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Justine Mutlu

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THESE

Pour obtenir le diplôme de doctorat

Psychologie

Préparée au sein de l'Université de Caen Normandie

Connectivité fonctionnelle au repos : relation avec la topographie et la propagation des atteintes structurales, fonctionnelles et moléculaires dans la maladie d'Alzheimer

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*« (...) ne crois pas que l'âme soit en paix
parce que le corps demeure couché.
Souvent le repos n'est rien moins que le repos. »*

Sénèque, Lettres à Lucilius, livre LVI, 60 av JC.

Avant-propos

La maladie d'Alzheimer est un problème majeur de santé publique. La meilleure façon de lutter contre cette maladie est de l'identifier le plus tôt possible. La maladie d'Alzheimer se caractérise par des pertes de mémoire mais aussi par des modifications cérébrales présentes précocement dans le développement de la pathologie. Pour les étudier, les principaux outils d'imagerie *in vivo* reposent sur l'imagerie par résonance magnétique structurale, qui permet la visualisation des régions atrophiées, et la tomographie par émission de positons marquée au [18F]-2-fluoro-2-deoxy-D-glucose ou au florbetapir qui révèle respectivement les régions cérébrales consommant moins de glucose et qui ont donc un fonctionnement réduit, et celles qui sont envahies par des plaques amyloïdes, une des lésions neuropathologiques caractéristiques de la maladie d'Alzheimer. Ces techniques ont mis en évidence que la maladie d'Alzheimer se caractérisait par une atrophie prédominante au niveau de la région hippocampique, un hypométabolisme du cortex cingulaire postérieur et temporo-pariétal et des dépôts amyloïdes dans le neocortex. L'imagerie par résonance magnétique fonctionnelle au repos est une technique d'imagerie complémentaire en plein essor qui permet d'accéder à la connectivité fonctionnelle ou intrinsèque. Lorsque le cerveau est au repos, certaines régions cérébrales travaillent ensemble sous la forme de réseaux. Un intérêt particulier est porté au réseau par défaut car il implique les régions les plus sévèrement touchées dans la maladie d'Alzheimer, dont l'hippocampe et le cortex cingulaire postérieur. Les analyses menées en neuroimagerie ont révélé une analogie entre la topographie des lésions et les réseaux identifiés en imagerie par résonance magnétique fonctionnelle au repos. Ceci a conduit à l'hypothèse de la neurodégénérescence transneuronal selon laquelle la connectivité fonctionnelle conditionnerait la topographie et la propagation des lésions survenant dans la maladie d'Alzheimer.

Dans ce contexte, l'objectif de cette thèse était de préciser les liens qu'entretient la connectivité fonctionnelle au repos avec l'atrophie, l'hypométabolisme et les dépôts amyloïdes dans la maladie d'Alzheimer. Une connaissance plus approfondie de ces relations pourra permettre d'améliorer la compréhension des règles qui régissent la topographie et la propagation des lésions afin d'identifier, à terme, un moyen efficace de les combattre.

Liste des abréviations

A β : protéine β -amyloïde

ACI : Analyse en composantes indépendantes

ApoE : Apolipoprotéine E

BOLD : Blood Oxygen Level Dependent

CCP : Cortex Cingulaire Postérieur

DMN : Default Mode Network

DNF : Dégénérescences Neuro-Fibrillaires

EVP : Effets de Volume Partiel

FDG : [18]-fluoro-2-désoxy-D-glucose

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

IRM : Imagerie par résonance magnétique

IWG : International Working Group

LCR : Liquide céphalo-rachidien

MA : Maladie d'Alzheimer

MCI : Mild Cognitive Impairment

MMSE : Mini-Mental State Examination

NIA-AA : National Institute of Aging and Alzheimer Association

NINCDS-ADRDA : National Institute of Neurological and Communicative Disorders and
Stroke – the Alzheimer's disease and Related Disorders Association

PAQUID : Personnes âgées Aquitaine ou QUID des personnes âgées

PIB : Pittsburg Compound B

PSEN : Presenilin

Tau : Tubulin-Associated Unit

TEP : Tomographie par Emission de Positons

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1. Introduction générale

1.1. Epidémiologie

1.1.1. Prévalence et incidence

La Maladie d'Alzheimer (MA) est la première cause de démence du sujet âgé et représente au moins 70 % des cas (Winblad et al., 2016). A l'heure actuelle, il n'existe pas d'étude s'intéressant spécifiquement à la prévalence et à l'incidence de la MA, cette dernière étant plus largement évaluée dans le cadre des démences.

Selon un rapport de 2015 de *l'Alzheimer's Disease International*, 46,8 millions d'individus étaient atteints de démence et 9,9 millions nouveaux cas de démence apparaîtraient chaque année dans le monde (Prince et al., 2015). *L'Alzheimer's Disease International* estime aussi qu'avec un nouveau cas recensé toutes les 3,2 secondes dans le monde, le nombre de personnes atteintes de démence devrait presque doubler tous les 20 ans en passant de 74,7 millions en 2030 à 131,5 millions en 2050.

Les données épidémiologiques portant sur les démences en France sont principalement issues de l'étude PAQUID (Personnes âgées Aquitaine ou QUID des personnes âgées) et de l'étude des 3 cités (ou 3C). Avec 900 000 patients atteints de la MA en 2015, la France est l'un des pays les plus touchés par cette pathologie. Selon l'étude PAQUID, la prévalence de la démence était estimée à 17,8 % chez les individus âgés de 75 ans et plus, et cette prévalence augmenterait très significativement avec l'âge en doublant quasiment tous les 5 ans (Helmer et al., 2006; Querfurth et LaFerla, 2010). Chaque année, la France compte ainsi 225 000 nouveaux cas de démence diagnostiqués, dont environ 180 000 cas de MA. Selon les projections, un Français de plus de 65 ans sur quatre sera atteint de la MA en 2020 et la MA touchera ainsi 3 millions de personnes en prenant en compte les malades et les proches aidants.

Ces chiffres, bien que déjà très alarmants, ne sont probablement qu'une sous-estimation de la situation car le diagnostic de la MA peut s'avérer difficile. En effet, seule la moitié des patients atteints de démence serait identifiée en France (cf. Rapport Gallez 2005) comme à l'étranger (Tyas et al., 2006). Il est cependant important de noter que ces estimations pourraient être revues à la baisse suite à différentes études menées en Europe et aux Etats-Unis qui ont mis en évidence que les taux de prévalence et d'incidence de la démence auraient diminué au cours de cette dernière décennie (Lobo et al., 2007; Matthews et al.,

2013). Ceci pourrait s'expliquer par une meilleure prise en charge des facteurs prédisposant à la MA, comme les risques cardiovasculaires par exemple.

1.1.2. Etiologie de la MA

La MA présente une étiologie complexe du fait de son origine multifactorielle. L'identification des facteurs de risque et de protection de la MA permet d'améliorer la compréhension de ses causes et de sélectionner les individus les plus à même de la déclarer, facilitant ainsi l'exploration de ses stades les plus précoces. De plus, la distinction des facteurs de risque et de protection en facteurs modifiables et non modifiables est cruciale pour le développement des stratégies de prévention et d'intervention (Donnell et al., 2015).

1.1.2.1. Facteurs de risque et de protection non modifiables

1.1.2.1.1. Facteurs démographiques

Le facteur de risque majeur de la MA est l'avancée en âge de l'individu (Helmer et al., 2006). Bien que son rôle ne soit pas consensuel, le sexe semble également influencer le développement de la MA. Des études européenne (Eurodem), française (PAQUID) et américaine (*Cardiovascular Health study*) ont ainsi montré que les taux de prévalence et d'incidence sont plus élevés chez les femmes, surtout après l'âge de 90 ans (Helmer et al., 2006). Ceci peut s'expliquer par une espérance de vie plus longue de 7 ans chez les femmes (données INSEE, Gicquaud, 2015), mais aussi par des facteurs hormonaux dont la diminution post-ménopausique des œstrogènes endogènes (pour revue voir Pike, 2017). L'origine ethnique est également associée à un risque accru de développer la MA chez les individus d'origine afro-américaine ou hispanique comme le rapportent différentes études américaines (Chen et Panegyres, 2016; Gurland et al., 1999; Shadlen et al., 2006). Ceci pourrait s'expliquer par une plus grande vulnérabilité de ces populations aux risques cardiovasculaires (Fitzpatrick et al., 2004).

1.1.2.1.2. Facteurs génétiques

Soixante-dix à quatre-vingt pourcents des MA sporadiques impliquent le risque génétique (Slegers et al., 2010; Wingo et al., 2012). Parmi la vingtaine de gènes de susceptibilité à la MA identifiés à ce jour, le gène codant pour l'Apolipoprotéine E (APOE) est le plus impliqué. Ce gène est situé sur le chromosome 19 et peut se trouver sous la forme de 3 allèles : ϵ_2 , ϵ_3 et ϵ_4 , présents respectivement dans 7 à 8 %, 75 à 80 % et 15 % de la population (Cedazo-

Mínguez et Cowburn, 2001). Alors que l'allèle $\epsilon 2$ réduirait de 40 % le risque de développer la MA (Farrer et al., 1997; Corder et al., 1994), l'allèle $\epsilon 4$ a clairement été identifié comme étant un facteur de risque en augmentant la prévalence et en diminuant l'âge de début de la maladie (Liu et al., 2013). Le nombre d'individus malades augmenterait proportionnellement avec la fréquence de l'allèle $\epsilon 4$. En effet, la MA atteint seulement 20 % des porteurs $\epsilon 2/ \epsilon 3$ et $\epsilon 3/ \epsilon 3$ contre 48 % des porteurs $\epsilon 3/ \epsilon 4$ ou $\epsilon 2/ \epsilon 4$ et 92 % des porteurs $\epsilon 4/ \epsilon 4$. Ainsi, le risque de développer la MA est multiplié par trois pour les individus hétérozygotes porteurs d'un allèle $\epsilon 4$ et est multiplié par douze pour les individus homozygotes $\epsilon 4/ \epsilon 4$ (Verghese et al., 2011). Le risque génétique s'exprime également dans les formes familiales à transmission autosomique dominante de la MA. Ces formes de MA représentent moins d'1 % des cas (Campion et al., 1999) et se développent généralement plus précocement que les formes sporadiques. Les individus sont principalement porteurs de mutations au niveau du gène de la presenililn (PSEN) PSEN1 situé sur le chromosome 14 (69 %), de mutations ou de duplications du gène APP (*Amyloid Precursor Protein*) situé sur le chromosome 21 (13 % et 7,5 % respectivement) ou plus rarement de mutations du gène PSEN2 situé sur le chromosome 14 (2 %) (Janssen et al., 2003; Raux, 2005). D'autres gènes impliqués dans ces formes autosomiques dominantes de la MA sont encore en cours d'identification (Cacace et al., 2016). Du fait de la très forte pénétrance de ces mutations, les individus porteurs développeront inévitablement la MA avant l'âge de 61 ans (Campion et al., 1999).

1.1.2.2. Facteurs de risque et de protection modifiables

1.1.2.2.1. Antécédents médicaux et comorbidités

L'existence de certaines pathologies peut favoriser la survenue de la MA. En effet, les maladies cardiovasculaires telles que l'athérosclérose (Arvanitakis et al., 2016), l'hypertension artérielle (Perrotta et al., 2016), l'hypercholestérolémie (Gamba et al., 2012) augmentent le risque de développer la MA. Le diabète de type 2 (Baglietto-Vargas et al., 2016; Biessels et al., 2006), l'obésité, la surcharge pondérale (Peditizi et al., 2016) et les traumatismes cérébraux (Gupta et Sen, 2016) prédisposent également à la déclaration de la MA. Enfin, la neuroinflammation contribuerait à la toxicité de l'A β dans la MA (Minter et al., 2016).

1.1.2.2.2. Facteurs liés au mode de vie

Une alimentation pauvre en homocystéine et en acides gras et riche en acides gras polyinsaturés telle que le régime de type méditerranéen – qui privilégie la consommation de poissons et un bon apport en vitamines B6, B12, folates, antioxydantes (A, C, E) et D – semble être un facteur protecteur de la MA (Petersson et Philippou, 2016; Singh et al., 2014). Plusieurs travaux issus de l'étude PAQUID ont rapporté qu'une consommation d'alcool légère à modérée réduirait le risque de développer la MA (Letenneur, 2004). Le tabagisme est associé à une augmentation du risque de démence de 50 à 80 % et le tabagisme passif se révèle être également délétère (Barnes et al., 2010; R. Chen, 2012). Ainsi, la réduction de l'incidence du tabagisme a été associée à une diminution de la prévalence future de la MA (Durazzo et al., 2014). L'activité physique régulière a été rapportée comme étant bénéfique contre la MA (pour revue voir Stephen et al., 2017). L'équilibre affectif et social s'avère être également important pour lutter contre la MA, notamment par l'implication dans des activités sociales ou de loisirs cognitivement stimulantes (Marioni et al., 2015), tandis que la solitude augmenterait le risque de développer la MA à un stade tardif (Wilson et al., 2007). Enfin, un haut niveau d'éducation semble diminuer l'incidence et la prévalence de la MA avec une réduction de 7 % du risque de développer la MA par année d'éducation réalisée (Xu et al., 2015). Il est important de noter que tous ces facteurs interagissent très fortement entre eux et ainsi, un haut niveau d'éducation est souvent le reflet d'un haut statut socio-économique et donc concerne des individus qui ont accès à une meilleure qualité de vie intégrant une meilleure alimentation, davantage d'activités physiques et cognitives. L'effet protecteur d'un haut niveau d'éducation sur la MA peut être interpréter à la lumière de la théorie de la réserve cognitive (Stern et al., 1994) qui explique que des individus ayant une forte réserve cognitive (avec souvent un haut niveau d'éducation) mettront en place des stratégies de compensation leur permettant de tolérer davantage d'altérations cérébrales avant d'en ressentir les symptômes, contrairement à des individus ayant une réserve plus faible (Bartrés-Faz et Arenaza-Urquijo, 2011).

Près d'un tiers des cas de MA recensés dans le monde sont attribuables à ces facteurs de risque potentiellement modifiables (Norton et al., 2014). La prévention des facteurs de

risque vasculaire et une meilleure qualité de vie permettraient ainsi de réduire le risque de survenue de la MA (Barnes et Yaffe, 2011).

1.2. Neuropsychologie de la MA

Dans les phases précoces de la maladie, la plainte la plus communément rapportée par les patients et/ou leur entourage concerne les perturbations de la mémoire (Guériot-Milandre et al., 1997). La MA affecte les différents systèmes de la mémoire (Tulving, 1995) de manière hétérogène. Elle s'attaque d'abord à la mémoire épisodique puis progressivement aux autres systèmes mnésiques, tels que la mémoire de travail et la mémoire sémantique. Les systèmes moins élaborés qui s'appuient sur des processus automatiques, comme la mémoire procédurale et le système de représentations perceptives, semblent épargnés, du moins dans les stades précoces de la MA (Desgranges et al., 1996; Eustache et al., 2006).

La mémoire épisodique permet l'encodage, le stockage et la récupération d'événements personnellement vécus situés dans leur contexte temporel et spatial (Tulving, 2004). Dans la MA, la mémoire épisodique est perturbée au niveau des processus d'encodage et de récupération (Carlesimo et Oscar-Berman, 1992; Eustache et al., 2006; Salmon et Lange, 2001). Ainsi, les évaluations neuropsychologiques mettent en évidence chez les patients MA une diminution des performances de rappel libre (Grober et al., 2000) , indicé (Tounsi et al., 1999) et de reconnaissance (Wilson et al., 1983), que le matériel utilisé soit verbal, visuel (Greene et al., 1996; Barbeau et al., 2004) ou visuo-spatial (Pengas et al., 2010). De plus, des troubles du stockage de la mémoire épisodique sont constatés dès les stades les plus précoces de la MA (Lekeu et Van der Linden, 2005).

La mémoire sémantique, qui sous-tend la mémorisation des concepts et des connaissances générales sur le monde indépendamment de leur contexte temporel et spatial d'acquisition (Tulving, 1972), peut aussi être précocement atteinte dans la MA (Chertkow et al., 2008). Ceci se traduit par un discours vague reposant sur des mots imprécis et des périphrases.

La mémoire autobiographique permet de conserver les informations et les souvenirs propres à un individu accumulés depuis son enfance qui lui confèrent un sentiment d'identité et de continuité. Elle repose sur une composante épisodique, qui permet de revivre en détail des souvenirs d'évènements personnels situés dans leur contexte spatio-temporel, et sur une composante sémantique qui contient les connaissances générales sur soi (par exemple le

nom de mes collègues) et sur des événements répétés ou étendus (le voyage aux Etats-Unis) sans accès à un contexte d'apprentissage particulier (Piolino, 2000). L'atteinte de la composante épisodique survient précocement dans la MA (Addis et Tippett, 2001) et suit le gradient temporel de Ribot selon lequel les souvenirs les plus anciens sont relativement intacts par rapport aux souvenirs récents (Piolino et al., 2003). La composante sémantique de la mémoire autobiographique semble quant à elle être préservée, ou tout du moins (Seidl et al., 2011) jusqu'à un stade modéré de la MA.

La mémoire de travail permet de maintenir temporairement des informations nécessaires à la réalisation d'une tâche (par exemple, retenir un numéro de téléphone pour le composer juste après). Elle peut être atteinte dès le stade léger de la MA (Collette et al., 1999), en lien avec des déficits attentionnels et s'altère de plus en plus avec l'évolution de la maladie (Baddeley et al., 1991).

La mémoire procédurale permet l'acquisition d'habilités et de savoir-faire sans avoir recours au rappel volontaire. Elle est relativement préservée jusqu'à des stades avancés de la MA (Desgranges et al., 1996), surtout pour les apprentissages qui reposent sur des processus perceptivo-moteurs (Hirono et al., 1997; Van Halteren-Van Tilborg et al., 2007), tandis que les apprentissages mettant en jeu des traitements cognitifs complexes semblent plus vulnérables à la MA, notamment dans les premières phases d'apprentissage (Beaunieux et al., 2012).

A côté des troubles mnésiques, les fonctions exécutives et attentionnelles sont elles aussi précocement perturbées dans la MA (pour revue Perry et al., 2000; Perry et Hodges, 1999). Les fonctions exécutives sous-tendent des processus complexes, tels que l'élaboration de stratégies, l'inhibition de réponses non pertinentes et/ou la planification de tâches dirigées vers un but. L'atteinte des fonctions exécutives dans la MA se traduit par une réduction des capacités de flexibilité mentale (Amieva et al., 1998; Baudic et al., 2006), d'inhibition de processus automatiques (Amieva et al., 2004; Binetti et al., 1996; Collette et al., 1999; Perry et al., 2000; Spieler et al., 1996) ou de planification (Franceschi et al., 2007; Lange et al., 1995). Les troubles attentionnels qui surviennent précocement dans la MA sont mis en évidence lors de tâches qui font appel à l'attention divisée tandis que les capacités d'attention sélective et soutenue résisteraient mieux à la maladie (Perry et Hodges, 1999).

Enfin, des perturbations des fonctions instrumentales sont également présentes dès les stades précoces de la MA avec les troubles lexico-sémantiques caractérisés par un manque du mot et des paraphasies sémantiques mais aussi à des stades plus avancés avec les troubles praxiques et gnosiques.

1.3. Critères diagnostiques de la Maladie d'Alzheimer appliqués en clinique

1.3.1. Critères de la Maladie d'Alzheimer

De nos jours, le diagnostic de la MA repose sur des critères cliniques qui sont de plus en plus couramment complétés par les données d'imagerie, dont l'utilisation comme outil de détection a fait l'objet de plusieurs révisions (cf. partie 2.5). Le diagnostic clinique de la MA probable repose sur des critères définis par le *National Institute of Neurological and Communicative Disorders and Stroke – the Alzheimer's Disease and Related Disorders Association* (ou NINCDS-ADRDA) (McKhann et al., 1984). Selon ces critères, le diagnostic clinique de la MA probable peut être posé si un syndrome démentiel (établi à l'aide de tests neuropsychologiques tels que le *Mini-Mental State Examination* ou MMSE), accompagné d'une détérioration d'au moins deux fonctions cognitives et d'une dégradation progressive des capacités mnésiques et cognitives, survient chez un individu entre 40 et 90 ans (le plus fréquemment, au-delà de 65 ans) sans que des troubles de la conscience n'aient été constatés et après avoir exclu toute pathologie systémique ou cérébrale qui pourrait expliquer le déclin mnésique et cognitif observé chez cet individu. Ce diagnostic peut être renforcé par le constat d'un déclin des fonctions instrumentales (aphasie, apraxie et agnosie), de la perturbation de la vie quotidienne, des troubles comportementaux, d'une histoire familiale de MA (surtout si confirmée histologiquement), et également comme mentionné plus haut, par des examens complémentaires (ponction lombaire, électro-encéphalogramme, et imagerie anatomique) attestant de la présence d'une atrophie cérébrale progressive et permettant d'exclure toute autre anomalie qui pourrait expliquer le tableau clinique. Le diagnostic de la MA est rendu incertain ou improbable si les troubles surviennent brusquement, ou si des déficits neurologiques focaux (tels que l'hémiplégie, l'hypoesthésie, déficit du champ visuel ou incoordination motrice), des crises convulsives ou des troubles de la marche sont constatés à un stade précoce de la maladie.

