	.201	–	–
CA1									
L	878 ± 152	966 ± 112	0.533	.470	0.470	4.257	.047	6.45	.016
R	877 ± 114	1,001 ± 153	1.835	.184	0.294	4.711	.037	4.17	.049
CA2-3/DG									
L	857 ± 162	1,083 ± 153	10.43	.003	0.008	1.105	.300	4.69	.037
R	890 ± 180	1,068 ± 162	7.341	.010	0.020	0.371	.546	–	–
Subiculum									
L	773 ± 164	841 ± 111	0.805	.376	0.429	2.271	.141	–	–
R	830 ± 156	899 ± 112	1.105	.300	0.400	1.561	.219	–	–
Tail									
L	503 ± 77	621 ± 250	–	–	–	–	–	–	–
R	404 ± 133	605 ± 228	–	–	–	–	–	–	–

Abbreviations: L = left; R = right

small sample) prior to the statistical evaluation (Burnham, Anderson, & Huyvaert, 2011; R Core Team, 2018).

Levene tests were performed to check the homogeneity of variance: *p* values were superior to .05 for all volumes except for the tail region. However, this tail region has been disregarded a priori within this study as the anatomy of the hippocampal tail is complex and subfields cannot be distinguished in this area. Still, we reported the measurements for the tail region for the sake of completeness of our data.

Then, when the hippocampal subfields volumes were significantly different between groups, we conducted partial correlations between the TIV-adjusted volumes and the three scores (intrusion, hyperarousal, and avoidance) of the IES-R scale assessing for symptom severity. We also performed partial correlations with PTSD duration and age of onset. To adjust for multiple comparisons, we applied a FDR correction (False Discovery Rate, (Benjamini & Hochberg, 1995)), using the function "p.adjust()" of the package "stats" in R (R Core Team, 2018).

3 | RESULTS

3.1 | Participant characteristics

Participant characteristics are displayed in Table 1. There were no significant differences between groups for age and IQ. PTSD patients showed significantly higher levels of symptom severity on the three scores of the IES-R scale (intrusion: $t = 4.76$, $p < .001$; hyperarousal: $t = 6.26$, $p < .001$; and avoidance: $t = 4.07$, $p < .001$) compared to controls. They also had a higher score on the depression scale (CDI score: $t = 4.57$, $p < .001$) compared to controls.

3.2 | Hippocampal alterations in PTSD

TIV-adjusted volumes (mean ± SD) of the hippocampal subfields and GLMs results are summarized in Table 2. Concerning the whole hippocampus, the volumes of left and right hippocampi were significantly smaller in the PTSD group compared to controls. Concerning hippocampal subfields, no significant differences were found between the groups for the subiculum and CA1 volumes. However, the CA2-3/DG volumes were smaller in the PTSD group compared to controls on both (left and right) sides (Figure 2).

3.3 | Hippocampal alterations in PTSD controlling for depression symptoms

Although screening excluded patients with major depression, the PTSD group presented a higher score on the depression scale (CDI) compared to controls. As depression could be related to structural changes in hippocampal subfields (Huang et al., 2013), we added the depression score (CDI) as nuisance covariate in our analyses. The significant results remained unchanged: we found smaller hippocampal and CA2-3/DG volumes in the PTSD group (See Table 3).

3.4 | Correlations with symptom severity

The relation between CA2-3/DG volumes and symptom severity were explored using partial correlations (controlling for sex, age, and depression). The left CA2-3/DG was negatively correlated with the intrusion score ($r = -0.74$, $p = .006$, $p_{FDR} = 0.036$; Figure 2), but was not correlated with the hyperarousal score ($r = -0.50$, $p = .099$, $p_{FDR} = 0.297$), nor with the avoidance score ($r = -0.19$, $p = .55$, $p_{FDR} = 0.66$). The right CA2-3/DG was not correlated with any of the three IES-R scores (intrusion score: $r = -0.36$, $p = .26$, $p_{FDR} = 0.52$; hyperarousal score: $r = -0.14$, $p = .66$, $p_{FDR} = 0.66$; avoidance score: $r = 0.24$, $p = .46$, $p_{FDR} = 0.66$).

3.5 | Correlations with PTSD duration and age of onset

Partial correlations (controlling for sex, age, and depression) were also conducted between PTSD duration, age of onset and CA2-3/DG volumes. However, none of these correlations were significant ($p > .05$).