Cependant, si les critères présentés ci-dessus sont satisfaits, ils ne sont pas suffisants pour établir avec certitude le diagnostic de la MA et doivent être corroborés à des analyses histologiques (suite à une biopsie ou à l'autopsie).

Des critères de démence de type Alzheimer ont également été définis dans le *Diagnostic and Statistical Manual of mental disorders* (DSM-IV-TR). Selon ces critères, une démence de type Alzheimer peut être diagnostiquée si une altération de la mémoire accompagnée d'au moins une perturbation cognitive (telle que l'aphasie, l'apraxie, l'agnosie ou des troubles exécutifs) a des répercussions significatives dans la vie sociale ou professionnelle de l'individu. L'évolution doit être caractérisée par un début progressif et un déclin cognitif continu et les troubles cognitifs ne doivent pas être attribuables à d'autres affections neurologiques, systémiques, psychiatriques ou induites par une substance.

1.3.2. Critères de Mild Cognitive Impairment

Les critères diagnostiques de la MA exigent la présence d'un syndrome démentiel accompagné de déficits mnésiques et cognitifs ayant un retentissement important sur la vie quotidienne de l'individu. En conséquence, ces critères ne permettent la détection de la maladie qu'à un stade déjà très avancé. Or, la MA débute de manière insidieuse et très progressive, ce qui se traduit par l'apparition de troubles qui peuvent être détectés objectivement mais qui ne sont pas assez importants pour satisfaire les critères de démence. Cette phase prodromale, symptomatique et pré-démentielle de la MA représente un enjeu majeur dans l'étude des mécanismes physiopathologiques survenant au tout début de la maladie ainsi que la mise en place de stratégies interventionnelles précoces pour tenter de prévenir ou du moins retarder la déclaration de la démence.

Le concept retenu de nos jours pour désigner cet état cognitif est « *Mild Cognitive Impairment* » (MCI), proposé par Flicker et al. en 1991. Les critères initialement définis par Petersen et al. en 1999 impliquaient une plainte du patient relative à sa mémoire (si possible confirmée par un proche), l'identification de déficits mnésiques à l'aide de valeurs de référence issues de tests neuropsychologiques, une préservation des fonctions cognitives ne faisant pas appel à des capacités mnésiques. En outre, ces troubles ne devaient pas avoir d'impact suffisant pour altérer les activités de la vie quotidienne ni provoquer la déclaration d'un syndrome démentiel. Les patients qui remplissaient ces critères de MCI avaient un taux

de conversion vers la MA de 12 % par an contre 1 à 2 % pour des sujets du même âge ne présentant aucun trouble cognitif. Le taux de conversion des patients MCI vers la MA est très variable selon les études (Petersen et al., 2009). Les critères de MCI ont ensuite été affinés afin de distinguer les sous-populations de MCI qui évolueront vers des pathologies différentes (Gauthier et al., 2006; Petersen et al., 2001; Petersen, 2004; Winblad et al., 2004). Ainsi, la population MCI a d'abord été classée en deux catégories suivant la présence ou non de déficits mnésiques (MCI amnésiques *versus* MCI non amnésiques) puis chacune de ces catégories a été sous-divisée en fonction de l'atteinte d'une ou de plusieurs fonctions cognitives (*single domain versus multidomain*). L'ensemble de cette classification est représenté dans la partie gauche de la Figure 1. Ainsi, en fonction du sous-groupe auquel ils sont rattachés, les patients MCI évolueront vers des troubles différents (MA, autre étiologie neurodégénérative, vasculaire ou psychiatrique, comme l'indique la partie droite de la figure 1) ; avec un risque accru de développer la MA pour les MCI amnésiques comparés aux non-amnésiques, de même que pour les *multiple domain* par rapport aux *single domain* (Nordlund et al., 2010; Petersen et al., 2009; Ritchie et Tuokko, 2010). Cependant, pour une partie des patients MCI amnésiques, les troubles cognitifs n'évolueront pas davantage (Mitchell et Shiri-Feshki, 2009) ou pourraient même n'être que temporaires et ainsi, à la résorption de ces déficits, ces patients seraient reclassés comme « normaux » .

Bien que la catégorie des MCI amnésiques reste encore hétérogène, la sélection de ces patients sur des critères cliniques et neuropsychologiques est pour le moment la meilleure méthode permettant d'identifier des patients en phase prédéméntielle de la MA .

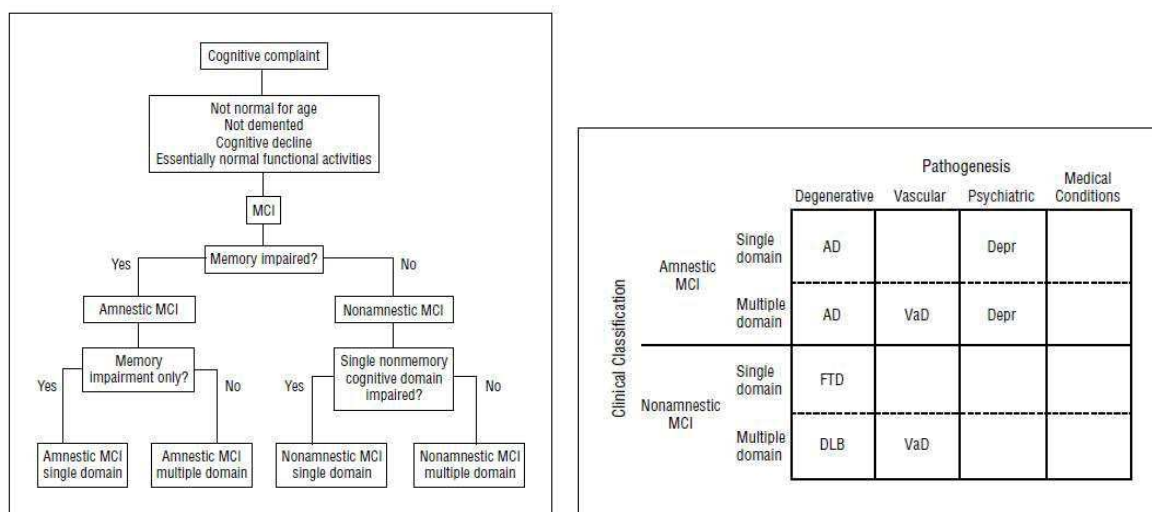


Figure 1 : Classification des patients MCI (d'après Petersen et al., 2009)

Afin d'obtenir le diagnostic définitif de MA, un examen anatomo-pathologique du patient est nécessaire.

1.4. Caractérisation neuropathologique

Historiquement, la première autopsie qui a mis en évidence les lésions neuropathologiques liées à la MA a été réalisée en 1907 sur une patiente qui souffrait d'atteintes comportementales et cognitives. Le médecin nota l'accumulation intra-neuronale des dégénérescences neurofibrillaires (DNF) et extracellulaires de plaques neuritiques qu'il dénomma « foci milaires » ainsi qu'une très forte perte neuronale (voir la traduction de Stelzmann et al., 1995). Ce médecin n'était autre que le Docteur Aloïs Alzheimer qui décrivit ainsi des altérations liées à une démence particulière à laquelle il laissa son nom. Depuis cette première autopsie, les atteintes neuropathologiques de la MA ont largement été explorées et caractérisées (Duyckaerts et al., 2009). Les lésions positives correspondent à l'accumulation intra-neuronale des DNF composées de formes clivées et hyperphosphorylées de la protéine tau (*Tubulin-Associated Unit*) associées aux microtubules et à l'accumulation extraneuronale des plaques neuritiques, encore appelées plaques séniles ou β -amyloïdes ($A\beta$) du nom du principal peptide qui les forme. Le terme de plaques neuritiques correspond aux agrégats extracellulaires du peptide $A\beta$ entouré de neurites dystrophiques (dendrites) contenant des agrégats de la protéine tau. A ces atteintes s'ajoutent les lésions négatives qui font référence aux pertes neuronales et synaptiques. Ces dernières, bien que d'une très grande importance physiopathologique, sont peu spécifiques de la MA et seules les lésions positives permettent véritablement d'établir le diagnostic de la MA.

1.4.1. Lésions positives de la MA

L'accumulation de la protéine tau phosphorylée en DNF et la formation de plaques séniles suites aux dépôts $A\beta$ sont caractéristiques de la MA.

1.4.1.1. Plaques $A\beta$

1.4.1.1.1. Le peptide $A\beta$

Le peptide $A\beta$ est le principal constituant des plaques séniles et est physiologiquement produit dans le cerveau (Seubert et al., 1992). Il est issu du clivage de la protéine transmembranaire β -APP (pour *β -Amyloid Precursor Protein*) sous l'action enzymatique de

β -secrétase puis de la γ -secrétase (Duyckaerts et al., 2009). Le clivage par la γ -secrétase est parfois variable, conduisant à une hétérogénéité de peptides $A\beta$ qui se distinguent par leur extrémité Carboxy-terminale. Ainsi, il existe différents peptides $A\beta$ contenant entre 38 et 43 acides aminés (Thinakaran et Koo, 2008), ceux se terminant au 40^{ème} acide aminé ($A\beta_{40}$) sont les plus fréquents (80 à 90 %) avec le peptide $A\beta_{42}$ (5 à 10 %). Les formes légèrement plus longues de l' $A\beta$, particulièrement l' $A\beta_{42}$, sont plus hydrophobes et ont tendance à s'agréger en fibrilles et à prendre une conformation en feuillets β plissés insolubles, constituant ainsi les principaux dépôts amyloïdes ($A\beta$) cérébraux (Ittner et Götz, 2011 ; Querfurth et LaFerla, 2010 ; Selkoe, 2001). Une photographie du marquage immunohistologique de la protéine $A\beta_{42}$ observé en microscopie au niveau de l'hippocampe après l'autopsie d'un patient MA est présentée dans la Figure 2.

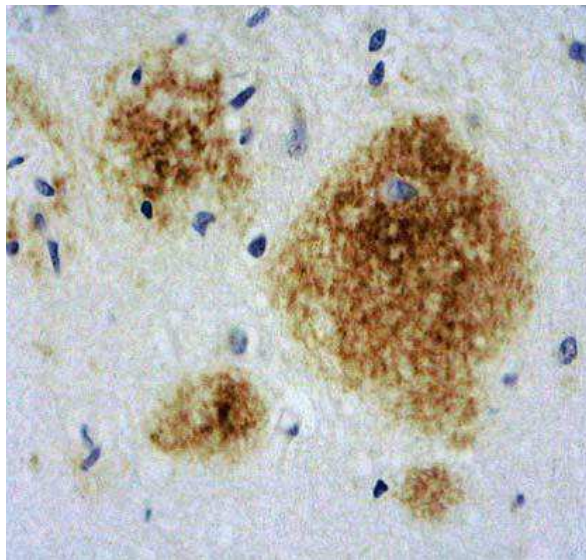


Figure 2 : Marquage immunohistologique de la protéine $A\beta_{42}$ au niveau de l'hippocampe après autopsie d'un patient MA (d'après Small et al., 2008)

1.4.1.1.2. Topographie des dépôts $A\beta$

La répartition des dépôts $A\beta$ dans le cerveau est hétérogène, avec une localisation préférentielle des dépôts diffus ou focaux au niveau de l'isocortex et seulement diffus dans le striatum (Gearing et al., 1997), le thalamus (Rüb et al., 2002), et plus tardivement dans le cervelet (Mann et al., 1990) et le tronc cérébral (Iseki et al., 1989).

L'évolution de la topographie des dépôts $A\beta$ diffus et focaux est stéréotypée et a été décrite sous la forme de trois stades par Braak et Braak en 1991 (Figure 3A). Le stade 1 décrit la topographie initiale du peptide $A\beta$ dans le cortex basal, les lobes frontaux, temporaux

occipitaux. Au stade 2, les dépôts s'étendent à toutes les aires isocorticales associatives comprenant le reste des lobes frontaux et les lobes pariétaux. Enfin au stade 3, l'ensemble de l'isocortex est atteint, incluant les régions sensorielles et motrices. Cette évolution de la topographie des dépôts amyloïdes a été décrite de manière plus précise (Figure 3B) en distinguant non plus 3 mais 5 stades de propagation allant de l'isocortex jusqu'au cervelet (Thal et al., 2002). Dès la première phase, les dépôts A β sont retrouvés dans le néocortex frontal, pariétal, temporal et occipital. Dans la deuxième phase, ces dépôts gagnent la région entorhinale, le sous-champ hippocampique CA1 et le cortex insulaire. Dans 33 à 50 % des cas, des dépôts apparaissent également au niveau de l'amygdale, du gyrus cingulaire et de la région du subiculum. L'extension de la topographie des dépôts A β se poursuit dans la phase 3 et concerne les régions sous-corticales telles que les noyaux caudés, le putamen, le thalamus, l'hypothalamus et la substance blanche. La quatrième phase est caractérisée par la progression des dépôts A β au sein des noyaux du tronc cérébral dont le noyau inférieur olivaire, la substance noire et les colliculi supérieurs et inférieurs. Enfin, la cinquième et dernière phase est marquée par l'extension de la topographie des dépôts A β au sein du pons et du cervelet.

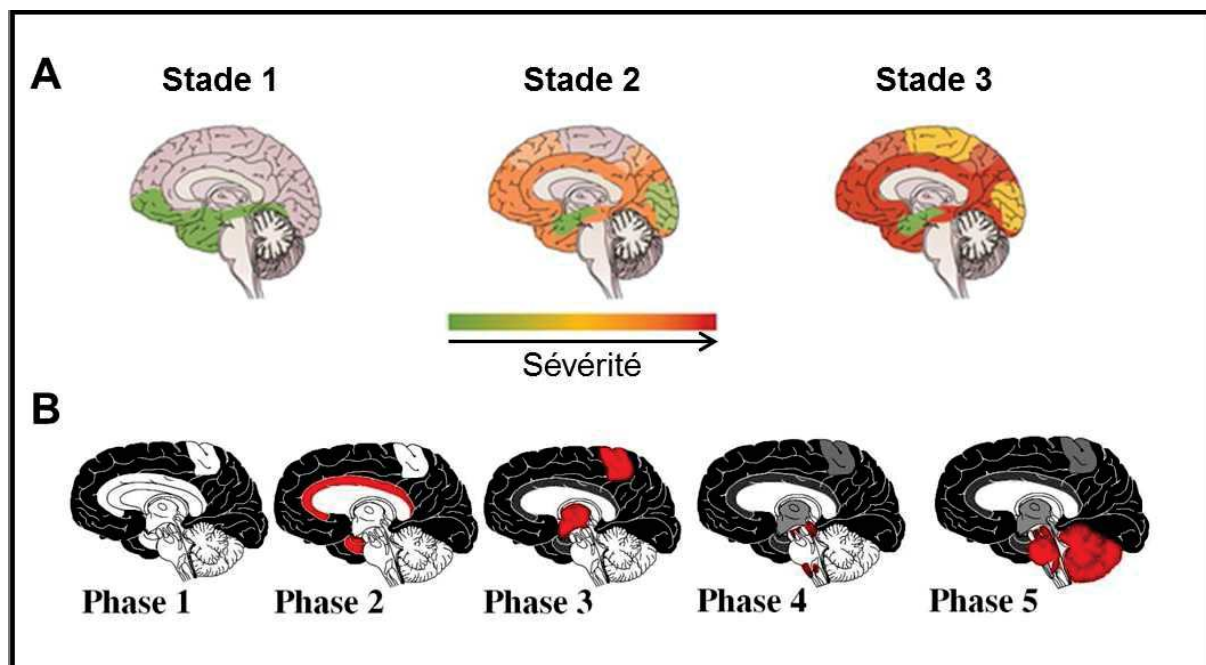


Figure 3 : Evolution topographique des dépôts A β en trois stades selon le modèle de Braak et Braak (1991) (A) et en 5 phases selon le modèle de Thal et al., 2002 (B) pour lequel les régions en noir présentent des dépôts amyloïdes et les régions en rouge correspondent à celles nouvellement touchées.

1.4.1.2. Les dégénérescences neurofibrillaires

Les DNF accumulées dans le corps cellulaire des neurones sont l'un des 3 aspects de la pathologie neurofibrillaire avec les dystrophies neuritiques présentes dans la couronne des plaques neuritiques et les fibres tortueuses situées dans les dendrites des neurones atteints de DNF (Duyckaerts et al., 2009). Toutes ces lésions neurofibrillaires sont le résultat de l'accumulation anormale de la protéine tau hyperphosphorylée (Grundke-Iqbal et al., 1986).

1.4.1.2.1. La protéine tau

La protéine tau fait partie de la famille des protéines MAP (pour *Microtubule-Associated Proteins*) associées aux microtubules. Physiologiquement, la protéine tau assure l'assemblage et la stabilisation des microtubules et est donc impliquée dans la régulation du transport axonal. La fonction de la protéine tau dépend de son état de phosphorylation. L'incorporation de groupements phosphate dans la protéine tau dépend de sa conformation et de l'équilibre entre les activités des kinases (enzymes qui ont une action phosphorylante) et des phosphatases (enzymes qui déphosphorylent) de la protéine tau. Le changement de conformation de la protéine tau par augmentation de sa phosphorylation provoque son détachement des microtubules et joue un rôle très important dans la neurodégénérescence modulée par tau (Dixit et al., 2008; Fischer et al., 2009). La protéine tau est 3 à 4 fois plus hyperphosphorylée dans le cerveau d'un patient MA comparativement à un cerveau adulte non pathologique. L'excès de protéine tau hyperphosphorylée se polymérise en paires de filaments hélicoïdaux (Grundke-Iqbal et al., 1986) et contribue ainsi à la pathologie neurofibrillaire dont les DNF (Ittner et Götz, 2011 ; Querfurth et LaFerla, 2010 ; Selkoe, 2001). Une photographie du marquage immunohistologique de la protéine tau phosphorylée observé en microscopie au niveau de l'hippocampe après l'autopsie d'un patient MA est présentée dans la Figure 4.

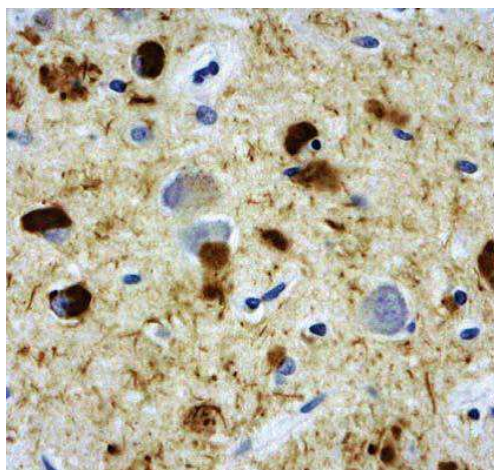


Figure 4 : Marquage immunohistochimique de la protéine tau phosphorylée au niveau de l'hippocampe après autopsie d'un patient MA (d'après Small et al., 2008)

1.4.1.2.2. Topographie des DNF

La répartition des DNF dans la MA touche le cerveau de manière hétérogène, que ce soit à l'échelle cellulaire ou régionale. Les neurones pyramidaux semblent particulièrement vulnérables aux DNF, notamment dans le sous-champ hippocampique CA1, la couche II du cortex entorhinal et la couche III de l'isocortex ainsi que dans les neurones multipolaires du noyau basal de Meynert. L'évolution de la topographie des DNF suit un processus séquentiel et hiérarchisé lié aux connexions cortico-corticales. La progression des DNF a ainsi été décrite selon six stades (Braak et Braak, 1991) représentés dans la figure 5A. Au stade I, la localisation des DNF est restreinte au cortex transentorhinal. Le stade II est marqué par une augmentation du nombre de DNF dans le cortex transentorhinal ainsi qu'à leur apparition, à une moindre densité, dans le cortex entorhinal et l'hippocampe (notamment au niveau du sous-champ CA1 et du subiculum). Les stades I et II sont rassemblés sous le nom de « stades transentorhinal » car les DNF sont essentiellement localisées dans la région transentorhinale. Au stade III, les régions transentorhinale et entorhinale sont toutes deux plus sévèrement touchées par les DNF notamment dans l'hippocampe au niveau des neurones pyramidaux du subiculum et d'autres régions sont concernées par les DNF comme l'amygdale et les noyaux thalamiques. Le quatrième stade est marqué par une aggravation des lésions observées précédemment ainsi que par leur apparition modérée au niveau de l'isocortex associatif. Les stades III et IV sont regroupés sous le terme de « stades limbiques ». Au cours du stade V, l'ensemble de l'isocortex associatif est touché par les DNF qui provoquent de fortes atteintes notamment au niveau de la région retrospléniale, de la partie inférieure des lobes temporaux et occipitaux, et des parties antéro-basales de l'ins

et du cortex orbito-frontal. Le stade VI marque la prolifération des DNF à l'ensemble du cerveau et est caractérisé par l'implication du système extrapyramidal. Les stades V et VI sont rassemblés sous le terme de « stades isocorticaux ». Ces stades de propagation des DNF ont ensuite été sous-divisés par (Delacourte et al., 1999) pour atteindre le nombre de 10 et dont le nom correspond à la structure nouvellement atteinte (Figure 5B). Ainsi, les stades I à III précédemment décrits (Braak et Braak, 1991) correspondent aux stades 1 à 4 de Delacourte traduisant l'apparition des DNF dans le cortex transentorhinal (stade 1) puis son extension au cortex entorhinal (stade 2), hippocampique (stade 3) et temporal antérieur (stade 4). Le stade IV de Braak et Braak (1991) correspond aux stades 5 et 6 marquant respectivement la propagation des atteintes neurofibrillaires aux cortex temporal inférieur et au cortex temporal moyen. Enfin, les stades V et VI de Braak et Braak (1991) ont été décomposés en 4 stades, marqués tout d'abord par la progression des DNF dans les cortex frontal antérieur, temporal supérieur et pariétal inférieur (stade 7), puis dans l'aire de Broca (stade 8), le cortex moteur et les aires occipitales (stade 9) avant d'affecter l'ensemble des aires corticales (stade 10).

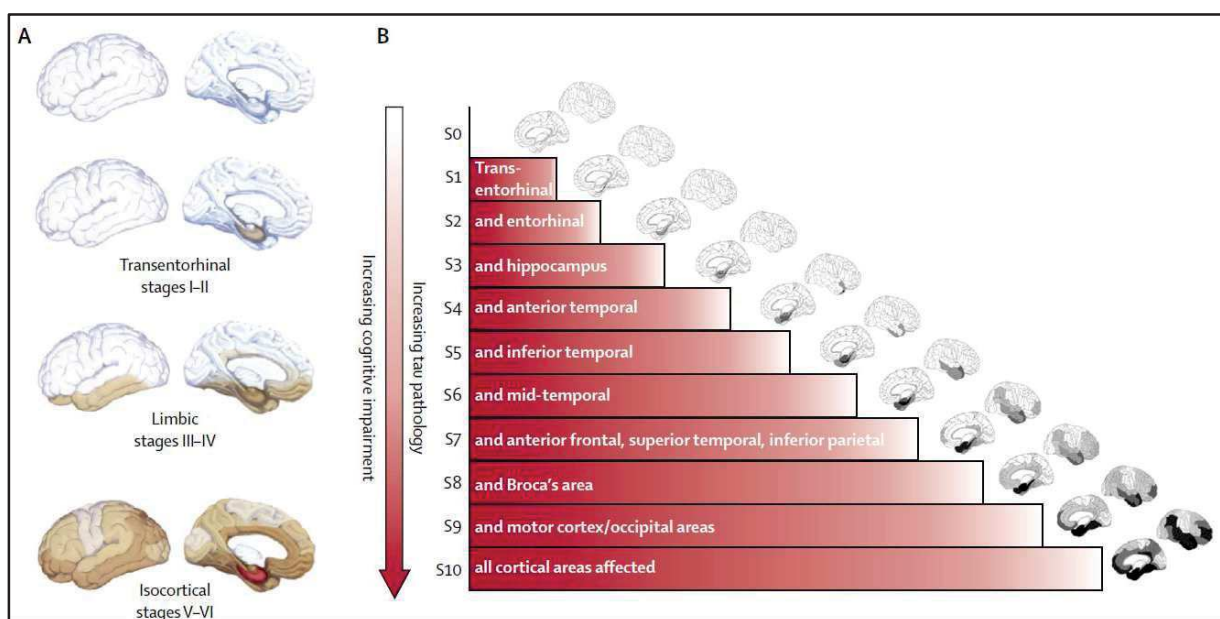


Figure 5 : Progression de l'accumulation de la protéine tau dans la MA selon les stades de Braak et Braak, 1991 (A) et Delacourte et al., 1999 (B). D'après la revue de Villemagne et al., 2015.

Ces dernières années, la propagation de tau a fait couler beaucoup d'encre en suggérant que la MA pourrait être une pathologie semblable aux maladies à prions, la plus célèbre étant la maladie de Creutzfeldt-Jakob. Les maladies à prions ont pour point commun qu'une

protéine physiologique, mais mal conformée (protéine prion), induit sa mal-conformation aux protéines adjacentes provoquant ainsi des agrégations qui aboutissent à une dégénérescence du système nerveux central. Dans le cadre de la MA, la protéine tau hyperphosphorylée et la protéine A β auraient des propriétés communes aux protéines à prions du fait de leur capacité à propager leur conformation altérée comme l'ont montré un grand nombre d'études réalisées *in vitro* et *in vivo* (Alonso et al., 2016; Eisele et Duyckaerts, 2016; Frost et Diamond, 2009a, 2009b; Frost et al., 2009).

1.4.2. Lésions négatives de la MA

1.4.2.1. Pertes neuronales

En l'absence de correction, l'évaluation de la perte neuronale en microscopie est surestimée à cause des grands neurones qui ont plus de chances d'être coupés (Duyckaerts et al., 1989). Pour s'affranchir de ce biais, des méthodes stéréologiques (telles que le « di-secteur » où seuls les neurones présents sur une coupe et absents de l'autre sont comptabilisés) ont été développées pour reconstituer la densité de neurones dans un volume à partir de son estimation sur une coupe histologique.

La perte neuronale est focalisée dans des aires et des couches corticales spécifiques. Elle est ainsi particulièrement marquée dans le lobe temporal interne et notamment au niveau du cortex entorhinal où elle peut atteindre dans des stades tardifs de la MA jusqu'à 90% pour les neurones de la couche II et 70% pour les neurones de la couche IV (Gómez-Isla et al., 1996) et de l'hippocampe (surtout les sous-champs CA1 et CA3) (Padurariu et al., 2012). La perte neuronale touche également le lobe temporal externe au niveau du gyrus temporal supérieur (Gomez-Isla et al., 1997) et le lobe pariétal dans le gyrus supramarginal (Grignon et al., 1998).

L'importance de la perte neuronale a fait l'objet de controverses. En effet, certaines études la rapportent comme étant un élément précoce de la physiopathologie et responsable des symptômes (Gomez-Isla et al., 1997; Gómez-Isla et al., 1996) tandis que d'autres l'envisagent comme un phénomène tardif, survenant après l'apparition des symptômes (Grignon et al., 1998). Le mécanisme conduisant à la mort neuronale est lui aussi débattu. La topographie préférentielle des pertes neuronales dans les couches corticales III et IV est corrélée à la densité des DNF (Fukutani et al., 2000; Gomez-Isla et al., 1997; Grignon et al., 1998)

suggérant ainsi que les DNF seraient à l'origine de la mort neuronale. Les DNF peuvent subsister dans l'espace extracellulaire sous forme de « fantômes » lorsque les neurones dont elles occupaient le cytoplasme meurent. Le nombre de « fantômes » étant proche de celui des neurones morts, il peut ainsi évaluer de manière indirecte la perte neuronale imputable aux DNF (Cras et al., 1995). Cependant, la perte neuronale serait en excès par rapport aux DNF suggérant ainsi que les DNF ne peuvent à elles seules expliquer la mort neuronale (Gomez-Isla et al., 1997; Kril et al., 2002). L'apoptose liée à la toxicité A β est également avancée comme cause de la mort neuronale (voir pour revue Duyckaerts et al., 2009).

1.4.2.2. Pertes synaptiques

Parallèlement aux pertes neuronales, les pertes synaptiques contribuent elles aussi à l'atrophie corticale survenant dans la MA. Une réduction de la densité des synapses a été révélée par microscopie électronique de manière concomitante à l'augmentation de leur surface d'apposition dans le cortex frontal, pariétal et le gyrus denté, permettant ainsi de compenser la réduction du nombre de synapses pour maintenir la surface totale de contact (DeKosky et Scheff, 1990; Scheff et al., 1996; Scheff et Price, 1993). Cependant, à un stade plus tardif de la MA, ce mécanisme compensatoire disparaît (DeKosky et Scheff, 1990).

Les pertes synaptiques ont été mises en évidence dans le cortex frontal (DeKosky et Scheff, 1990), temporal (Scheff et Price, 1993), ainsi que dans l'hippocampe au niveau du gyrus denté (Scheff et al., 1996) et du champ CA1 (Scheff et al., 2007), mais pas dans le cortex entorhinal (Scheff et al., 1993).

Les avis sont partagés concernant l'origine des pertes synaptiques : certaines études montrent en effet qu'elles seraient influencées par l'A β soluble (Pozueta et al., 2013; Selkoe, 2008; Tu et al., 2014) tandis que d'autres mettent en évidence l'implication de la protéine tau (Falke et al., 2003 ou pour revue Jadhav et al., 2015).

Pour établir avec certitude le diagnostic de MA, les critères cliniques de MA probable et leur confirmation par les analyses histopathologiques permises par la biopsie et l'autopsie du cerveau restent les seules méthodes fiables, à défaut d'autres marqueurs. Cependant, le développement des outils de neuroimagerie permet d'explorer *in-vivo* avec des méthodes de plus en plus fiables l'apparition et la propagation des altérations neuropathologiques survenant dans la MA.

2. Données d'imagerie

2.1. Atrophie de la substance grise

2.1.1. Considérations méthodologiques

L'atrophie de la substance grise peut être étudiée *in vivo* à l'aide de l'imagerie par résonance magnétique (IRM) structurale ou anatomique qui permet d'évaluer les changements de volume ou de densité de substance grise dans l'ensemble du cerveau de manière non-invasive et non-irradiante. Brièvement, le principe repose sur la propriété magnétique (spin) des protons contenus dans les molécules d'eau qui représentent 80 % du poids du cerveau. Lors d'une première étape, un champ magnétique (B0) est appliqué et les spins se polarisent en s'orientant dans le même sens conduisant à l'apparition d'un moment magnétique M0 qui correspond à la somme de tous les spins. La deuxième étape est constituée par le phénomène de résonance induit par l'impulsion d'un autre champ magnétique (B1) perpendiculaire à B0 qui provoque un moment de torsion sur M0 dans une direction où B0 est nul. Enfin, la phase de relaxation débute une fois que le champ magnétique B1 cesse d'être appliqué et correspond au retour de l'équilibre initial des protons. Le temps de relaxation T1 correspond au temps nécessaire à la composante M pour retrouver son état initial. On parle alors de séquence pondérée en T1 qui est sensible à la nature des tissus. La séquence T1 est utilisée dans l'étude des atteintes structurales cérébrales car elle fournit le meilleur contraste entre la substance grise et la substance blanche. Les images du cerveau acquises sont d'une très bonne résolution spatiale avec une précision en dessous du millimètre.

2.1.2. Imagerie de l'atrophie de la substance grise dans la MA

Les études en IRM anatomique (IRMa) ont mis en évidence que l'atrophie corticale touche dans un premier temps le lobe temporal médian qui présente ainsi une perte de volume allant de 20 à 52 % en comparaison avec des sujets sains (Chételat et Baron, 2003) puis elle s'étend à l'amygdale, aux régions temporales et pariétales avant d'atteindre les aires primaires unimodales qui restent relativement préservées jusqu'à un stade avancé de la MA (Apostolova et al., 2007; Dickerson et al., 2009; Frisoni et al., 2009; Lerch et al., 2005; Prestia et al., 2010; Singh et al., 2006; Thompson et al., 2003).

L'étude de l'atrophie de l'hippocampe est particulièrement pertinente dans le cadre de la MA car cette structure est atteinte dès le stade présymptomatique de MCI amnésique dont la perte de volume s'élève de 11 à 50 % selon les études, probablement du fait de

différences méthodologiques et de sévérité de la démence des patients (Chételat et Baron, 2003; Colliot et al., 2008; Gaugler et al., 2013; Morra et al., 2009; Small et al., 2008). L'atrophie hippocampique est considérée comme étant un biomarqueur robuste de la MA car elle permet de distinguer les patients des sujets contrôles avec une sensibilité et une spécificité supérieure à 80 % (Lehéricy et al., 2007).

2.1.3. Lien avec la neuropathologie

L'atrophie détectée en IRMa serait le reflet d'une perte neuronale, synaptique ou d'une atteinte dendritique (Murray et al., 2014). De fortes corrélations ont en effet été montrées entre le volume de substance grise mesuré en IRM et le nombre de neurones obtenu par des analyses histologiques au sein de l'hippocampe (Bobinski et al., 2000). La confrontation entre l'évaluation de l'atrophie cérébrale au moyen de l'IRMa et les analyses histopathologiques *post-mortem* a ainsi permis de valider l'utilisation de l'IRMa comme étant un biomarqueur fiable de la neurodégénérescence dans la MA (Bobinski et al., 2000; Whitwell et al., 2012). De plus, le fait que le profil d'atrophie de la MA révélé par l'IRMa soit en accord avec les stades d'évolution des DNF décrits par Braak et Braak (1991) et qu'il existe une corrélation négative entre la densité des DNF et le nombre de neurones (Gomez-Isla et al., 1997), valide l'utilisation de l'IRM structurale en tant que biomarqueur permettant d'évaluer les pertes neuronales associées aux DNF (Gosche et al., 2002; Jack et al., 2002; Silbert et al., 2003).

Récemment, une revue (Dallaire-Théroux et al., 2017) a corrélé les données issues de l'IRM *ante-mortem* (dont le volume cérébral total, le aSTAND-Score (pour score de l'index des anomalies structurales ajustées, qui reflète le degré et le profil d'atrophie cérébrale ajustés pour l'âge et le genre), le volume ventriculaire, le taux d'atrophie du lobe temporal médian, le volume hippocampique, le volume total des hyperintensités de substance blanche ou périventriculaire, volume de la substance blanche profonde) avec celles de la neuropathologie (dont les plaques diffuses, les plaques neuritiques, les DNF, les stades de Braak, l'artériosclérose, l'artériolosclérose, les microinfarcts, les hémorragies, l'angiopathie cérébrale amyloïde, la sclérose hippocampique, les corps de Lewy, la TDP-43, l'atteinte de la paroi ventriculaire et la démyélinisation de la substance blanche profonde) dans la MA (Figure 6).

	Diffuse Plaques	NPs	NFTs	Braak Stage	Arteriosclerosis	Arteriosclerosis	Microinfarcts	Hemorrhages	CAA	HS	Lewy Bodies	TDP-43	Loss of Ventricular Lining	Deep WM Demyelination
Whole-Brain Volume		Significant	Highly significant	Significant					Significant					
aSTAND-Score		Significant		Significant										
Ventricular Volume		Highly significant	Significant	Significant										Significant
MTL Atrophy Rating		Significant		Highly significant										
HV		Significant		Highly significant			Significant		Highly significant	Highly significant		Significant		
Total WMH Volume				Significant		Highly significant	Significant						Significant	
Periventricular WMH Volume				Significant		Highly significant	Significant						Significant	
Deep WMH Volume	Significant						Significant	Highly significant						Significant

Figure 6 : Corrélation entre les données issues de l'IRMa *ante-mortem* et d'études neuropathologiques dans la maladie d'Alzheimer, d'après Dallaire-Théroux et al., 2017

Les principaux résultats sur lesquels nous nous concentrerons concernent la corrélation entre l'atrophie cérébrale de la substance grise et les atteintes neuropathologiques. Il est intéressant de noter que l'atrophie globale corrèle plus significativement avec les DNF par rapport à tous les autres éléments neuropathologiques. De plus, les stades de Braak montrent de fortes corrélations avec les atteintes de la substance grise mesurées en IRM anatomique avec dans l'ordre croissant l'atrophie cérébrale globale, le volume hippocampique et le taux d'atrophie du lobe temporal médian.

2.2. Hypométabolisme

2.2.1. Considérations méthodologiques

L'hypométabolisme cérébral reflète la réduction de la consommation de glucose et peut être mesuré en tomographie par émission de positons (TEP) marquée au [18F]-2-fluoro-2-deoxy-D-glucose (FDG) (Chételat et al., 2003; Drzezga et al., 2005; Minoshima, 2003; Mosconi, 2005; Silverman et al., 2001). Ainsi, l'accumulation du traceur FDG dans une région cérébrale est proportionnelle au taux de métabolisme du glucose. Le glucose est la principale source énergétique du cerveau et sa consommation est corrélée à l'activité neuronale, en particulier au niveau synaptique (Reivich et al., 1979; Sokoloff, 1993). Cependant, les astrocytes et la microglie contribuent également au métabolisme glucidique (Zimmer et al., 2017) ce qui suggère que le métabolisme cérébral mesuré en TEP est à la fois le reflet de

l'activité neuronale mais aussi de l'activité gliale. Contrairement à l'IRM, la TEP est une technique invasive car elle nécessite l'injection d'un traceur marqué par un isotope radioactif, émetteur de positons. Classiquement, le métabolisme cérébral du glucose est mesuré pendant environ une heure, le sujet étant éveillé, en condition de repos. Après avoir été injecté par voie intraveineuse, le radiotracer passe dans les tissus biologiques et va émettre un positon. Ce positon, doté d'une certaine énergie cinétique, va parcourir un à deux millimètres avant de s'annihiler avec un électron, résultant en l'émission diamétralement opposée de 2 photons γ . La caméra TEP comporte des détecteurs de photons γ répartis en anneau à 360° autour de l'individu. Deux détecteurs opposés de 180° vont pouvoir arrêter le rayonnement émis et déterminer l'énergie du photon incident ainsi que le moment de son émission. Seuls deux photons détectés avec une énergie voisine de 511 keV et qui sont émis dans une fenêtre temporelle de l'ordre de 10ns peuvent être enregistrés et le processus de reconstruction tomographique peut ensuite recalculer le lieu d'annihilation. Cet enregistrement peut être répété à plusieurs secondes d'intervalle en générant ainsi plusieurs coupes séquentielles de l'ensemble du cerveau. Ceci permet l'obtention d'une image brute de la distribution et de la concentration locale du radiotracer. Cependant, la résolution spatiale de la TEP est relativement faible ce qui rend les images vulnérables aux effets de volume partiel (EVP) correspondant au fait que le signal mesuré dans un voxel peut provenir de différents tissus (substance grise, substance blanche ou liquide céphalo-rachidien (LCR)). Ainsi, le signal mesuré en TEP dans une région cérébrale, peut être contaminé par les voxels situés aux alentours et peut également s'étaler à d'autres régions. En l'absence de correction des images, les EVP induisent une sous-estimation des valeurs fonctionnelles mesurées dans les voxels. La correction des EVP est particulièrement importante pour les régions cérébrales de petite taille mais également dans le cadre de la MA où l'atrophie des régions cérébrales peut induire une diminution du signal TEP, non pas en raison d'un hypométabolisme, mais du fait que le signal comprend en plus de la substance grise du LCR (dont le signal est nul). Plusieurs méthodes existent pour corriger les EVP des images TEP (Giovacchini et al., 2004; Quarantelli et al., 2004) et reposent sur l'utilisation des données du même sujet obtenues en IRMa qui présentent une meilleure résolution spatiale.

2.2.2. Profil d'hypométabolisme cérébral dans le MCI et la MA

Les études menées en TEP ont révélé un hypométabolisme particulièrement précoce du cortex cingulaire postérieur (CCP) et de la région temporo-pariétale tandis que le cortex sensorimoteur primaire et le cortex visuel semble relativement préservés (pour revue Alavi et al., 1986). L'hypométabolisme du CCP et de la région temporo-pariétale a largement été décrit dans la littérature et constitue un biomarqueur caractéristique de la MA (Chételat et al., 2008; Desgranges et al., 1998; Grothe et Teipel, 2016; Ibanez et al., 1998; Ishii et al., 2005; La Joie et al., 2012; Meltzer et al., 1996; Minoshima et al., 1997; Salmon et al., 2000).

L'hypométabolisme du gyrus cingulaire apparaît très précocement et est retrouvé dès le stade de MCI amnésique (Chételat et al., 2003; Grothe et Teipel, 2016; Nestor et al., 2003a; Nestor et al., 2003b). A un stade plus tardif, l'hypométabolisme gagne le cortex frontal dont l'atteinte semble marquer la conversion des patients MCI amnésiques vers le stade démentiel (Drzezga et al., 2003; Fouquet et al., 2009).