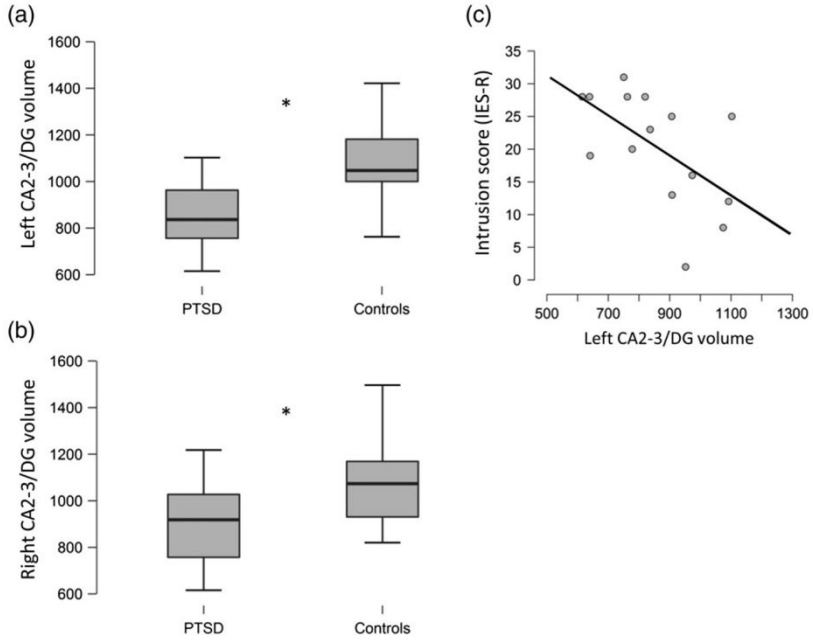

FIGURE 2 (a, b) Significant differences (*p_{FDR} < 0.05) in TIV-adjusted CA2-3/DG volumes (mm^3) between the PTSD group and the healthy controls; (c) Negative correlation between the TIV-adjusted left CA2-3/DG volume (mm^3) and the intrusion score (IES-R) in the PTSD group

3.6 | Supplementary analyses

The significant results remained unchanged if we only considered the female subjects (nPTSD = 13, nControls = 12). The hippocampal volumes were significantly smaller in adolescents with PTSD compared to controls (left hippocampus: F = 11.70, p = .003; right hippocampus: F = 18.25, p = .003). The CA2-3/DG regions were significantly smaller in the PTSD group compared to controls (left CA2-3/DG: F = 9.18, p = .006; right CA2-3/DG: F = 13.68, p = .001). And the left CA2-3/DG volume was negatively correlated with the intrusion score (r = −0.74, p = .008).

4 | DISCUSSION

This study presents the first investigation of alterations within hippocampal subfields and their links to reexperiencing symptoms in adolescent PTSD. Using high resolution MRI and manual segmentation, we show that the hippocampal volumes are smaller in adolescents with PTSD compared to controls and that these alterations are specific to the CA2-3/DG region. Noteworthy, these differences between groups are still significant after controlling for depression symptoms. In addition, we report a negative correlation between the intrusions score and the left CA2-3/DG volume in the PTSD group. Our results suggest that an alteration in the hippocampal subregion CA2-3/DG could participate in the emergence of reexperiencing symptoms in adolescents with PTSD.

Hippocampal volumes were smaller in adolescents with PTSD compared to controls. PTSD has been previously associated with hippocampal alterations in adults. Indeed, the ENIGMA consortium reported smaller hippocampal volumes on a large cohort (1,868 subjects) in civilians and veterans with PTSD compared to controls and, a negative correlation between hippocampal volumes and PTSD severity (Logue et al., 2018). In contrast, most of pediatric studies failed to report any hippocampal alterations in children and adolescents with PTSD compared to healthy subjects (Morey et al., 2016; Woon & Hedges, 2008) (but see (Mutluer et al., 2017)). Woon and Hedges (2008) hypothesized that the trauma and the development of PTSD could have a subsequent effect on hippocampal maturation and thus, the atrophy could only be detectable in adults. However, these studies could have failed to detect any alteration because of the use of low resolution structural MRI images or segmentation techniques that may not have been adapted to pediatric populations. Indeed, using high-resolution MRI images and manual segmentation, we found smaller hippocampal volumes in adolescents with PTSD, in accordance with Mutluer et al. (2017) who also manually segmented the whole hippocampus in adolescents with PTSD.