2.3. Imagerie moléculaire des dépôts A β

2.3.1. Considérations méthodologiques

Le PiB (pour Pittsburgh Compound-B) , marqué au carbone ^{11}C , est le radiotracer le plus fréquemment utilisé pour l'imagerie de l'amyloïde beta et il a été le premier radiotracer sélectif de A β permettant de différencier les patients MCI des patients MA par la TEP (Klunk et al., 2004; Rowe et al., 2010 et pour revue Counts et al., 2016). Les radiotraceurs marqués au ^{18}F sont également largement utilisés, comme le Florbetaben (Rowe et al., 2008), le Flutemetamol (Koole et al., 2009) et le Florbetapir (Choi et al., 2009). L'avantage du radioisotope ^{18}F est qu'il n'a pas besoin d'être produit sur le lieu d'examen étant donné sa demi-vie de 110 minutes, ce qui représente un avantage logistique non négligeable, surtout pour les centres d'imagerie ne disposant pas d'un cyclotron à proximité. L'apparition de l'imagerie *in vivo* de la pathologie amyloïde depuis une dizaine d'années a révolutionné l'étude de la MA en permettant l'évaluation des dépôts A β à travers le temps de manière fiable et reproductible à tel point qu'il est à présent utilisé comme un outil clinique et de recherche pour le recrutement des patients et l'évaluation des essais thérapeutiques anti-amyloïde. Ainsi, la *Food and Drug Administration* (FDA) a autorisé l'utilisation et la commercialisation à des fins cliniques et de recherche du Florbetapir sous le nom d'AmyvidTM depuis 2012, du Flutemetamol sous le nom de VizamyTM depuis 2013 et du

Florbetaben contenu dans le produit NeuraceqTM depuis 2014. Dans la pratique clinique, l'interprétation des images TEP présentant un marquage amyloïde peut être réalisée visuellement permettant ainsi d'identifier les patients β -amyloïdes positifs ($A\beta^+$) qui présentent un fort marquage cortical comparés aux patients β -amyloïdes négatifs ($A\beta^-$).

L'analyse quantitative du marquage permet d'obtenir une mesure plus précise de la quantité et de la répartition topographique des dépôts $A\beta$. La quantification du marquage peut se faire soit dans des régions d'intérêt prédéterminées, soit à l'aide d'analyses voxel à voxel du cerveau entier. De nombreuses méthodologies permettant la quantification des données TEP existent (Edison et al., 2011), telles que le calcul des *Standard Uptake Value Ratio* (SUVR) ou des *distribution volume ratio* (DVR) qui présentent chacune des avantages et des limites mais que nous n'aborderons pas ici. On peut toutefois noter l'importance méthodologique résidant dans la correction de l'effet des volumes partiels et le choix de la région utilisée comme référence pour effectuer la normalisation des images amyloïdes (cervelet ou pons le plus souvent) (Edison et al., 2012) dont l'influence sur les résultats est non négligeable. La quantification globale des dépôts $A\beta$ est obtenue suite à l'extraction des valeurs dans le néocortex ou par la moyenne de valeurs extraites dans des régions d'intérêt (Chételat et al., 2010; Mormino et al., 2012; Villain et al., 2012). A partir de ces valeurs, il devient alors possible de distinguer les individus $A\beta^+$ des $A\beta^-$, mais là encore, la méthode par laquelle le seuil de positivité est déterminé peut également être responsable de la variabilité des résultats constatée entre les études (Fleisher et al., 2011; Mormino et al., 2012).

2.3.2. Profil de l'accumulation amyloïde dans la MA

De manière assez consensuelle, les études menées chez les patients MA rapportent que le marquage des dépôts $A\beta$ est fortement présent dans le néocortex frontal, temporal, pariétal, cingulaire ainsi que dans le striatum, plus discret dans le lobe occipital et le thalamus et très peu différent des sujets sains dans le cortex sensori-moteur et le lobe temporal (Chételat et al., 2011; Edison et al., 2007; Kemppainen et al., 2006; Klunk et al., 2004; La Joie et al., 2012; Rabinovici et al., 2007; Rabinovici et al., 2010; Rowe et al., 2007; Shin et al., 2008). La répartition topographique des plaques amyloïdes obtenue par le marquage TEP correspond aux descriptions neuropathologiques des études *post-mortem* (Figure 7) avec notamment une plus forte concentration d' $A\beta$ dans le cortex frontal que dans l'hippocampe (Ikonomic et al., 2008; Wolk, 2011; Wong et al., 2013).

¹¹C-PIB

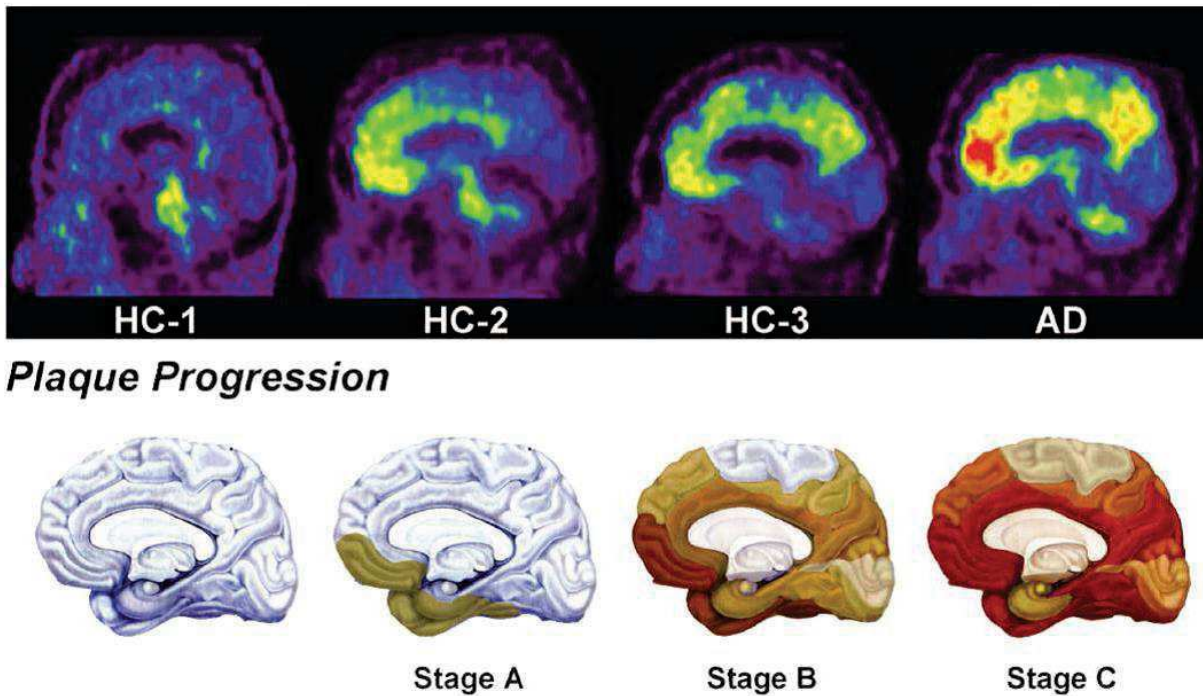


Figure 7 : Correspondance entre la topographie du marquage PIB de 4 individus (d'après Rowe et al. 2007) et les stades de la progression des plaques amyloïdes selon les stades décrits par Braak et Braak (1991)

2.3.3. Profil de l'accumulation amyloïde chez les patients MCI

La topographie du marquage PIB chez les patients MCI semble être intermédiaire entre celle des sujets âgés sains et des patients MA (Devanand et al., 2010; Jagust et al., 2010; Lopresti et al., 2005; Price et al., 2005; Rowe et al., 2010). Cependant, le profil amyloïde des patients MCI ne constitue pas une troisième catégorie mais semble plutôt faire l'objet d'une dichotomie. En effet, certains patients MCI présentent des scans amyloïdes positifs, avec un fort marquage PIB cortical, qui se rapprochent du profil des patients MA, tandis que d'autres présentent des scans amyloïdes négatifs, avec une faible fixation corticale du traceur, et ont donc un profil similaire à ceux des sujets sains (Klunk, 2011). Selon les études, 50 à 70 % des patients MCI seraient amyloïdes-positifs (Forsberg et al., 2008; Jansen et al., 2015; Kemppainen et al., 2007; Lowe et al., 2009; Mormino et al., 2009; Pike et al., 2007; Vandenberghe et al., 2010) avec une plus grande proportion (83 %) chez les patients MCI amnésiques *multidomain* contre 46 % chez les MCI amnésiques *single-domain* (Wolk et al., 2009). A l'inverse, les patients MCI non-amnésiques et plus particulièrement les *single-domain* présentent une faible rétention corticale du traceur amyloïde, ce qui est en accord avec l'hypothèse selon laquelle les mécanismes physiopathologiques de ces patients ne seraient pas liés à la MA (Lowe et al., 2009; Pike et al., 2007). Bien que de nombreuses

études ne montrent pas de lien entre l'accumulation amyloïde et les troubles mnésiques ou la sévérité de la démence chez les patients MA, une forte accumulation des dépôts A β chez les patients MCI est associée à de faibles performances en mémoire épisodique (Mormino et al., 2009; Ong et al., 2013; Pike et al., 2007).

2.4. Imagerie moléculaire des DNF

2.4.1. Considérations méthodologiques

Récemment, des radiotraceurs marqués au ^{18}F ont été développés pour étudier la quantité et la topographie des dépôts tau ainsi que leur propagation *in vivo*. Le marquage de tau obtenu en TEP corrèle significativement avec les mesures de tau issues des analyses du LCR (Chhatwal et al., 2016; Gordon et al., 2016). Parmi les nouveaux traceurs tau, les plus utilisés dans les études menées chez l'Homme sont le T807 (ou ^{18}F -AV1451 ; Chien et al., 2013), le T808 (Chien et al., 2014), le THK-5317 (Chiotis et al., 2016) et le THK-5351 (Lockhart et al., 2016) mais cette liste est loin d'être exhaustive vu l'innovation fulgurante de ce nouveau pan de l'imagerie.

De nombreux radiotraceurs sont en effet fabriqués mais bon nombre ne sont pas retenus suite aux essais *in vitro* ou *in vivo*. L'élaboration d'un traceur fiable reflétant la topographie de tau doit faire face à plusieurs défis liés principalement aux caractéristiques intrinsèques aux dépôts tau : le fait que les dépôts soient intracellulaires, qu'il existe 6 isoformes de tau, l'agrégation de tau dans la substance blanche, et plus spécifiquement dans le cadre de la MA, la plus faible concentration de tau par rapport à A β et la coexistence des dépôts de ces deux protéines. Les traceurs tau utilisés en TEP doivent donc présenter une forte spécificité pour tau comparé à l'A β , avoir une forte affinité, passer la barrière hémato-encéphalique, se marquer facilement avec des radio-isotopes à la demi-vie assez longue, présenter un faible marquage non spécifique et ne pas être métabolisés (pour revue Villemagne et al., 2015). Ainsi, il n'existe pas à l'heure actuelle de traceur tau optimal, chacun ayant des avantages et des inconvénients. A titre d'exemple, le T807 qui est utilisé dans les études menées chez l'Homme présente un marquage globalement en accord avec les descriptions neuropathologiques de la topographie de tau issue des stades de Braak (Schöll et al., 2016) mais sa forte rétention dans la région striatale, même chez les individus cognitivement sains, reste inexpliquée et incohérente avec la neuropathologie et pourrait conduire à une surestimation de l'accumulation de tau dans l'insula (Figure 8).

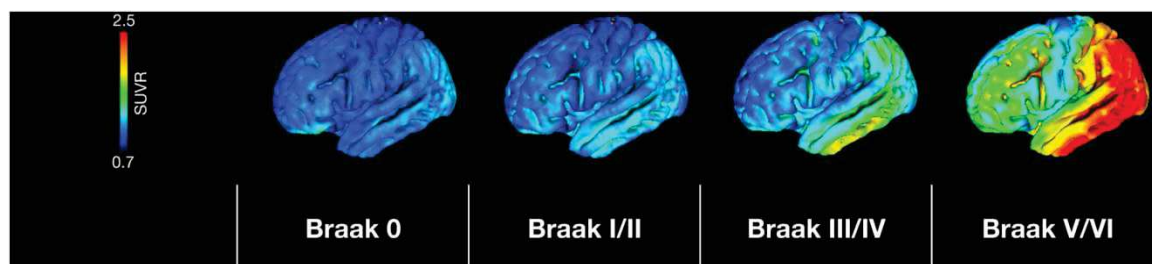


Figure 8 : Topographie du marquage AV1451 (T807) répartie selon les stades de Braak chez des individus jeunes (stade 0) et âgés sains (stade 0 à III/IV) et chez des patients MA (stade V/VI), d'après Schöll et al., 2016

2.4.2. Imagerie moléculaire des DNF dans le MCI et la MA

Bien que les résultats obtenus à l'aide de l'imagerie tau soient à prendre avec précaution compte tenu des limites que nous venons d'aborder, nous pouvons tout de même mentionner qu'un consensus se dégage à travers les études, d'après l'utilisation de différents traceurs tau. En effet, de nombreux travaux rapportent une augmentation de la rétention du radiotracer chez les patients MCI et MA dans les régions temporales, pariétales et orbitofrontales comparativement aux sujets sains (Chiotis et al., 2016; Lockhart et al., 2016). Le marquage tau observé dans le gyrus temporal inférieur semble être le plus pertinent pour discriminer les patients MA des sujets contrôles (Chiotis et al., 2016; Cho et al., 2016; Harada et al., 2015; Johnson et al., 2016; Lockhart et al., 2016).

Le développement de l'imagerie tau représente un véritable enjeu car elle pourrait contribuer à une meilleure identification des patients, que ce soit dans un but de diagnostic clinique ou de sélection de patients lors d'évaluations thérapeutiques (pour revue, Dani et al., 2016).

2.5. Apport des biomarqueurs dans le diagnostic de la MA

Compte tenu de la pertinence des biomarqueurs d'imagerie que nous venons d'aborder mais aussi des biomarqueurs biologiques (e.g. mesures des taux de protéines tau ou amyloïde dans le LCR), les critères diagnostiques utilisés en recherche ont peu à peu intégré ces mesures comme outils d'investigation.

Comme nous l'avons vu précédemment, le diagnostic clinique de la MA probable est basé sur les critères NINCDS-ADRDA définis par McKhann en 1984. A partir de ces critères, deux groupes de travail ont caractérisé de manière plus précise les différents stades de la MA en s'appuyant sur les biomarqueurs permettant une meilleure détection de la pathologie à l'aide des critères ainsi redéfinis.

Le *National Institute of Aging-Alzheimer's Association* (NIA-AA) s'est formé en 2009 dans le but de redéfinir les critères diagnostiques et de recherche de la MA et s'est subdivisé en 3 groupes de travail se consacrant chacun à une phase particulière de la MA : la phase démentielle (McKhann et al., 2011) ; la phase pré-démentielle, symptomatique (Albert et al., 2011); et la phase préclinique, asymptomatique de la MA (Sperling et al., 2011). Ainsi, le groupe assigné à la caractérisation du stade démentiel de la MA a proposé des critères de classification de la MA en i) « MA probable » (qui remplit les critères définis par McKhann en 1984, et qui consiste en une présentation amnésique ou non-amnésique – avec des déficits dans le domaine du langage, visuospatial ou des fonctions exécutives – et qui requiert l'absence de comorbidités), ii) « MA possible » (qui peut présenter une progression atypique avec un début soudain et qui remplit les critères cliniques de la MA en présence de facteurs de comorbidité) et iii) « MA probable ou possible » avec la présence de marqueurs de la physiopathologie de la MA. L'application des biomarqueurs au diagnostic de MA en recherche clinique chez les patients symptomatiques a été abordée en divisant les biomarqueurs en deux catégories, avec d'une part, les biomarqueurs cérébraux d'A β (niveaux faibles dans le LCR pour A β 42 et élevés en imagerie) et d'autre part, les biomarqueurs dits de neurodégénérescence (concentrations élevées de tau et phospho-tau dans le LCR, hypométabolisme du glucose temporopariétal constaté à l'aide de la TEP-FDG, et atrophie temporale (dont l'hippocampe) et pariétale médiane mesurées en IRM structurale). Le groupe spécialisé dans la caractérisation de la phase préclinique de la MA a différencié 3 stades de MA préclinique suivant un *continuum* temporel. Le stade 1 correspond à une amyloïdose cérébrale asymptomatique et concerne donc les individus présentant des biomarqueurs amyloïdes anormaux ; le stade 2 concerne des individus qui, en plus des critères du stade 1, présentent des biomarqueurs anormaux révélant la présence de neurodégénérescence ; et enfin, le stade 3 concerne les individus qui, en plus des anomalies constatées au stade 2, présentent des changements cognitifs subtils (reflétant un déclin des performances propres au sujet par rapport à son passé mais restant dans les normes neuropsychologiques). Pour résumer, ces critères de MA précliniques se basent sur l'hypothèse de la cascade amyloïde qui stipule que la MA serait initiée par une accumulation du peptide amyloïde et qu'ensuite les autres phénomènes physiopathologiques, observables par les biomarqueurs de neurodégénérescence, apparaîtraient. Cette séquence

hypothétique est représentée dans le modèle de progression de la MA proposé par (Jack et al., 2010), résumé dans la figure 9.

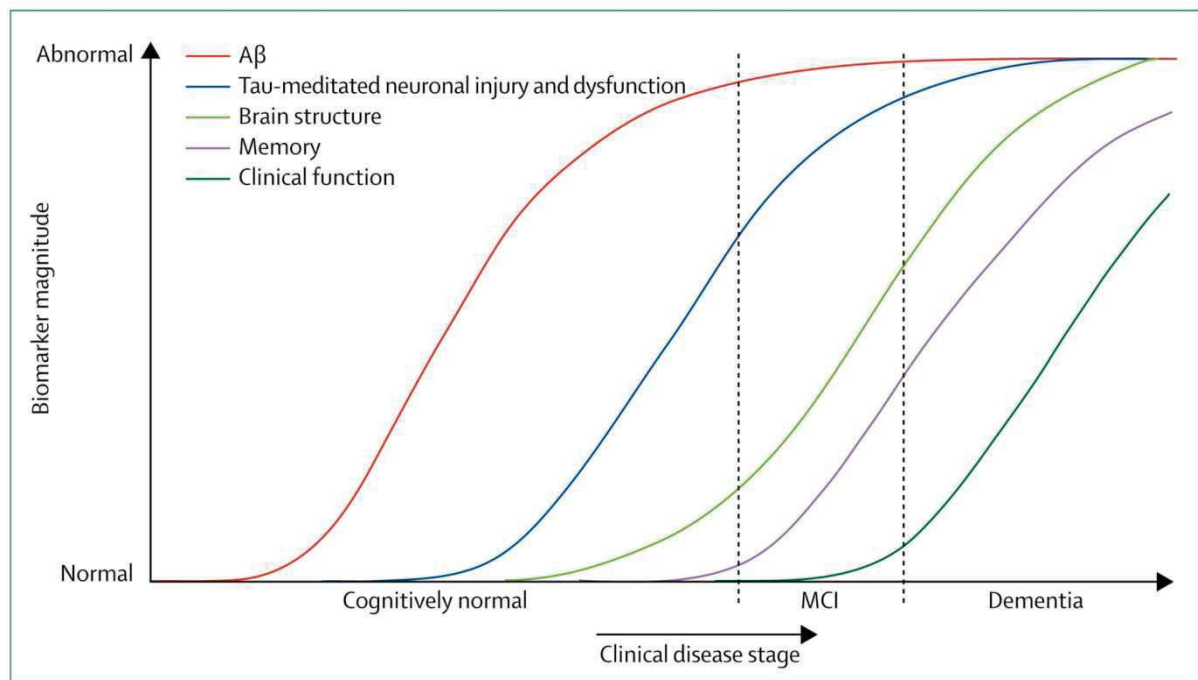


Figure 9 : Modèle de progression de la MA selon Jack et al., 2010

Pendant près de 20 ans, cette hypothèse de la cascade amyloïde a prédominé pour expliquer les différents phénomènes physiopathologiques à l'origine de la neurodégénérescence dans la MA. Cependant, une première remise en cause avait été soulevée par des études neuropathologiques suggérant que les DNF pourraient précéder ou se former de manière indépendantes aux plaques amyloïdes (Schönheit et al., 2004). L'avènement de l'imagerie moléculaire est venu fortement appuyer cette controverse relative à la cascade amyloïde, comme présenté par la figure 10 (Chételat, 2013). En effet, de récents travaux ont mis en évidence que les biomarqueurs de neurodégénérescence pouvaient être indépendants de l'amyloïdose beta (Jagust et Landau, 2012; Knopman et al., 2013; Reiman et al., 2012). Ainsi, la neurodégénérescence serait causée par différents facteurs, en partie indépendamment des dépôts A β . Les pathologies amyloïdes et tau pourraient se développer en parallèle, sous la modulation des facteurs génétiques et environnementaux et provoquer des altérations cérébrales mises en évidence par les biomarqueurs en imagerie de la MA (Figure 9). Une révision du modèle de progression de la MA a en outre été proposée par Jack et al. conciliant ainsi les deux hypothèses d'initiation de la MA par la pathologie amyloïde ou la pathologie tau (Jack et al., 2013, 2016).