Furthermore, our results showed that hippocampal alterations in PTSD adolescents are specific to the CA2-3/DG region. These findings are in line with Wang et al. (2010) who found smaller CA3/DG volumes in veterans with PTSD compared to veterans without PTSD. Hippocampal subfields have distinctive histological characteristics. Interestingly, neurogenesis in the dentate gyrus is thought to be present during the entire life span (Boldrini et al., 2018; Eriksson et al., 1998; Spalding et al., 2013), but this process can be negatively affected in diverse pathological conditions. Hippocampal differences described in PTSD populations could then be related to the development of comorbidities, such as major depression (see (Huang et al., 2013)). In our study, although screening excluded patients with major depression, they presented a higher score on the depression scale (CDI) compared to controls. Depression was thus added as a nuisance covariate in all our analyses. Even controlling for depression, we found

TABLE 3 Hippocampal alterations in adolescent PTSD controlling for depression symptoms

	Group			Sex		Depression		Age	
	F	*p*	p_{FDR}	F	*p*	F	*p*	F	*p*
Hippocampus									
L	8.853	.0053	0.016	1.346	.254	0.420	.521	–	–
R	16.518	.0003	0.002	1.847	.183	1.306	.261	–	–
CA1									
L	2.251	.1427	0.169	4.812	.035	2.609	.116	7.155	.011
R	3.948	.0550	0.088	5.245	.028	2.336	.136	4.648	.038
CA2-3/DG									
L	7.902	.0081	0.017	1.099	.302	0.057	.812	4.607	.039
R	7.684	.0084	0.017	0.425	.519	0.905	.348	–	–
Subiculum									
L	1.364	.2507	0.251	2.347	.135	0.585	.449	–	–
R	2.185	.1483	0.169	1.691	.202	1.163	.288	–	–

Abbreviations: L = left; R = right

smaller volumes of the CA2-3/DG region in the PTSD group. This result suggests that hippocampal alterations are related to PTSD and are not exclusively associated with other comorbidities, like depression.

Mechanisms underlying hippocampal alterations in PTSD still remain elusive: the smaller hippocampal volumes reported in patients could result from trauma exposure or be a preexisting condition and, thus, be a vulnerability factor for the development of PTSD (Gilbertson et al., 2002; Pitman et al., 2012). First, hippocampal alterations could be caused by the massive amount of stress generated during the traumatic event. Indeed, the hippocampus comprises many glucocorticoid receptors and pathological stress is known to reduce dendritic branching in the Cornu Ammonis and to negatively affect neurogenesis (Gould, 2007; Schoenfeld, McCausland, Morris, Padmanaban, & Cameron, 2017). Nonetheless, CA3/DG modifications are thought to be reversible after a certain time without stress exposure (Gould, 2007; Heine, Maslam, Zareno, Joëls, & Lucassen, 2004). Hence, the small volumes of CA2-3/DG reported in the PTSD group could reflect a deficient process of recovery from trauma exposure.

However, one study, realized in identical twins discordant for trauma exposure, suggests that PTSD patients could already have smaller hippocampi before the trauma (Gilbertson et al., 2002). They found that the veterans with PTSD and their unexposed co-twins had similar hippocampal volumes and these two groups had smaller hippocampal volumes compared to the veterans without PTSD and the unexposed non-PTSD co-twins. Hence, having small hippocampal volumes, and especially small CA2-3/DG volumes, could be considered as a risk factor to develop PTSD. According to Kempermann's hypothesis (Kempermann, 2008), the newborn hippocampal neurons (in the dentate gyrus) constitute a "neurogenic reserve" and could be considered as an adaptive advantage to face novelty and complex situations. This neural reserve is also thought to have a compensatory potential to maintain the hippocampal function in pathological conditions. Hence, the initial neurogenesis capacity in the dentate gyrus (before the trauma) could influence the way a person will face the traumatic event and overcome the potential consequences. In line with this hypothesis, Hill, Sahay, and Hen (2015) showed that mice with initial increased neurogenesis developed less anxiety-related behaviors compared to controls during a chronic stress paradigm. Further work is required to understand to which extent an enhanced neurogenesis capacity in the dentate gyrus (before the trauma) could be protective, help to overcome the alterations caused by the stress of the traumatic event and, thus, prevent the development of PTSD.