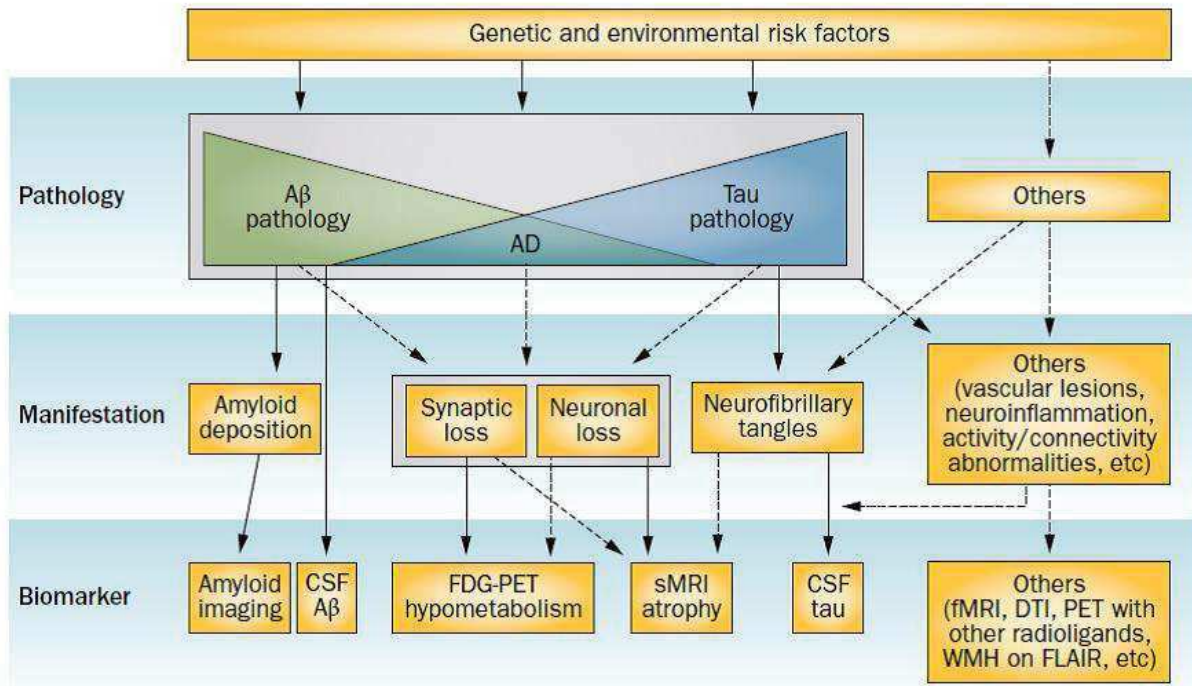


Figure 10 : Mécanismes physiopathologiques dans la MA, d'après Chételat 2013

L'International Working Group (IWG) for New Research Criteria for the Diagnosis of Alzheimer's Disease a également proposé de nouveaux critères diagnostiques de la MA. Ainsi, selon ces nouveaux critères, l'altération progressive de la mémoire épisodique – constatée par un déficit dans le rappel libre non normalisé par un indice – doit être accompagnée par au moins un biomarqueur biologique ou d'imagerie. Parmi les biomarqueurs en imagerie possibles, figurent l'atrophie temporelle interne révélée au moyen de l'IRMa, l'hypométabolisme temporo-pariétal obtenu en TEP-FDG et l'accumulation de peptide amyloïde mesuré en TEP-PIB. D'autres biomarqueurs biologiques peuvent également être utilisés comme critères diagnostiques, tels qu'une concentration anormalement diminuée de protéine Aβ₄₂ et/ou une augmentation de la concentration de tau-totale et/ou de Phospho-tau dans le LCR ; ou la détection d'une mutation génétique autosomale dominante (Dubois et al., 2007). Avec l'amélioration des connaissances de la physiopathologie de la MA, notamment grâce au développement des biomarqueurs *in-vivo*, ces critères définis en 2007 ont fait l'objet d'une précision conceptuelle (Dubois et al., 2010). Ces auteurs ont introduit la distinction entre « maladie d'Alzheimer », qui se réfère au trouble clinique et qui regroupe les phases prédéméntielle et démentielle, et « pathologie d'Alzheimer », qui désigne les changements neurobiologiques responsables de la MA incluant des lésions neuronales spécifiques (plaques séniles neuritiques et DNF, perte

synaptique, dépôts A β vasculaires dans le cortex cérébral) indépendamment de l'existence de troubles cliniques. Ce travail a également défini les notions de « MA typique » (manifestation clinique la plus rencontrée dans la MA avec un trouble précoce et significatif de la mémoire épisodique corroboré par au moins un biomarqueur *in-vivo* de la pathologie d'Alzheimer), « MA atypique » (plus rare, s'exprime par un déficit cognitif non-mnésique et le marquage amyloïde et des concentrations anormales dans le LCR d'amyloïde, tau ou phospho-tau) et de « MA mixte » (qui correspond à la MA typique accompagnée de biomarqueurs d'imagerie ou biologiques révélant la présence de comorbidité). Enfin, ces auteurs ont subdivisé l'état préclinique de MA en « asymptomatique à risque de développer la MA » (en l'absence de trouble cognitif et en présence d'un biomarqueur d'imagerie ou biologique révélant une amyloïdose cérébrale) et en « présymptomatique de MA » (présence d'une mutation autosomale monogénique dominante). Les critères diagnostiques définis par ce groupe en 2007 ont ensuite été appliqués avec plus de précision à ces nouveaux concepts (Dubois et al., 2014). Dernièrement, une redéfinition de la notion de stade préclinique de MA et de nouvelles recommandations de l'utilisation des biomarqueurs dans le diagnostic ont été proposées (Dubois et al., 2016). Ces auteurs recommandent d'utiliser le terme de « MA préclinique » pour les individus présentant des niveaux de tau et amyloïde supérieurs aux seuils pathologiques et le terme de « asymptomatique à risque de développer la MA » pour les individus dont l'évolution vers la MA est moins certaine, qui ne présentent qu'un seul marqueur physiopathologique anormal. Concernant le rôle des biomarqueurs dans le diagnostic des différents stades de MA, l'IRM et la TEP ne sont pas recommandées pour définir la MA préclinique, mais elles peuvent être utilisées pour la détection des individus à risque de développer la MA. Les biomarqueurs *in-vivo* (TEP ou dosage LCR) mettant en évidence la présence concomitante de tauopathie et d'amyloïdopathie permettent le diagnostic de la MA à un stade préclinique mais ces techniques nécessitent une meilleure standardisation afin d'être véritablement fiables. Concernant l'évaluation de la progression de la maladie, les auteurs recommandent d'augmenter les périodes de suivi dans les études longitudinales, d'utiliser le taux de changement longitudinal estimé en IRM structurale et en TEP-FDG pour suivre la progression vers la MA des individus asymptomatiques.

D'autres outils d'imagerie permettent d'investiguer les altérations survenant dans la MA, notamment concernant les atteintes de connectivité fonctionnelle. Depuis quelques années,

la connectivité fonctionnelle au repos a pris une place très importante dans l'étude de la physiopathologie de la MA, permettant de mieux comprendre le fonctionnement des réseaux et leur altération dans la MA. Cependant, Dubois et al. (2016) soulignent qu'à l'heure actuelle, le profil caractéristique du changement des altérations de la connectivité fonctionnelle survenant dans la MA qui pourrait être utilisé comme prédicteur d'une progression future vers la MA clinique n'a toujours pas été identifié.

3. Atteinte des réseaux fonctionnels dans la maladie d'Alzheimer

3.1. La MA, un syndrome de déconnexion ?

Afin d'expliquer certaines discordances dans la topographie des altérations morphologiques de la substance grise constatées en IRMa et les atteintes métaboliques mesurées en TEP-FDG, montrant une atteinte prédominante de l'hippocampe et du CCP respectivement, l'hypothèse de déconnexion a été proposée (Delbeuck et al., 2003). Selon cette hypothèse, l'atteinte initiale d'une région conduirait à la réduction de communication entre deux régions cérébrales (celle initialement atteinte et une autre) aboutissant à la rupture de la communication neurale nécessaire au bon fonctionnement cognitif. Ainsi, dans le cadre de la MA, l'atrophie de l'hippocampe serait due à la désafférentation des fibres hippocampo-cingulaires qui entrainerait des altérations fonctionnelles à distance se traduisant par l'hypométabolisme du CCP, par un phénomène de diaschisis non-transitoire hippocampo-cingulaire. Cependant, deux nuances importantes doivent être mentionnées par rapport à cette hypothèse de déconnexion. En effet, la MA apparait progressivement, contrairement aux autres pathologies de déconnexion telles que l'accident vasculaire cérébral où l'ischémie d'une région survient brutalement suite à l'obstruction d'un vaisseau sanguin. De plus, des altérations sont observées dans des régions non connectées au site précocement atteint et sont corrélées à des réseaux au repos (Brier et al., 2012) suggérant ainsi que le mécanisme seul de déconnexion à partir de la région initialement atteinte ne peut suffire à expliquer la topographie et la propagation des lésions dans la MA. Des travaux menés en *voxel based morphometry* (VBM) dans le cadre de la MA ont conforté cette hypothèse en mettant en évidence que l'atrophie hippocampique initiale serait liée à l'atrophie du cingulum qui elle-même expliquerait le degré d'évolution de l'hypométabolisme dans le CCP (Villain et al., 2008, 2010). Les études réalisées en connectivité fonctionnelle au repos ont permis elles aussi d'améliorer la compréhension de cette déconnexion survenant entre ces deux régions clés de la MA que sont l'hippocampe et le CCP. En l'absence de pathologie, le CCP présente une forte connectivité fonctionnelle au repos avec l'hippocampe et est intégré plus largement dans le réseau mnésique hippocampo-pariétal (Kahn et al., 2008; Vincent et al., 2006). Dans le cadre de la MA, il a été mis en évidence une altération de la connectivité entre ces deux régions (Greicius et al., 2004) qui reflète la déconnexion de l'axe hippocampo-cingulaire postérieur et il a même été constaté une disparition totale de la corrélation du décours temporel entre l'hippocampe et le CCP chez les patients MCI amnésiques (Sorg et al., 2007). L'étude de l'altération de la connectivité fonctionnelle dans

ces deux régions suscite un grand intérêt dans le cadre de la MA car elle serait impliquée dans les déficits des fonctions mnésiques et cognitives comprenant l'altération de la mémoire épisodique observés chez les MCI amnésiques (Bai et al., 2009; Dunn et al., 2014).

3.2. Connectivité fonctionnelle en IRMf au repos

3.2.1. Considérations méthodologiques

L'IRM fonctionnelle (IRMf) au repos permet d'observer *in vivo* et de manière non invasive l'activité cérébrale spontanée. Classiquement, le sujet est en état de repos éveillé, allongé dans l'IRM les yeux fermés ou fixant une croix pendant une dizaine de minutes. Le principe de l'IRMf au repos consiste à enregistrer les fluctuations basses fréquences (0.01 à 0.1 Hz) du signal BOLD (pour Blood Oxygen Level Dependent) (Ogawa et al., 1990) en l'absence de tâche cognitive. Initialement, ces fluctuations étaient considérées comme étant du bruit et étaient éliminées dans le traitement des images IRM d'activation afin d'obtenir le signal cérébral sous-tendant la tâche réalisée. Cependant, Biswal et al. (1995) ont révélé la présence d'une forte corrélation entre les fluctuations basses fréquences des cortex moteurs gauche et droit alors même que l'individu était immobile, placé au repos. Ils ont ainsi mis en évidence l'existence de fluctuations cérébrales synchronisées à l'état de repos qui correspondent à l'activité intrinsèque des régions cérébrales. Par une étude réalisée en TEP au repos, Raichle et al., (2001) ont montré que des aires cérébrales étaient plus actives au repos que lors d'une tâche cognitive, renforçant ainsi l'idée de l'existence d'un réseau sous-tendant le mode par défaut du cerveau. Ce réseau par défaut (ou DMN, pour *Default Mode Network*) a ensuite été confirmé en IRMf au repos par (Greicius et al., 2003). La technique d'IRMf au repos permet donc d'estimer la connectivité fonctionnelle au repos du cerveau qui est sous-tendue par la corrélation des décours temporels de plusieurs régions cérébrales topographiquement dispersées et qui fonctionnent de manière synchrone, formant des réseaux fonctionnels. Ainsi, plusieurs réseaux au repos ont été identifiés de manière constante sur différentes cohortes de sujets (Beckmann, 2005; Damoiseaux et al., 2006; Fox et al., 2005). Toutefois, il faut noter que la technique de l'IRMf au repos est sensible à plusieurs facteurs confondants, tels que les mouvements de la tête du sujet (Power et al., 2012; van Dijk et al., 2012), les artéfacts dus aux bruits physiologiques, dont les rythmes respiratoires et cardiaques (Birn et al., 2008), la pression artérielle et l'auto-régulation cérébrale (voir pour revue Murphy et al., 2013) mais aussi l'état de veille du sujet. Afin de

s'affranchir des diverses sources de bruit, la plupart des études appliquent une régression du signal global, de la substance blanche et des ventricules et appliquent aussi un filtre passe-bande entre 0.01 et 0.1 Hz pour enlever les fluctuations du signal provoquées par les bruits cardiaques et respiratoires (dont les fréquences sont respectivement de 1 Hz et 0.3Hz; pour revue, Murphy et al., 2013). Il est important de noter que le traitement du signal de l'IRMf au repos décrit ci-dessus n'est pas une procédure standardisée et qu'il existe notamment des controverses relatives à l'impact de la régression ou non du signal global. En effet, si l'introduction du signal global moyen permet de tenir compte de différentes sources de bruits physiologiques, elle introduirait également de fausses corrélations négatives dans les analyses (Fox et al., 2009; Murphy et al., 2009).

3.2.2. Méthodologie d'étude

Trois méthodes sont principalement utilisées pour estimer la connectivité fonctionnelle au repos.

3.2.2.1. *Analyses a priori : analyses « Seed-based »*

Cette technique nécessite la sélection d'une région d'intérêt *a priori* (ou *seed*) qui peut être de forme géométrique (e.g sphère entre 4 et 6 mm) ou définie selon une région d'intérêt anatomique. La détermination de la région d'intérêt (choix de la taille, de la forme) doit permettre une mesure optimale de l'effet d'intérêt et ne doit pas juste réduire le bruit, mais aussi éviter d'effectuer une moyenne sur différents signaux. Par exemple, les régions d'intérêt anatomiques effectuent souvent des moyennes du signal BOLD sur de grandes régions, ce qui permet d'éviter l'erreur d'échantillon, mais elles ne respectent pas les divisions fonctionnelles. Les fluctuations du signal BOLD sont extraites dans la région d'intérêt et corrélées à celles du reste du cerveau. Ainsi, après avoir défini un seuil statistique, l'analyse *seed-based* permet d'identifier les régions dont les fluctuations hémodynamiques sont significativement corrélées entre elles et sont donc fonctionnellement connectées (Figure 11). Cependant, cette technique doit permettre de répondre à une question bien précise car elle repose sur un *a priori* et ne permet pas d'identifier toutes les connexions fonctionnelles possibles au sein du cerveau.

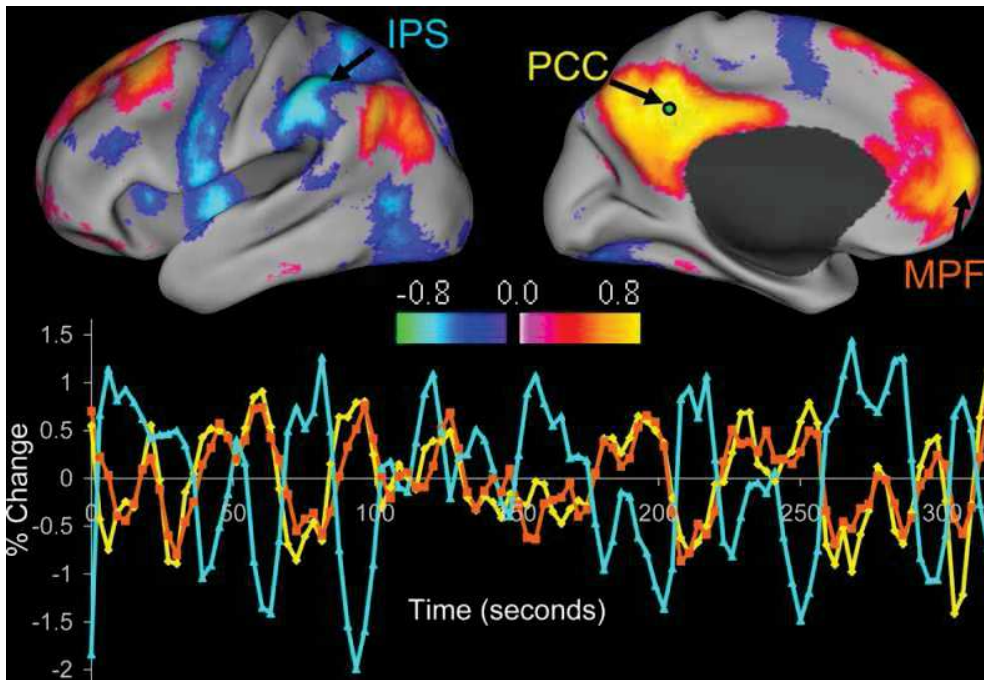


Figure 11 : Principe de la connectivité fonctionnelle au repos. Les décours temporels de la seed PCC (jaune) et de la région préfrontale médiane (MPF en orange) sont corrélés, ils sont donc fonctionnellement connectés tandis que le décours temporel de l'IPS (bleu) est anti-corrélé (d'après Fox et al., 2005).

3.2.2.2. *Analyses exploratoires*

3.2.2.2.1. **L'analyse en composantes indépendantes**

L'analyse en composantes indépendantes (ACI) consiste à diviser le signal BOLD en un certain nombre de composantes afin d'identifier différents réseaux cérébraux présents au repos dans lesquels les régions ont un décours temporel synchronisé. A ce jour, une dizaine de réseaux au repos ont été identifiés chez le sujet sain (Figure 12) tels que le réseau par défaut, le réseau de la salience, les réseaux frontopariétaux gauche et droit, les réseaux du contrôle exécutif, du langage, sensorimoteur, cérébellothalamocortical, et visuels médial et latéral (Pievani et al., 2014). Ce type d'analyse est influencé par le choix du nombre de composantes par lequel on décide de diviser le signal cérébral. En effet, un nombre trop important de composantes risque de sous-diviser des réseaux au repos, et inversement, un nombre trop petit de composantes risque d'ajouter des réseaux au repos distincts.

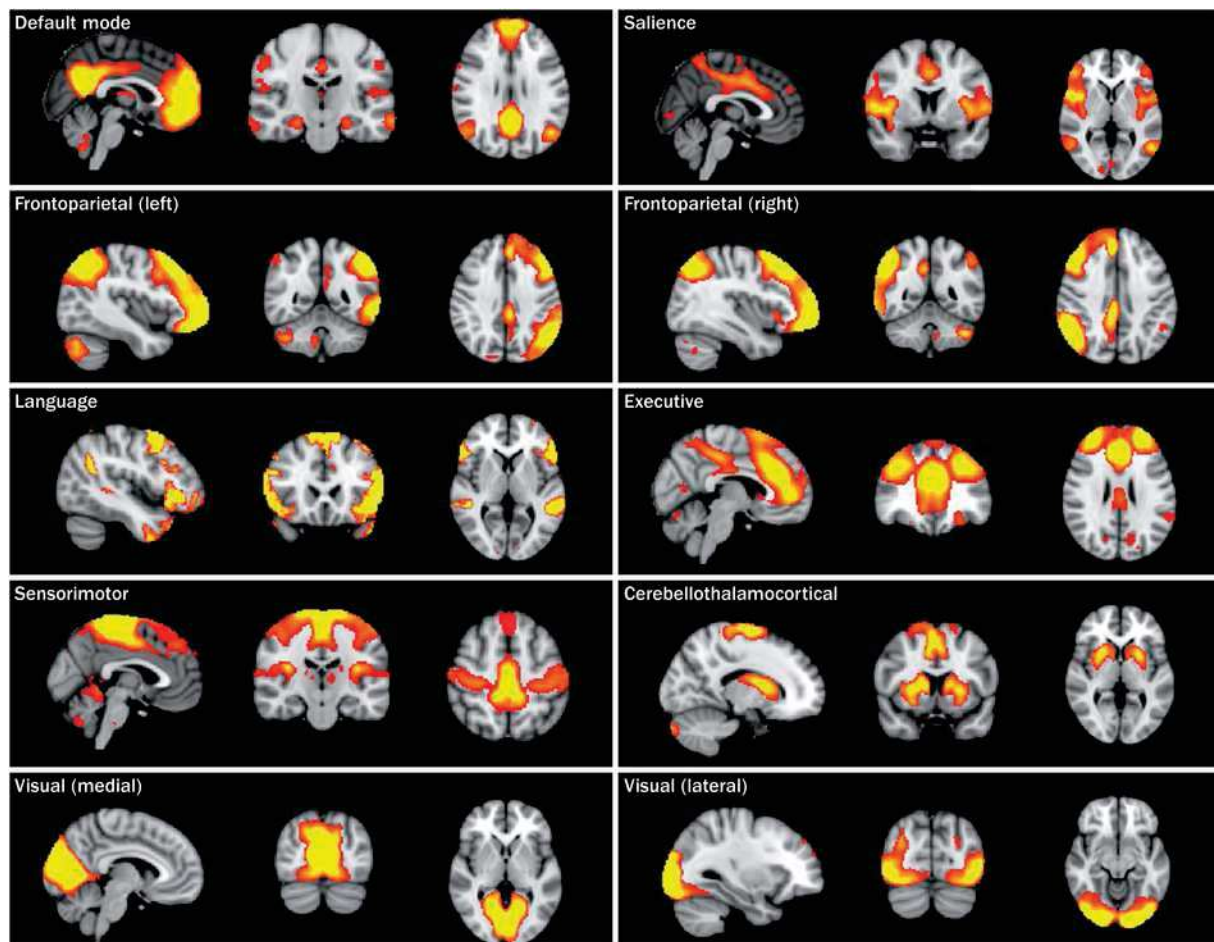


Figure 12 : Principaux réseaux au repos identifiés chez des sujets sains suite à une analyse en composantes indépendantes, d'après Pievani et al., 2014

3.2.2.2.2. La théorie des graphes

Dans la théorie des graphes, les données d'IRMf au repos sont spatialement parcellisées en régions cérébrales modélisées par des nœuds et les corrélations entre les décours temporels de chaque paire de nœuds sont calculées afin de déterminer les connexions fonctionnelles représentées par des arrêtes. Ainsi, l'ensemble des régions et leurs connexions constituent un réseau symbolisé par un graphe constitué de nœuds reliés par des arrêtes. La figure 13 représente les principales étapes nécessaires à une analyse utilisant la théorie des graphes. Chaque étape implique des choix qui peuvent influencer les résultats. La première étape consiste à définir les nœuds composant le réseau. Certains atlas proposent une parcellisation du cerveau selon les propriétés anatomiques tels que *l'automated anatomical labelling (AAL)* qui divise le cerveau en 90 régions (Tzourio-Mazoyer et al., 2002), l'atlas Harvard-Oxford (HO) basé sur les délimitations des gyri et sillons, ou fonctionnelles tels que l'atlas de Dosenbach et al. (2010) ou de Power et al. (2011) construits à partir de méta-analyses d'études menées en IRMf au repos et qui proposent respectivement une

parcellisation cérébrale en 160 et 264 régions. Vu les différences en termes de taille et de nombre de régions, le choix de l'atlas doit donc être adapté avec soin à la problématique de l'étude. Lors de la deuxième étape, différentes mesures peuvent être utilisées pour étudier les relations entre les différentes régions, telles que la connectivité structurale (liens anatomiques), fonctionnelle ou effective (relation directe ou causale). Ici, nous ne nous intéresserons qu'à la connectivité fonctionnelle. Dans la troisième étape, les relations entre le décours temporel de ces différentes régions cérébrales peuvent être intégrées dans une matrice individuelle de N régions par N régions où chaque ligne et chaque colonne correspond aux corrélations que présente une région particulière avec toutes les autres. Dans la plupart des analyses, un seuil est appliqué à cette matrice afin d'obtenir une matrice de corrélation binaire (les valeurs sont égales à 1 s'il y a une corrélation entre les nœuds et sont nulles dans le cas contraire). Le choix du seuil est déterminant car en fonction de la valeur choisie, différents graphes peuvent être créés. A partir de cette matrice, la théorie des graphes permet de calculer de nombreux paramètres propres aux réseaux (étape 4). Parmi ces différentes mesures, nous pouvons citer le « degré du nœud » qui représente le nombre de connexions entre ce nœud et le reste du réseau ; le « coefficient de *clustering* » qui quantifie le nombre de connexions qui existent entre les voisins les plus proches d'un nœud par rapport au nombre maximal de connexions (un cluster étant formé par un ensemble de nœuds voisins proches, tous reliés entre eux) ; la « longueur de pas » qui correspond au nombre minimal d'arrêtes à traverser pour aller d'un nœud à l'autre et est inversement liée à l'efficacité du réseau ; l'identification des « hubs » qui sont des régions avec un fort degré ou une centralité élevée (qui correspond au nombre de pas les plus courts qui passent par cette région) et sont ainsi primordiaux pour assurer une communication efficace au sein du réseau. Enfin, les réseaux complexes sont sous-divisés en modules peu connectés entre eux et qui contiennent chacun des nœuds interconnectés. Les hubs au sein d'un module seront dits « provinciaux », tandis que les hubs qui relient différents modules seront dits « connecteurs ». Toutes les informations qui peuvent potentiellement être dérivées de la théorie des graphes ne sont pas listées de manière exhaustive ici, mais les quelques mesures mentionnées ci-dessus constituent d'ores et déjà un bon reflet de l'organisation fonctionnelle du graphe (c'est-à-dire du réseau) à un niveau local ou global. Les régions « hubs », qui présentent une forte connectivité globale et qui occupent une

position centrale au niveau de l'organisation globale du réseau, peuvent ainsi être identifiées.

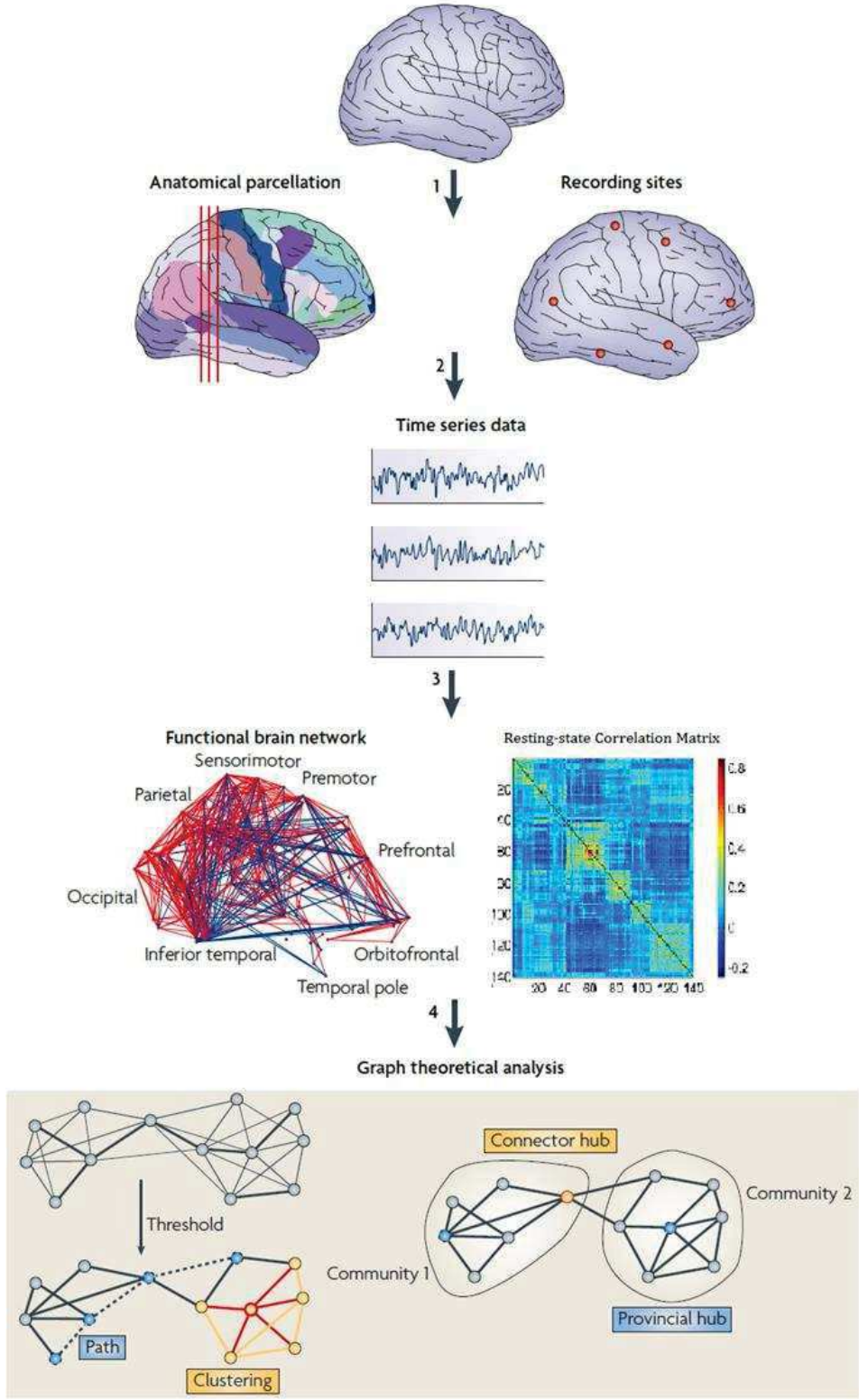


Figure 13 : Principe des analyses de théorie des graphes, d'après (Ed Bullmore et Sporns, 2009 et Di et al., 2013)

3.3. Atteintes de la connectivité fonctionnelle au repos dans le MCI et la MA

3.3.1. Principales altérations de la connectivité fonctionnelle dans le MCI amnésique et la MA

Le tableau 1 présente un récapitulatif non exhaustif des travaux menés en connectivité fonctionnelle dans le MCI et la MA. Un certain consensus se dégage à travers toutes ces études avec une diminution de la connectivité au sein du DMN, particulièrement précoce pour sa partie postérieure et qui peut faire suite à une augmentation transitoire au stade de MA. Aussi, comme nous venons de le mentionner ci-dessus, la connectivité fonctionnelle entre le CCP et l'hippocampe semble particulièrement compromise chez les patients MCI amnésiques et MA.

L'étude de la connectivité fonctionnelle au repos dans le cadre de la MA permet ainsi d'identifier des régions et des réseaux cérébraux qui seraient plus vulnérables à la pathologie.

Référence	Population	Technique utilisée	Atteinte en connectivité fonctionnelle au repos chez les patients
Greicius et al., 2004)	13 sujets contrôles vs 13 patients MA	ACI	↘ dans l'hcp et le CCP
(Wang et al., 2006)	13 sujets contrôles vs 13 patients MA	<i>Seed-based</i> hippocampe antérieur bilatéral	hcp droit : ↘ cortex préfrontal médian, cortex cingulaire antérieur ventral, cortex inférotemporal droit, cunéus bilatéral, précunéus droit, gyrus temporal supérieur et moyen droit et CCP hcp gauche : ↗ cortex préfrontal latéral droit.
(Sorg et al., 2007)	16 contrôles et 24 patients MCIa	ACI	↘ CCP gauche, cortex préfrontal médian droit, cortex pariétal bilatéral, lobes pariétal supérieurs bilatéraux, cortex préfrontal droit
(Supekar et al., 2008)	18 contrôles et 21 patients MA	théorie des graphes (analyses en ondelettes)	↘ du coefficient de <i>clustering</i> notamment au niveau des hippocampes
(Bai et al., 2009)	26 contrôles et 30 patients MCIa	<i>seed-based</i> à partir du CCP	↘ gyrus temporal moyen bilatéral, gyrus fusiforme droit ↗ gyrus frontal supérieur gauche, gyrus frontal médian bilatéral, gyrus frontal inférieur gauche, gyrus temporal inférieur gauche
(Qi et al., 2010)	14 contrôles et 14 patients MCIa	ACI	↘ dans le CCP et le précuneus bilatéraux, le lobule pariétal inférieur droit et le gyrus fusiforme gauche (et une tendance dans le lobe temporal médian droit) ↗ dans le cortex préfrontal gauche, le lobule pariétal inférieur et le gyrus temporal moyen
(Jones et al., 2011)	56 contrôles et 28 patients MA	ACI et <i>seed-based</i> à partir du précunéus et du cortex préfrontal médian	↘ dans le DMN postérieur (CCP, précunéus et lobule pariétal inférieur gauche) ↗ dans le DMN antérieur (lobe frontal)

Référence	Population	Technique utilisée	Atteinte en connectivité fonctionnelle au repos chez les patients
(Wu et al., 2011)	16 contrôles et 15 patients MA	ACI	∇CCP, cortex préfrontal médian, cortex pariétal inférieur, temporal inférieur et hippocampe
(Agosta et al., 2012)	13 contrôles, 12 patients MCIa et 13 MA	ACI	MCIa : ∇ DMN (précunéus) MA : ∇ DMN (précunéus, CCP, Lobe pariétal inférieur bilatéral, cortex cingulaire antérieur, cortex cingulaire moyen bilatéral) ; ∇réseau fronto-pariétal (frontal moyen droit, temporal inférieur gauche, ↗lobe pariétal inférieur bilatéral) ; ↗ réseau exécutif et de salience
(Brier et al., 2014) ^b	205 contrôles (CDR 0), 90 MCI (CDR 0.5) et 31 MA (CDR 1)	théorie des graphes	∇coefficient de clustering et modularité chez les MA
(Koch et al., 2015)	16 contrôles et 24 MCI	ACI	∇DMN postérieur (précunéus) et réseau attentionnel droit (lobe pariétal inférieur)
(Liu et al., 2015)	21 contrôles, 18 MCI, 17 MA modérés et 18 MA sévères	<i>seed-based</i> à partir du parahippocampe bilatéral	parahippocampe Gauche : ∇CCP /précunéus et gyrus temporal médian gauche Parahippocampe Droit : ∇ CCP, précuneus, cuneus, gyrus temporal médian postérieur et antérieur gauches, cortex préfrontal médian, gyrus angulaire et temporal supérieur gauche, gyrus frontal moyen, lobe pariétal supérieur
(Dillen et al., 2016)	25 contrôles, 27 SCI et 24 MCI	<i>Seed based</i> à partir du cortex rétrospénial (RSC) et du CCP	<u>RSC</u> : SCI : ↗cortex frontal médian ; MCI : ↗cortex occipital latéral <u>PCC</u> : MCI : ↗gyrus lingual
(Nuttall et al., 2016)	29 contrôles, 21 MCI précoces, 18 MCI tardif et 22 MA	ACI	∇ DMN antérieur, postéro-ventral, postéro dorsal, réseaux attentionnel gauche et droit, auditif, sensorimoteur et visuel

Table 1 : Principales études menées en connectivité fonctionnelle au repos dans la MA (MCIa : MCI amnésiques ; SCI : Subjective Cognitive Decline ; RSC : Cortex rétrospénial ; CDR : Clinical Dementia Rating)

3.3.2. Le Default Mode Network

Comme nous venons de le voir, une grande partie des études s'intéressant à l'atteinte de la connectivité fonctionnelle au repos dans le MCI et la MA se sont focalisées sur le DMN. Le DMN regroupe un ensemble de régions qui sont plus actives lorsque le cerveau est au repos, dans un état dit par « défaut » (Raichle et al., 2001). Le DMN suscite un intérêt majeur dans le cadre de la MA car il sous-tendrait les capacités d'introspection (Buckner et al., 2008; Mevel et al., 2010; Raichle, 2015), dont la mémoire épisodique autobiographique (Andrews-Hanna et al., 2014), la planification et la conscience du soi (Davey, 2016) et aurait un rôle dans la consolidation mnésique (Fox et Raichle, 2007). Le DMN regroupe des régions hubs qui jouent un rôle très important dans l'intégration des informations telles que le CCP et le cortex préfrontal médian et dorsolatéral, mais aussi le précuneus et le cortex cingulaire antérieur ventral. De manière moins constante, d'autres régions sont également retrouvées comme appartenant au DMN telles que le cortex pariétal inférieur, le lobe occipital, le gyrus cingulaire médian, les gyri fusiforme et angulaire, le lobe temporal médian et le gyrus temporal supérieur (pour revue Buckner et al., 2008; Mevel et al., 2010; Raichle, 2015).

Il est intéressant de noter que les régions appartenant au DMN semblent être particulièrement vulnérables à la MA. En condition physiologique, ces régions présentent la plus forte activité glycolytique par rapport au reste du cerveau, mais en condition pathologique (*i.e.* chez les patients MA), ces mêmes régions sont les plus hypométaboliques. Or, les dépôts amyloïdes surviendraient préférentiellement dans les régions présentant un fort métabolisme au cours de la vie (Buckner et al., 2005; Vlassenko et al., 2010; Vlassenko et Raichle, 2015). Ainsi, il a été mis en évidence que les régions du DMN sont particulièrement sensibles à l'hypométabolisme et aux dépôts amyloïdes dans le cadre de la MA (Buckner et al., 2005; Sheline et Raichle, 2013) (Figure 14). Le DMN s'étend sur un grand nombre de régions fortement corrélées entre elles chez le sujet sain. Il peut se décomposer en deux à quatre sous-réseaux (Allen et al., 2011) dont l'étude dans le cadre de la MA permet une analyse spatiale plus fine des répercussions de la pathologie. Il a ainsi été montré une atteinte hétérogène de ce réseau avec une diminution de la connectivité pour la partie postérieure, tandis que la partie antérieure présenterait une augmentation de la connectivité chez les patients MA comparés aux sujets sains (Jones et al., 2011). Cependant, cette augmentation de la connectivité dans la partie antérieure du DMN ne serait que

transitoire et ces régions seraient progressivement sujettes, elles aussi, à une diminution de la connectivité comme l'atteste l'étude longitudinale de Damoiseaux et al. (2012). Quoiqu'il en soit, la partie postérieure du DMN semble présenter une réduction de la connectivité plus précoce avec une atteinte hétérogène dans la MA des différentes parties du cortex postéro-médian qui renferme le CCP et le précuneus (Xia et al., 2014).

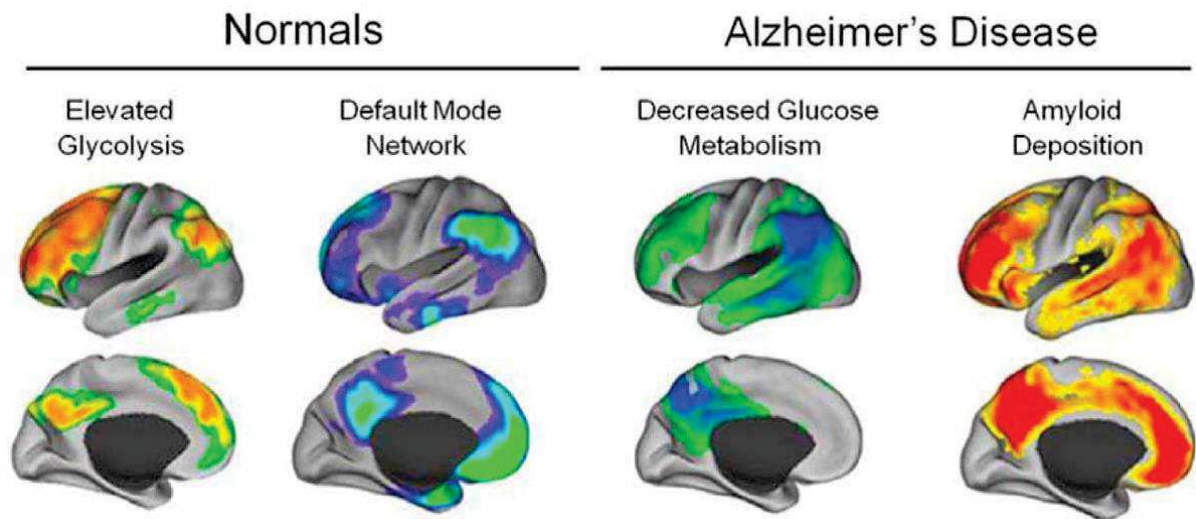


Figure 14 : Les régions du DMN présentent une forte activité glycolytique chez le sujet sain et sont particulièrement vulnérables dans la MA. D'après Sheline et Raichle (2013).

De nombreuses études rapportent une perturbation de la connectivité fonctionnelle au sein des régions du DMN qui s'intensifie avec la sévérité de la maladie (Brier et al., 2012; Qi et al., 2010) et touche particulièrement l'hippocampe, le précuneus et le CCP dont la connectivité avec le reste du cerveau est diminuée (Greicius et al., 2004; Jones et al., 2011; Qi et al., 2010; Supekar et al., 2008; Wang et al., 2006; Wu et al., 2011).