It is widely acknowledged that the hippocampus and its different subfields play a crucial role in memory processes (Horner & Doeller, 2017; Rolls, 2016). The dentate gyrus is thought to underlie pattern separation (Berron et al., 2016) and thus, reduces interferences between new information and similar stored memories (Besnard & Sahay, 2016; Kheirbek, Klemenhagen, Sahay, & Hen, 2012). This function is crucial to encode precise episodic memories and to further discriminate similar contextual representations. This mechanism permits to generate adaptive behaviors to our environment by allowing, for instance, the discrimination of contextual information previously associated with safety or danger. In animal studies, a reduced production of neurons in the dentate gyrus has been associated with pattern separation impairment (Clelland et al., 2009; Tronel et al., 2012). Hence, the smaller dentate gyrus volumes reported in the PTSD group could reflect reduced pattern separation capacities compared to controls. Although we did not assess pattern separation abilities in this study, this hypothesis is consistent with several studies reporting impoverished autobiographical memories in adults with PTSD (Lapidow & Brown, 2015). Indeed, this difficulty to recall specific and detailed episodes of their past (reported as overgeneralized memory) could be partly caused by a low capacity to reduce the overlap between the memory traces of two similar experiences.

In addition to their implication in memory deficits, the CA2-3/DG alterations could be at the core of some psychopathological symptoms. Our study provides, for the first time in humans, evidence of a relation between specific hippocampal subfields alterations and intrusions in PTSD. Our results showed a negative correlation between the volume of the left CA2-3/DG region and the intrusion score in the PTSD group. As discussed previously, a reduced dentate gyrus volume could reflect low pattern separation capacities in the PTSD group. According to the theoretical model proposed by Besnard and Sahay

(2016), if the interferences between a new experience and the memory of the traumatic event are not resolved, nonrelated trauma cues could be recruited and associated with the memory trace of the traumatic event. This incorporation of nonrelated trauma cues could then lead to higher probabilities to reactivate the trauma memory in safe environments, and promote overgeneralization of fear (Besnard & Sahay, 2016). Therefore, an alteration in the hippocampal subregion CA2-3/DG, known to be involved in pattern separation, could participate in the apparition of reexperiencing symptoms in adolescents with PTSD.

4.1 | Methodological considerations and future directions

This study presents some methodological limitations. First, we included a small sample because (1) it is very difficult to recruit teenagers with post-traumatic stress disorder without any other comorbidity and (2) manual segmentation is a laborious and very time consuming methodology. Even though the results of this study corroborate adult literature (Wang et al., 2010) and resonate with several theoretical models (Besnard & Sahay, 2016; Liberzon & Abelson, 2016), further studies with larger sample are needed to confirm these results. Second, because of the cross-sectional design, we were not able to investigate the effects of trauma exposure and the development of PTSD on hippocampal maturation. The brain, and more precisely the hippocampus, undergoes several structural changes during adolescence. This plasticity is thought to be an adaptive response which allows adolescents to learn how to face new experiences without the care of their parents and, thus to be prepared for adulthood (Curlik, DiFeo, & Shors, 2014). However, despite this plasticity, some studies consider that the adolescent brain is more vulnerable to the effects of stress exposure than adults (Holder & Blaustein, 2014; Romeo, 2017). In addition, a stress perceived during adolescence could negatively affect hippocampal maturation and cause negative long-term effects which could last into adulthood (Holder & Blaustein, 2014; Hueston, Cryan, & Nolan, 2017). Therefore, further studies are required to: (1) understand if the vulnerability to the effects of stress exposure on the brain during adolescence can be a risk factor to develop PTSD; and (2) investigate the effects of the development of PTSD on the maturation of hippocampal subfields. Third, we had a majority of adolescent females in the PTSD group. This can be explained by the fact that the prevalence of developing PTSD is higher in females than males (McLaughlin et al., 2013). As a consequence, we were unable to assess if there was an effect of sex on hippocampal subfield alterations in adolescent PTSD. Nonetheless, studies in adults reported no significant hippocampal differences between females and males suffering from PTSD and thus, suggest that the hippocampal alterations are independent of sex (Woon & Hedges, 2011). In addition, we conducted analyses on females only and we did not observe any difference with previous analyses performed on the whole group.

5 | CONCLUSIONS

Adolescent PTSD was associated with hippocampal alterations. Using high-resolution images and manual segmentation, we found smaller volumes of the whole hippocampus (in both hemispheres) in the PTSD group. This first result highlights the importance of using segmentation methods adapted to an adolescent population to characterize brain differences in PTSD. Moreover, the hippocampal alterations were specific to CA2-3/DG and, the volume of this region was negatively correlated with intrusion symptoms. Hence, our study provides, for the first time in humans, evidence of a relation between specific hippocampal subfields alterations and reexperiencing symptoms in PTSD. These findings resonate with recent theoretical models (Besnard & Sahay, 2016; Liberzon & Abelson, 2016) which propose that a reduced pattern separation (function subtended by CA3 and the dentate gyrus) could be at the core of the intrusions symptoms.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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6.6. CURRICULUM VITAE DE LA CANDIDATE

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FORMATION UNIVERSITAIRE

DIPLOMES

2015-2019 **Doctorat de Neuropsychologie et Neurosciences**
Unité Inserm-EPHE-Unicaen 1077, Dir. : Pr Francis Eustache (Caen, France).
Modifications du sommeil liées à l'âge : liens avec la cognition et les biomarqueurs du vieillissement et de la maladie d'Alzheimer en neuroimagerie. Co-supervision : Dr Géraldine RAUCHS (unité Inserm U1077) et Dr Gaël CHETELAT (unité Inserm U1237).

2013-2015 **Master de Sciences Biomédicales, spécialité Neurosciences (Université de Caen, France)**

- *Stage de Master 2 (Janvier-Juillet 2015) : Qualité du sommeil chez des sujets sains et des patients atteints de Mild Cognitive Impairment: comparaison des méthodes objectives et subjectives de mesure du sommeil, et liens avec le déclin cognitif.* Co-supervision : Dr Géraldine RAUCHS (unité Inserm U1077) et Dr Gaël CHETELAT (unité Inserm U1237).
- *Stage de Master 1 (Mars-Juin 2014) : Liens entre le couplage d'oscillations neuronales lors du sommeil et la cognition.* Supervision: Dr Thien Thanh DANG-VU, Concordia University (Montreal, Canada).

2011-2013 **Licence de Biochimie, Biologie cellulaire et moléculaire et Physiologie (Université de Rouen, France)**

- *Stage de Licence 3 (Mai-Juin 2013) : Analyse de questionnaires de sommeil, et exploration des liens entre sommeil et mémoire.* Supervision : Dr Géraldine RAUCHS, Unité Inserm-EPHE-Unicaen 1077 (Caen, France).

FORMATIONS COMPLEMENTAIRES

2017 *Lecture et analyse de Polysomnographies – niveau 1*, Société Française de Recherche en Médecine du Sommeil (Marseille, France).

2017 MOOC *Introduction à la Statistique avec R,* MOOC Université Paris-Sud avec attestation de réussite.

2016 *Formation aux techniques de médiation scientifique – niveau 1*, Relais D'Sciences (Caen, France).

PRODUCTION SCIENTIFIQUE ET PUBLICATIONS

ARTICLES SCIENTIFIQUES ET CHAPITRES DE LIVRE

- 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 EM, 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 gray matter volume, perfusion, glucose metabolism and β-amyloid deposition in older adults. *(Soumis)*
- André C, Rehel S, Kuhn E, Moulinet I, Landeau B, Le Du G, Mézenge F, de la Sayette V, Vivien D, Chételat G*, Rauchs G*, and the Medit-Ageing Research Group. Multimodal neuroimaging correlates of NREM and REM sleep EEG spectral power in aging. *(en preparation)*
- André C, Tomadesso C, de Flores R, Branger P, Rehel S, Mézenge F, Landeau B, de la Sayette V, Eustache F, Chételat G*, Rauchs G*. (2019) Brain and cognitive correlates of sleep fragmentation in elderly subjects with and without cognitive deficits. *Alzheimers Dement (Amst),* 11:142-150.
- Postel C, Viard A, André C, Guénolé F, de Flores R, Baleyte J-M, Gérardin P, Eustache F, Dayan J, Guillery-Girard B. (2018) Hippocampal subfields alterations in adolescents with post-traumatic stress disorder. *Hum Brain Mapp*. 40(4):1244-1252. (IF 4.93)
- André C, Onen F, Rauchs G. (2016) Démences et Sommeil, p.221-233 du rapport Sommeil, rythmes et psychiatrie. Editions Dunod.
- Chételat G, Mézenge F, Tomadesso C, Landeau B, Arenaza-Urquijo EM, Rauchs G, André C, de Flores R, Egret S, Gonneaud J, Poisnel G, Chocat A, Quillard A, Desgranges B, Bloch J-G, Ricard M, Lutz A. (2017) Reduced age-associated brain changes in expert meditators: a multimodal neuroimaging pilot study. *Scientific Reports*, 7(1):10160. (IF 4.6)
- Branger P, Arenaza-Urquijo E, Tomadesso C, Mézenge F, André C, De Flores R, Mutlu J, De La Sayette V, Eustache F, Chételat G, Rauchs G. (2016) Relationships between sleep quality and brain volume, metabolism, and amyloid deposition in late adulthood. *Neurobiol Aging*, 41:107-114. (IF 5)

En tant que membre du Medit-Ageing Research Group :

- Poisnel G, Arenaza-Urquijo E, Collette F, Klimecki OM, Marchant NL, Wirth M, de la Sayette V, Rauchs G, Salmon E, Vuillemier P, Frison E, Maillard A, Vivien D, Lutz A, Chételat G; and the 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. *Alzheimers Dement (N Y)*, 4:714-723.