3.3.3. Focus sur le CCP

Le CCP est une région hub dont l'étude dans le cadre de la MA revêt une importance particulière étant donné son hypométabolisme précoce (La Joie et al., 2012), son rôle dans les processus de mémoire épisodique et autobiographique (Andrews-Hanna et al., 2014; Cabeza et Nyberg, 2000; Maddock et al., 2001; Svoboda et al., 2006; Wagner et al., 2005) et, comme nous venons de le mentionner, sa réduction de connectivité fonctionnelle avec le reste du cerveau.

Une subdivision du CCP en une partie ventrale et une partie dorsale a été proposée par plusieurs auteurs s'appuyant sur l'hétérogénéité structurale, fonctionnelle, et de

connectivité de cette région. En effet, la partie ventrale (aire v23 de Broadmann) du CCP présente, dans les couches II, III et V davantage de neurones pyramidaux que la partie dorsale (aires 23d et d23 de Broadmann) du CCP (Vogt et al., 2006; Vogt, 2005). Ces deux parties du CCP se distinguent également par la composition de leurs récepteurs aux neurotransmetteurs, le CCP ventral présentant une densité plus faible de récepteurs gabaergiques (GABA_B), muscariniques (M₃) et sérotoninergiques (5-HT_{1A}) et une densité plus importante de récepteurs muscariniques M₁ comparé au CCP dorsal (Palomero-Gallagher et al., 2009). Cette subdivision se retrouve également du point de vue fonctionnel. En effet, le CCP ventral serait impliqué dans les processus d'introspection (Johnson et al., 2002), de récupération en mémoire épisodique (Nielsen et al., 2005; Sugiura et al., 2005; Vogt, 2005) et autobiographique (Maddock et al., 2001), dans la production et la compréhension du langage (Awad et al., 2007) et le maintien des pensées et de l'attention internes (Leech et al., 2011). Le CCP dorsal, quant à lui, permettrait la navigation spatiale et l'orientation du corps et du soi dans l'espace visuel (Maguire et al., 1997; Maguire et al., 1998; Vogt et al., 2006). Enfin, cette dichotomie du CCP a été confirmée par l'étude du métabolisme cérébral au repos et de connectivité fonctionnelle qui a montré que le métabolisme basal du CCP ventral était plus corrélé au cortex cingulaire antérieur et aux aires subgénuaire, temporale, occipitale et orbitofrontale tandis que celui du CCP dorsal présentait une plus forte corrélation avec les aires prémotrices et pariétales (Vogt et al., 2006). Des études menées en connectivité fonctionnelle ont appuyé cette ségrégation du CCP en mettant en évidence que le CCP ventral était plus corrélé cortex préfrontal médian et au cortex pariétal moyen inférieur gauche et le CCP dorsal était corrélé aux aires préfrontales dorsomédiales et dorsolatérales (Bzdok et al., 2015). Ainsi, toutes ces études soulèvent l'importance de considérer le CCP non pas en une région homogène, mais en deux sous-régions qui, bien que fortement interconnectées (Parvizi et al., 2006), appartiennent à des sous-réseaux fonctionnels distincts et pourraient donc subir différemment les atteintes causées par la MA.

Si les perspectives de l'utilisation de l'IRM au repos comme biomarqueur permettant de distinguer les patients MA des sujets âgés sains paraissaient prometteuses il y a une dizaine d'années (Qi et al., 2010; Supekar et al., 2008), elles sont quelque peu différentes à présent, notamment en raison de son manque de sensibilité par rapport à une détection basée sur l'étude de la substance grise par exemple (Schouten et al., 2016; Teipel et al., 2017). Il

apparaît à présent que l'IRMf au repos serait plus adaptée pour identifier les régions les plus vulnérables à la MA et contribuer à la modélisation de la pathologie pour prédire la propagation des lésions (amyloïde, tau) à travers les réseaux fonctionnels.

3.3.4. Connectivité fonctionnelle au repos et prédiction des atteintes dans la MA

La hiérarchie des événements physiopathologiques survenant dans la MA est aujourd'hui encore mal connue et de nombreux modèles s'affrontent pour apporter la meilleure explication chronologique possible (Frisoni et al., 2010; Jack et al., 2010, 2013; Petersen, 2010; Sperling et al., 2011). Dans cette optique, il est crucial d'améliorer la compréhension des mécanismes qui sous-tendent l'apparition et la propagation des lésions dans la MA.

Que ce soit de manière séquentielle ou parallèle, il semblerait que les altérations structurales, métaboliques et moléculaires liées à la MA débutent chacune préférentiellement dans une région, que nous définirons comme étant l'épicentre, désignant le point de départ de l'atteinte. Ainsi, comme nous l'avons mentionné précédemment, au début de la MA, l'atrophie est caractéristiquement retrouvée au niveau du lobe temporal interne (et plus particulièrement au niveau de l'hippocampe), l'hypométabolisme concerne les régions temporo-pariétale et cingulaire postérieure et les dépôts amyloïdes présentent une accumulation particulièrement importante au niveau des régions frontales (cf. partie 2.3.2). Cette atteinte spécifique des régions en fonction du processus pathologique a été confirmée à l'aide d'une analyse en cluster par La Joie et al. (2012). Avec l'avancée de la maladie, les lésions s'étendent au reste des régions cérébrales suivant une progression stéréotypée.

Afin d'améliorer la compréhension de cette vulnérabilité préférentielle de certaines régions à la pathologie, Seeley et al. (2009) ont étudié la topographie de l'atrophie survenant dans cinq pathologies neurodégénératives différentes (MA, démence fronto-temporale comportementale, démence sémantique, aphasia primaire progressive non fluente et dégénérescence cortico-basale). Après avoir identifié la région la plus atteinte dans chacune de ces maladies, ils ont réalisé des études de connectivité fonctionnelle chez des sujets sains à partir de ces cinq régions «épicentres». Ils ont ensuite démontré de manière élégante que les profils d'atrophie de ces cinq pathologies étaient fortement corrélés à des réseaux spécifiques identifiés chez les sujets sains (Figure 15).

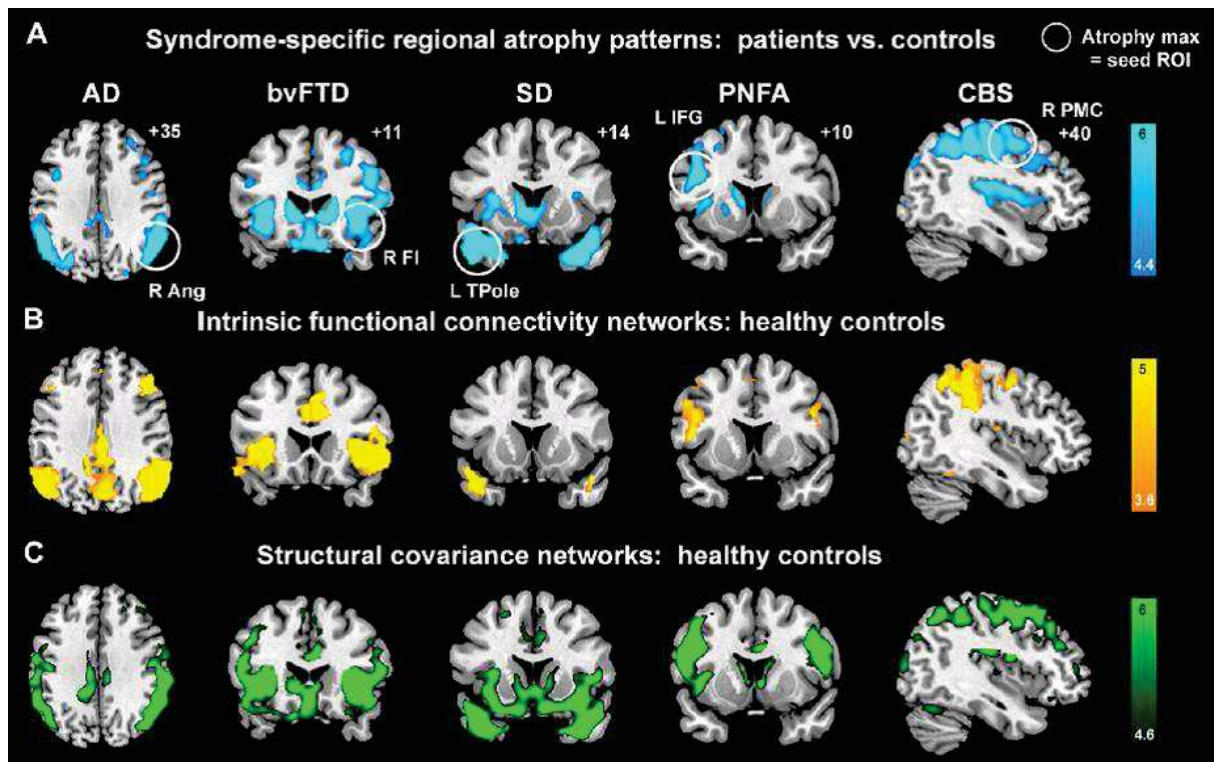


Figure 15 : Les profils d'atrophie survenant dans les maladies neurodégénératives correspondent à des réseaux fonctionnels identifiés chez les sujets sains, d'après Seeley et al., 2009

Ainsi, la propagation des lésions se ferait selon des réseaux fonctionnels spécifiques, confortant l'hypothèse d'une dégénérescence suivant les réseaux ou *network degeneration hypothesis* (Buckner et al., 2005; Du et al., 2007; Greicius et al., 2004; Sorg et al., 2007). Selon cette théorie, l'apparition et la propagation des syndromes neurodégénératifs se produiraient dans un premier temps au sein de réseaux cérébraux spécifiques (Greicius et Kimmel, 2012; Palop et al., 2006).

S'il paraît à présent évident que la topographie et la propagation des lésions ne se font pas de manière anarchique mais bien ciblées sur des réseaux spécifiques, la raison pour laquelle ces réseaux présentent une vulnérabilité particulière reste à élucider. A ce jour, plusieurs explications possibles sont proposées.

Certaines de ces hypothèses s'appuient sur les mécanismes de déconnexion qui peuvent être totaux ou partiels (Figure 16 ; Brier et al., 2014a). Dans le cas d'une déconnexion totale (Figure 16 B), la pathologie (tau et / ou $A\beta$) altère une région cérébrale particulière (Région A en rouge), dont les efférences vers les autres régions (B et C) ne sont plus fonctionnelles. Ces régions continuent cependant à recevoir d'autres afférences car seules les connexions avec la région A sont interrompues et donc à l'origine des éventuels déficits constatés. En se

basant sur ce modèle, Brier et al. (2014a) proposent qu'une région puisse être partiellement affectée par la pathologie et pourrait donc continuer à émettre des efférences vers d'autres régions mais de manière erronée, induisant ainsi des dysfonctionnements à ces régions situées en aval qui se transmettraient ainsi de suite (Figure 16C).

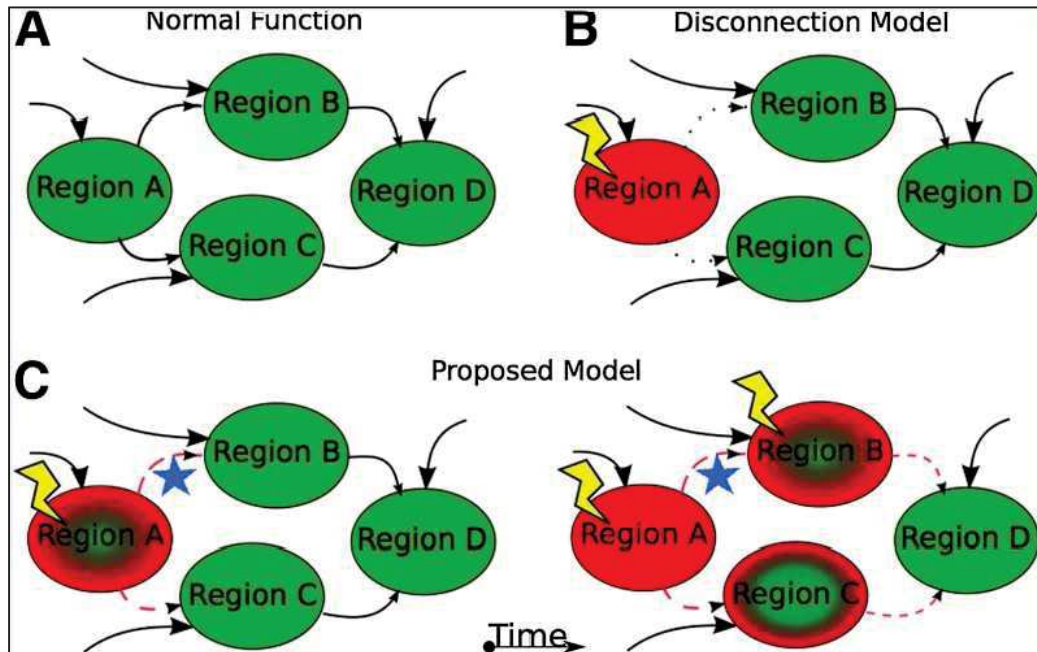


Figure 16 : Modèles de communication inter-régionale en condition physiologique (A) et de propagation des lésions (B et C), d'après Brier et al., 2014a

Cette dernière hypothèse est très semblable au modèle de propagation transneuronale des lésions. En effet, des études neuropathologiques ont mis en évidence que la protéine tau pouvait se propager d'une cellule à l'autre (Clavaguera et al., 2009; Frost et Diamond, 2009; Frost et al., 2009a; Frost et al., 2009b), suggérant que la protéine tau mal conformée se répandrait de neurone en neurone en partant du locus coeruleus à la région transentorhinale, de manière analogue à la propagation des protéines à prions (Braak et Del Tredici, 2011) (Figure 17). Pour mieux comprendre ce que signifie pleinement cette hypothèse, un rappel sur le mode de transmission des protéines à prions, que nous avons abordé plus haut, est nécessaire. Brièvement, en condition physiologique, une protéine à prions n'est pas pathologique, elle est exprimée de manière constitutive dans les cellules de l'organisme, et sa conformation est caractérisée par quelques feuillets β , mais elle est majoritairement composée d'hélices α . Pour une raison encore inconnue, la conformation de cette protéine s'enrichit en feuillets β , ce qui provoque l'agrégation de la protéine mal conformée, qui devient toxique pour la cellule. Cette protéine mal conformée sert ensuite

de modèle de conversion aux protéines non pathologiques et le nombre de protéines mal conformées agrégées s'amplifie de manière exponentielle. Ce mécanisme itératif induit ainsi la propagation de la pathologie d'une cellule à l'autre et à une plus grande échelle, d'une région cérébrale à l'autre par voie transneuronale (Stopschinski et Diamond, 2017). De même que la protéine tau, la protéine A β pourrait se comporter comme un prion, comme l'ont mis en évidence des études chez l'animal (Stöhr et al., 2012) mais aussi chez l'Homme, même si cette étude reste à confirmer (Jaunmuktane et al., 2015).

Ainsi, la MA mettrait en scène deux protéines semblables aux protéines à prions, qui seraient responsables individuellement des dommages constatés dans la MA, et dont leur association amplifierait leur effet délétère (Ittner et Götz, 2011; Nussbaum et al., 2013).

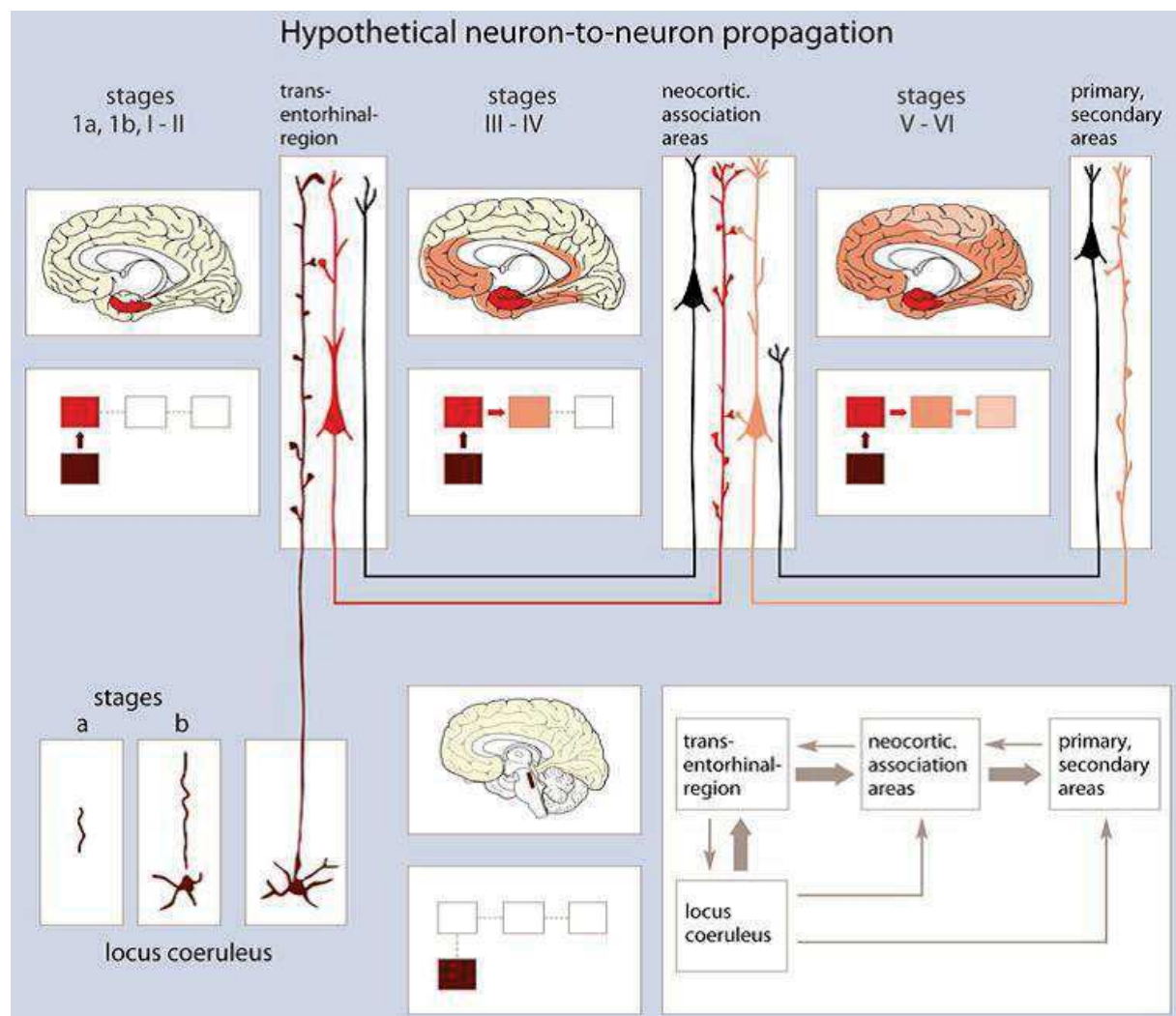


Figure 17 : Représentation schématique de l'hypothèse de la propagation neurone à neurone de la protéine tau dans la MA, d'après (Braak et Del Tredici, 2011)

Une autre hypothèse visant à expliquer la topographie et la propagation des lésions dans la MA serait la plus grande vulnérabilité des régions hubs à la pathologie (Buckner et al., 2009; Crossley et al., 2014). De manière intéressante, il a été montré qu'au stade préclinique de la MA, bien que l'organisation globale des réseaux cérébraux soit fortement perturbée, les symptômes ne s'expriment pas. C'est seulement lorsque les hubs sont altérés que l'on peut observer les premières manifestations cliniques (Brier et al., 2014). Ceci souligne donc l'importance primordiale que revêtent ces régions afin de maintenir l'intégrité du fonctionnement cognitif normal. Pour ce faire, les régions hubs sont très fortement sollicitées tout au long de la vie et sont au carrefour de l'information (van den Heuvel et Sporns, 2013). Les hubs reçoivent donc de très nombreux neurones de projection provenant pour certains de régions déjà touchées par la pathologie, ce qui pourrait les fragiliser (Kapogiannis et Mattson, 2011). A l'état physiologique, ces hubs présentent une très forte activité métabolique dont la déficience dans le cadre de la MA favoriserait l'accumulation amyloïde. De plus, la production et l'accumulation de peptide A β sembleraient dépendre de l'activité synaptique (de Haan et al., 2012). Les hubs ont également la particularité d'être organisés en *rich-club* afin de minimiser les coûts énergétiques et optimiser l'efficacité des réseaux, mais les points-clés de ces réseaux ont un coût énergétique beaucoup plus important que les autres régions pour pouvoir sous-tendre tout le flux d'information. Ainsi, si une diminution du métabolisme cérébral survient, ces régions seront plus sévèrement touchées (Bullmore et Sporns, 2012). Cependant, une analyse en *rich-club* a montré que la MA aurait un impact plus important sur les hubs périphériques plutôt que sur les plus gros hubs (Daianu et al., 2015).