- Lutz A, Klimecki OM, Collette F, Poisnel G, Arenaza-Urquijo E, Marchant NL, de la Sayette V, Rauchs G, Salmon E, Vuillemier P, Frison E, Vivien D, Chételat G, and the Medit-Ageing Research Group (2018). The Age-Well observational study on expert meditators in the Medit-Ageing European project. *Alzheimers Dement (N Y)*, 4:756-764.

COMMUNICATIONS ORALES EN CONGRES

- **Alzheimer's Association International Conference (Juillet 2019, Los Angeles, USA).** Obstructive sleep apnea severity and brain integrity in ageing: a multimodal neuroimaging study. André C, Rehel S, Kuhn E, Landeau B, De Flores R, Delcroix N, Vivien D, Chételat G*, Rauchs G*, and the Medit-Ageing research Group. Abstract publié dans *Alzheimer's and Dementia* (IF 12.7) (Présenté par G. Rauchs)
- **Réunion Francophone sur la Maladie d'Alzheimer et Syndromes Apparentés (Juin 2018, Lille, France).** Impact de la fragmentation du sommeil sur les atteintes cérébrales et cognitives chez des sujets âgés sains et des patients présentant des troubles cognitifs légers. André C, Tomadesso C, de Flores R, Branger P, Rehel S, Mézenge F, Landeau B, de la Sayette V, Eustache F, Chételat G*, Rauchs G*.
- **Alzheimer's Association International Conference (Juillet 2017, Londres, Royaume-Uni).** Age-related NREM-sleep fragmentation: relationships with structural and metabolic brain alterations, amyloid burden and cognitive performance. André C, Tomadesso C, Mézenge F, Branger P, De Flores R, Eustache F, Chételat G*, Rauchs G*. Abstract publié dans *Alzheimer's and Dementia* (IF 12.7)
- **23th Congress of the European Sleep Research Society (Septembre 2016, Bologne, Italie).** Relationships between sleep fragmentation and Alzheimer's disease biomarkers in healthy older adults: a multimodal neuroimaging study. André C, Fossey M, Malle C, Branger P, Mézenge F, Tomadesso C, de Flores R, Laniepce A, Eustache F, Chételat G*, Rauchs G*. Abstract publié dans *Journal of Sleep Research* (IF 3.4)

COMMUNICATIONS AFFICHEES EN CONGRES

- **17th ESBRA (European Society for Biomedical Research on Alcoholism) meeting (September 2019, Lille, France).** Withdrawal severity is associated with sleep and cognitive alterations in recently detoxified alcohol use disorder patients. Alice Laniepce, Nicolas Cabé, Françoise Bertran, Claire André, Céline Boudehent, François Vabret, Francis Eustache, Géraldine Rauchs*, Anne-Lise Pitel*.
- **Alzheimer's Association International Conference (Juillet 2019, Los Angeles, USA).** Association of perceived memory decline with multimodal neuroimaging at different stages of Alzheimer's disease. Kuhn E, de la Sayette V, Perrotin A, Tomadesso C, André C, Sherif S, Bejanin A, Moulinet I, Touron E, Landeau B, Mézenge F, Marchant N, Delarue M, Delcroix N, Abbas A, Manrique A, Eustache F, Vivien D, Chételat G, and the Medit-Ageing Research Group. Abstract publié dans *Alzheimer's and Dementia* (IF 12.7)
- **24th Congress of the European Sleep Research Society (Septembre 2018, Bâle, Suisse).** Links between circadian rhythm fragmentation, regular physical activity and amyloid burden in healthy older adults. Rehel S, André C*, Arenaza-Urquijo E*, Ourry V, Mézenge F, Vivien D, Chételat G, Rauchs G. Abstract publié dans *Journal of Sleep Research* (IF 3.4)

- 7th Congress of the European Academy of Paediatric Societies (Novembre 2018, Paris, France). Hippocampal subfields alterations in teenagers with post-traumatic stress disorder. Postel C, André C, Viard A, Guénolé F, Baleyte J-M, Gerardin P, Eustache F, Dayan J, Guillery-Girard B. Abstract publié dans *European Journal of Pediatrics* (IF 2.24)
- Réunion Francophone sur la Maladie d'Alzheimer et Syndromes Apparentés (Juin 2018, Lille, France). Liens entre fragmentation du cycle veille-sommeil, activité physique quotidienne et charge amyloïde chez des sujets âgés sains. Rehel S, André C*, Arenaza-Urquijo E*, Ourry V, Mézenge F, Chételat G, Rauchs G.
- Le Congrès du Sommeil (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*. Abstract publié dans *Médecine du Sommeil*.
- Le Congrès du Sommeil (Novembre 2017, Marseille, France). Liens entre les performances mnésiques, la structure cérébrale et les paramètres du sommeil chez des sujets âgés sains. Mutlu J, Bertran F, Harand C, Doidy F, André C, Laniepce A, Eustache F, Rauchs G. Abstract publié dans *Médecine du Sommeil*.
- Alzheimer's Association International Conference (Juillet 2017, Londres, Royaume-Uni). Association of self-perceived physical health with amyloid deposition in cognitively normal older adults. Ourry V, Gonneaud J, Tomadesso C, Egret S, Mézenge F, André C, La Joie R, Perrotin A, de la Sayette V, Desgranges B, Chételat G, Arenaza-Urquijo EM. Abstract publié dans *Alzheimer's and Dementia* (IF 12.7)
- Human Amyloid Imaging Conference (Janvier 2017, Miami, USA). Relationships between NREM-sleep fragmentation and changes in brain structure, metabolism, amyloid burden and cognitive performance in healthy older adults. André C, Tomadesso C, Mézenge F, Branger P, Fossey M, de Flores R, Laniepce A, Eustache F, Chételat G, Rauchs G. (Présenté par G. Rauchs)
- 1st International Conference on Sleep Spindling (Mai 2016, Budapest, Hongrie). A role for spindle-slow wave synchrony in sleep-dependent declarative memory consolidation. O'Byrne J, Weiner OM, André C, Debellemanière E, Boucetta S, Dang-Vu TT.
- Alzheimer's Association International Conference (Juillet 2015, Washington, USA). Difficulties Falling Asleep Are Associated with Higher Aβ Burden in Healthy Adults. Branger P, Mézenge F, André C, De Flores R, Egret S, Mutlu J, Tomadesso C, Eustache F, Chételat G, Rauchs G. Abstract publié dans *Alzheimer's and Dementia* (IF 12.7)
- 18th annual meeting of LARC-Neurosciences network (Octobre 2014, Caen, France). Difficulties to fall asleep are associated with higher amyloid burden in healthy adults. Branger P, Mézenge F, André C, De Flores R, Egret S, Mutlu J, Tomadesso C, Eustache F, Chételat G, Rauchs G.

COMPETENCES

- Enregistrements de sommeil : polysomnographie et actimétrie (recueil, scorage et analyse des données).
- Neuroimagerie : IRM et TEP (prétraitement, contrôle qualité et analyse avec SPM12), sous-champs hippocampiques (traçage manuel avec Anatomist, et segmentation automatique avec ASHS, contrôle qualité et analyse de données).
- Évaluation cognitive et comportementale : cotation et analyse des données.
- Statistiques : analyses avec Statistica, SPSS, R.
- Langues : Français (langue maternelle), Anglais (courant), Allemand et Espagnol (notions de base).

ACTIVITES D'ENCADREMENT ET D'ENSEIGNEMENT

- Encadrement de stages de recherche :
    - 2 étudiants de niveau Master 1 en neuropsychologie et neurosciences.
    - 1 étudiante de niveau Master 2 en neuroscience.
- Formation d'une étudiante en thèse (C. Postel) au traçage manuel des sous-champs hippocampiques.
- Présentation régulière de travaux de recherche à des étudiants de niveau lycée, licence ou master, en stage d'observation dans le laboratoire (>50 étudiants).
- 2016 : deux cours (4h) sur *Sommeil, mémoire et maladie d'Alzheimer* dispensés dans le cadre du DIU de Médecine du Sommeil appliquée à la Gérontologie (Hôpital Bichat, Université Paris-Descartes).

FINANCEMENTS OBTENUS

- 2015 – 2019 : Bourse de thèse (100 k€) cofinancée 50% Inserm et 50% Région Normandie, avec complément en 4^{e} année par l'École Pratique des Hautes Études.
- Bourses de voyage obtenues dans le cadre de congrès :
    - 2016 : European Sleep Research Society.
    - 2017 : Alzheimer's Association International Conference.
    - 2017 : Bourse Jeunes Chercheurs et Médecins du Sommeil (Congrès Français du Sommeil).

RESPONSABILITES COLLECTIVES ET ADMINISTRATIVES

- 2017 – 2019 : Représentante élue des doctorants au conseil de l'unité Inserm-EPHE-Unicaen U1077.
- 2016 – 2018 : Organisation des Journal Clubs au sein de l'équipe de G. Chételat.
- 2015 – 2018 : Recrutement des participants dans le cadre de l'étude AGE-WELL du projet européen Medit-Ageing.
    - Représentante « sommeil » lors des conférences grand public de recrutement.
    - Pré-screening des participants.

ACTIVITES DE MEDIATION ET VULGARISATION SCIENTIFIQUE

- 2015 – 2018 : Participation à la Fête de la Science - Conception et animation du stand de l'Unité Inserm-EPHE-Unicaen 1077.
- 2016 : Présentation dans le cadre de l'Atelier du Chercheur auprès d'un public lycéen.

Titre : Modifications du sommeil liées à l'âge : liens avec la cognition et les biomarqueurs du vieillissement et de la maladie d'Alzheimer en neuroimagerie.

Résumé: La qualité du sommeil se modifie avec l'âge, et les troubles du sommeil seraient associés au déclin cognitif et à un risque accru de développer une maladie d'Alzheimer (MA). Cependant, les mécanismes cérébraux sous-tendant cette association restent mal compris. L'objectif de cette thèse était de contribuer à une meilleure compréhension des corrélats cérébraux structuraux, fonctionnels et moléculaires des principales modifications objectives du sommeil dans le vieillissement, et d'explorer les liens avec les performances cognitives. Nos résultats montrent que les altérations des premiers cycles de sommeil et de l'activité à ondes lentes sont associées à un hypométabolisme, une hypoperfusion et/ou une diminution du volume de substance grise au niveau des aires fronto-cingulaires et hippocampiques. De plus, la présence d'un syndrome d'apnées obstructive du sommeil et l'altération de la microstructure du sommeil paradoxal étaient significativement associés à une augmentation de la charge amyloïde, respectivement au niveau du cortex cingulaire postérieur et du précunéus, ou de manière plus diffuse. En revanche, les liens avec la cognition restaient subtils voire absents, certaines modifications cérébrales étant asymptomatiques. Ainsi, le sommeil pourrait être un facteur de résilience face aux premières altérations neuropathologiques de la MA. Ces résultats supportent la nécessité de dépister et traiter les pathologies du sommeil dans le vieillissement, avant l'apparition des premiers déficits cognitifs, dans l'espoir de ralentir le déclin cognitif.

Title: Age-related sleep changes: associations with cognition, aging and Alzheimer's disease neuroimaging biomarkers.

Abstract: Sleep changes are a major feature of the ageing process, and sleep disturbances are increasingly recognized as a risk factor for cognitive decline and Alzheimer's disease (AD). However, the brain mechanisms underlying this association are still unclear. The objective of this thesis was to deepen our understanding about brain structural, functional and molecular correlates of the main objective sleep changes in ageing, and to assess the potential links with cognitive performance. Our results demonstrate that the fragmentation of the first sleep cycles and the alteration of slow wave activity, are associated with reduced gray matter metabolism, perfusion and/or volume in fronto-cingulate and hippocampal areas. Moreover, sleep-disordered breathing and rapid eye movement sleep microstructure alterations were related to increased amyloid burden respectively in the posterior cingulate cortex and precuneus, or more widespread neocortical areas. However, associations with cognitive performance remained subtle or inexistent, suggesting early and asymptomatic associations between sleep and brain changes. Therefore, sleep may contribute to resilience processes and may help to cope with early neuropathological changes in AD. These results support the need to screen and treat sleep disturbances in older adults, before the onset of the first cognitive signs, in order to slow cognitive decline.

Mots clés : Sommeil, Vieillissement, Maladie d'Alzheimer, Neuroimagerie, Cognition, Amyloïde, Imagerie par Résonance Magnétique, Tomographie par Emission de Positons.

Discipline : Biologie Humaine, Psychologie.

Laboratoire : Unité INSERM-EPHE-Université de Caen Normandie U1077 « Neuropsychologie et Imagerie de la Mémoire Humaine », GIP CYCERON, Bd Henri Becquerel, BP 5229, 14074 Caen Cedex.