Nous avons ainsi pu voir quelques-unes des contributions de la connectivité fonctionnelle au repos, en association avec les autres modalités d'imagerie, qui permettent d'avoir une meilleure vue d'ensemble de tous les phénomènes pathologiques survenant dans la MA. L'imagerie multimodale permet d'explorer *in vivo* les relations entre les mécanismes pathologiques clés à l'échelle moléculaire et leurs conséquences fonctionnelles à l'échelle macroscopique, du stade préclinique aux stades tardifs de la MA.

4. Etudes réalisées

4.1. Problématique générale des études

Comme nous venons de le voir, la neuroimagerie a permis une amélioration significative des connaissances relatives à la physiopathologie de la MA et du diagnostic précoce.

Compte tenu de la complexité de la physiopathologie de la MA, l'utilisation concomitante de plusieurs techniques d'imagerie dans les études multimodales a concouru à une meilleure compréhension des mécanismes sous-jacents à l'atrophie, l'hypométabolisme et l'accumulation des dépôts amyloïdes qui peuvent interagir et/ou évoluer en parallèle. L'atrophie hippocampique et l'hypométabolisme temporo-pariétal, respectivement révélés par l'IRM structurale et la TEP-FDG sont aujourd'hui reconnus comme étant des marqueurs fiables de la MA. Aussi, les études longitudinales se sont révélées indispensables pour améliorer les connaissances sur la progression de la maladie.

Les études menées en connectivité fonctionnelle au repos ont elles aussi apporté une large contribution par l'identification des réseaux et des régions spécifiquement vulnérables à la MA. Il est à présent établi que les régions appartenant au réseau du DMN sont le siège de perturbation de la connectivité fonctionnelle et qu'elles présentent une fragilité particulière dans le cadre de la MA. Une attention particulière a été portée concernant le CCP et l'hippocampe dont la perturbation de la connectivité fonctionnelle est pensée comme étant le reflet de mécanismes de déconnexion qui pourraient être responsables des altérations mnésiques survenant dans la MA. Cependant, des études ont mis en évidence que le CCP était une région hétérogène dont certaines parties appartiennent à des réseaux fonctionnels différents qui pourraient ainsi présenter des atteintes distinctes dans la MA. Ainsi, la connectivité fonctionnelle au repos permet d'isoler des réseaux et des sous-réseaux de régions cérébrales afin d'explorer plus finement les atteintes structurales, fonctionnelles et moléculaires survenant dans la MA et leur propagation.

Dans ce contexte, les objectifs de cette thèse étaient d'explorer les altérations précoces de réseaux fonctionnels dans la MA et d'essayer de prédire les altérations structurales et fonctionnelle au moyen d'études multimodales s'appuyant sur la connectivité au repos, l'IRM anatomique et la TEP-FDG et amyloïde.

La première étude s'est focalisée sur le CCP dont l'hypométabolisme précoce est caractéristique de la MA. Cette région peut être divisée en une région ventrale et une région

dorsale et cette première étude transversale s'est attachée à identifier les atteintes de connectivité fonctionnelle au repos, l'atrophie et l'hypométabolisme survenant au sein de ces deux réseaux chez patients MCI amnésiques d'une part et les patients MA d'autre part.

La deuxième étude toujours multimodale mais également longitudinale, visait à prédire les altérations structurales et fonctionnelles au moyen de la connectivité. Dans ce travail, nous avons distingué la « connectivité globale », qui présente de fortes valeurs dans les régions très fortement connectées avec le reste du cerveau, de la « connectivité spécifique », qui elle correspond à la connectivité entre une région épiceutre, point de départ de la pathologie (d'atrophie, hypométabolisme ou amyloïde) et le reste des régions cérébrales. Le but de cette étude était d'évaluer la contribution relative de ces deux types de connectivité sur la topographie et la propagation des lésions survenant dans la MA.

4.2. Contexte de la thèse

Cette thèse a évolué dans le cadre du protocole IMAP (Imagerie Multimodale de la maladie d'Alzheimer à un stade Précoce) dirigé par Gaëlle Chételat et Vincent de La Sayette au sein de l'unité de recherche U1077 dirigée par Francis Eustache et affiliée à l'Institut national de la santé et de la recherche médicale (Inserm), l'École Pratique des Hautes Études (EPHE), l'Université de Caen Normandie (UCN) et au CHU de Caen. L'objectif principal de ce protocole est de comparer l'efficacité de différents biomarqueurs *in vivo* pour prédire le déclin cognitif chez des populations à risque de développer la MA au moyen de mesures de neuroimagerie, de neuropsychologie et de biologie.

La Figure 18 illustre le projet IMAP dans son ensemble. Cinq groupes d'individus sont inclus dans ce programme de recherche. Cent-vingt sujets sains contrôles sont répartis en trois catégories selon leur âge: un tiers ayant entre 18 et 40 ans, un tiers ayant entre 40 et 60 ans et le dernier tiers ayant plus de 60 ans. L'étude implique également la participation d'environ 40 patients âgés présentant des troubles cognitifs objectifs infra-démenciels (patients MCI répondant aux critères de MCI amnésique), de 30 patients avec une maladie d'Alzheimer probable selon les critères NINCDS-ADRDA et deux groupes de sujets asymptomatiques à risque de développer la MA, *i.e.* 40 sujets avec des déficits cognitifs subjectifs (SCI pour *Subjective Cognitive Impairment*), et 50 individus membres asymptomatiques de familles porteuses de mutations génétiques à transmission

autosomique dominante (individus NORMA pour «NORMaux Apparentés à un patient atteint d'une forme génétique de la Maladie d'Alzheimer»). En plus de ces 5 groupes, 30 patients répondants aux critères de démence lobaire fronto-temporale (DLFT) ont également été inclus.

Le recrutement des sujets sains s'est effectué par le biais d'annonces publiées dans la presse locale et celui des patients a été réalisé suite aux consultations mémoires de Basse-Normandie, Rennes et Rouen. Tous les participants bénéficient d'exams cliniques, sanguins, neuropsychologiques et de neuroimagerie associant IRM structurale, fonctionnelle, TEP-FDG et TEP-florbetapir. L'ensemble de ces exams est répété après 18 mois de suivi pour tous les participants (sauf les DLFT), et une seconde fois après 36 mois pour les catégories de populations à risque (MCI, SCI, et NORMA) et les témoins âgés.

Dans le cadre de cette thèse, les données disponibles chez les sujets sains, les patients MCI et MA ont été analysées parallèlement à la participation au recrutement et à la passation des exams neuropsychologique, à l'acquisition des données d'imagerie et à la vérification de leur qualité.

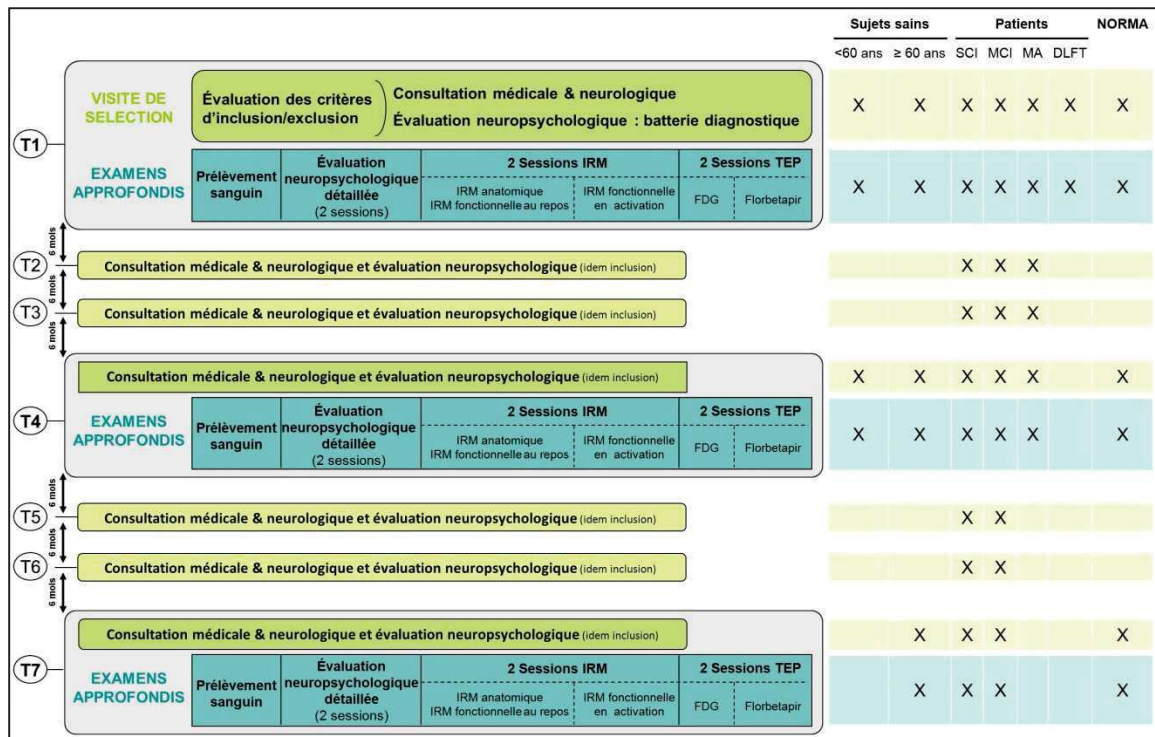


Figure 18 : Organisation générale du protocole IMAP. Les évaluations cliniques et neuropsychologiques utilisées pour le diagnostic des participants sont en vert et la partie expérimentale, comprenant les exams d'imagerie et les évaluations neuropsychologiques complémentaires, est en bleu. Les croix situées à droite indiquent si le groupe d'individus mentionné en haut a suivi ou non l'examen correspondant

4.3. Etude 1: *Connectivity disruption, atrophy and hypometabolism within posterior cingulate networks in Alzheimer's disease*

Le CCP est région particulièrement sensible à la MA. Des études menées en histologie et en imagerie fonctionnelle ont révélé une hétérogénéité au sein du CCP concernant l'organisation cellulaire le long de l'axe dorso-ventral (Vogt et al., 2006; Vogt, 2005) et la composition des récepteurs (Palomero-Gallagher et al., 2009) suggérant ainsi d'envisager le CCP en 2 sous-parties, l'une ventrale (vCPP) et l'autre dorsale (dCPP).

L'article qui va suivre a eu pour but d'étudier les atteintes de connectivité fonctionnelle, d'atrophie et d'hypométabolisme au sein des réseaux ventral et dorsal du CCP chez des patients MCI amnésiques ou MA comparés à des participants contrôles par une approche multimodale alliant l'IRM structurale, l'IRMf au repos et la TEP-FDG.

Les données recueillies dans le cadre du protocole IMAP chez 43 sujets âgés sains, ne présentant pas de trouble cognitif (68.7 +/- 6 ans), 34 patients MCI amnésiques (73.4 +/- 6.8 ans) et 24 patients MA (70.9 +/- 9.1 ans) ont été incluses dans ces analyses.

Les parties ventrale et dorsale du CCP ont été délimitées manuellement sur une image IRMa normalisée moyenne des sujets sains suivant les descriptions cytoarchitectoniques et fonctionnelles de ces deux sous-parties du CCP (Vogt et al., 2006; Yu et al., 2011). Ces deux sous-régions ont ensuite été masquées par un masque de substance grise puis utilisées comme *seed* pour la réalisation d'analyses de connectivité fonctionnelle *seed-based*. Les réseaux ventral et dorsal du CCP ont ensuite été identifiés chez les sujets sains en soustrayant les cartes de connectivité fonctionnelle obtenues pour une *seed* par celles obtenues par l'autre *seed* et vice-versa, afin d'identifier les régions spécifiquement connectées soit à la *seed* du CCP ventral (réseau ventral) soit à la *seed* du CCP dorsal (réseau dorsal).

Les altérations de connectivité fonctionnelle au repos, l'atrophie et l'hypométabolisme ont ensuite été caractérisées au sein de ces deux réseaux chez les patients MCI amnésiques d'une part et chez les patients MA d'autre part, comparativement aux participants contrôles.

Le réseau ventral est apparu plus précocement vulnérable, en présentant des atteintes dès le stade MCI en connectivité fonctionnelle et en atrophie (particulièrement au niveau de l'hippocampe) qui se sont étendues à davantage de régions chez les MA, tandis que le réseau dorsal présente une diminution de la connectivité fonctionnelle et une atrophie seulement au stade de MA. L'hypométabolisme en revanche, a été observé dans les deux réseaux chez les MCI amnésiques comme chez les MA, reflétant à la fois des altérations locales et à distance.

Ces résultats suggèrent une dynamique temporelle des propagations des lésions de la MA avec une altération de la connectivité fonctionnelle et une atrophie dans un premier temps dans le réseau ventral le long de l'axe hippocampo-cingulaire postérieur (dès le stade MCI amnésique) puis dans un second temps dans le réseau dorsal (au stade MA). En revanche, l'hypométabolisme semble lié à d'autres mécanismes sous-jacents du fait de sa présence au niveau des deux réseaux dès le stade MCI. Cette étude, bien que transversale, a permis d'améliorer la compréhension de la topographie des biomarqueurs de la MA à des stades distincts. Des études longitudinales seraient nécessaires pour confirmer la propagation différentielle des lésions au sein de ces deux réseaux.



Connectivity Disruption, Atrophy, and Hypometabolism within Posterior Cingulate Networks in Alzheimer's Disease

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The posterior cingulate cortex (PCC) is a critical brain network hub particularly sensitive to Alzheimer's disease (AD) and can be subdivided into ventral (vPCC) and dorsal (dPCC) regions. The aim of the present study was to highlight functional connectivity (FC) disruption, atrophy, and hypometabolism within the ventral and dorsal PCC networks in patients with amnesic mild cognitive impairment (aMCI) or AD. Forty-three healthy elders (HE) (68.7 ± 6 years), 34 aMCI (73.4 ± 6.8 years) and 24 AD (70.9 ± 9.1 years) patients underwent resting-state functional MRI, anatomical T1-weighted MRI and FDG-PET scans. We compared FC maps obtained from the vPCC and dPCC seeds in HE to identify the ventral and dorsal PCC networks. We then compared patients and HE on FC, gray matter volume and metabolism within each network. In HE, the ventral PCC network involved the hippocampus and posterior occipitotemporal and temporoparietal regions, whereas the dorsal PCC network included mainly frontal, middle temporal and temporoparietal areas. aMCI patients had impaired ventral network FC in the bilateral hippocampus, but dorsal network FC was preserved. In AD, the ventral network FC disruption had spread to the left parahippocampal and angular regions, while the dorsal network FC was also affected in the right middle temporal cortex. The ventral network was atrophied in the bilateral hippocampus in aMCI patients, and in the vPCC and angular regions as well in AD patients. The dorsal network was only atrophied in AD patients, in the dPCC, bilateral supramarginal and temporal regions. By contrast, hypometabolism was already present in both the vPCC and dPCC networks in aMCI patients, and further extended to include the whole networks in AD patients. The vPCC and dPCC connectivity networks were differentially sensitive to AD. Atrophy and FC disruption were only present in the vPCC network in aMCI patients, and extended to the dPCC network in AD patients, suggesting that the pathology spreads from the vPCC to the dPCC networks. By contrast, hypometabolism seemed to follow a different route, as it was present in both networks since the aMCI stage, possibly reflecting not only local disruption but also distant synaptic dysfunction.

Keywords: posterior cingulate cortex, Alzheimer's disease, resting-state functional connectivity, atrophy, hypometabolism

INTRODUCTION

Alzheimer's disease (AD) is the most widespread cause of dementia. This neurodegenerative disease is characterized by a progressive decline in cognitive performances, typically predominated by episodic memory deficits. Tau-rich neurofibrillary tangles and β -amyloid (A β) plaques are the two neuropathological landmarks of the disease. *In vivo* neuroimaging biomarkers of the disease include atrophy (predominantly in the hippocampus and temporal neocortex), hypometabolism (mainly in the posterior cingulate cortex (PCC), and temporo-parietal cortex), and amyloid deposition in medial frontal and parietal and temporo-parietal cortical areas (McKhann et al., 2011; Winblad et al., 2016). Moreover, connectivity has proved to be critical in the pathophysiology of the disease. Disconnection processes have been shown to be at least partly responsible for early hypometabolism in AD (Villain et al., 2010; Teipel and Grothe, 2016), and neuropathological research suggests that tau propagates transynaptically, neuron to neuron (Duyckaerts et al., 1997; Braak and Del Tredici, 2011; de Calignon et al., 2012; Ahmed et al., 2014). Finally, recent neuroimaging studies have shown that the topography of atrophy/hypometabolism in AD (and other forms of dementia) follows specific brain connectivity networks, as evidenced by resting-state functional magnetic resonance imaging (fMRI), for instance, leading to the network degeneration hypothesis (Seeley et al., 2009; La Joie et al., 2014). More specifically, the default mode network (DMN) includes those brain areas that are most sensitive to AD (i.e., sites of the earliest atrophy, hypometabolism and/or amyloid deposition), such as the PCC, precuneus, hippocampus, temporo-parietal, and medial frontal areas (Greicius et al., 2004; Sheline and Raichle, 2013).

Within this context, the PCC is thought to play a pivotal role as it is one of the main hubs of the DMN and connects different subsystems of this network (Buckner et al., 2008; Hagmann et al., 2008; Andrews-Hanna et al., 2010). Moreover, it is the earliest site of hypometabolism in AD (Minoshima et al., 1997; Chételat et al., 2008), which is thought to reflect disconnection from the hippocampus (Villain et al., 2008, 2010; Yakushev et al., 2011) and, in turn, to be related to hypometabolism in distant brain regions such as the frontal cortex (Fouquet et al., 2009; Villain et al., 2010). Finally, the PCC is involved in episodic/autobiographical memory processes (Cabeza and Nyberg, 2000; Maddock et al., 2001; Wagner et al., 2005; Svoboda et al., 2006; Fossati, 2013; Andrews-Hanna et al., 2014), and disruption of PCC connectivity and metabolism is known to be at least partly responsible for early episodic memory deficits in AD and amnesic mild cognitive impairment (aMCI) (Chételat et al., 2003; Bastin et al., 2010; La Joie et al., 2014).

The PCC is a heterogeneous structure, with cytoarchitectonic differences along the dorso-ventral axis (Vogt, 2005; Vogt et al., 2006) and in the receptor architecture (Palomero-Gallagher et al., 2009). Previous neuroimaging studies using a variety of techniques (e.g., diffusion tensor imaging, resting-state glucose metabolism, and resting-state fMRI) in healthy individuals have also highlighted specificities in the functional connectivity (FC) of the ventral (vPCC) vs. dorsal (dPCC) PCC. Thus, the vPCC

seems to be more strongly connected to medial temporal areas (Greicius et al., 2004; Vogt et al., 2006), including the hippocampus and parahippocampal gyrus (Maddock et al., 2001; Beckmann et al., 2009; Margulies et al., 2009), orbitofrontal and ventromedial prefrontal cortex (Vogt et al., 2006; Bzdok et al., 2015), anterior cingulate (Maddock et al., 2001; Vogt et al., 2006), occipital cortex (Vogt et al., 2006) and left inferior part of the parietal cortex (Bzdok et al., 2015). By contrast, the dPCC appears to be connected to the prefrontal cortex, especially its dorsomedial (Beckmann et al., 2009; Bzdok et al., 2015), dorsolateral (Bzdok et al., 2015) and ventromedial parts (Greicius et al., 2009; Margulies et al., 2009), the parietal cortex (Vogt et al., 2006; Beckmann et al., 2009) and the lateral temporal cortex (Margulies et al., 2009). Thus, while both parts of the DMN (Yu et al., 2011), each subregion yet belongs to distinct subnetworks.

Given the pivotal role of the PCC in AD and within the DMN, and the distinct cellular organization and connectivity profile of the vPCC vs. dPCC, the goal of the present study was to investigate structural and functional alterations of the vPCC and dPCC networks in patients with aMCI and demented patients with AD. More specifically, we sought to (i) identify the specific connectivity subnetworks of the vPCC vs. the dPCC in cognitively normal older adults and (ii) assess the profiles of connectivity disruption, atrophy and hypometabolism within the vPCC and dPCC networks in patients with aMCI or AD.

MATERIALS AND METHODS

Participants

One hundred and one right-handed native French-speaking participants from the « Imagerie Multimodale de la maladie d'Alzheimer à un stade Précoce » (IMAP+) study (Caen) were included in the present study: 43 healthy elders (HE), 34 patients with aMCI, and 24 patients with AD (Table 1). Some of them had been included in previous publications by our laboratory (La Joie et al., 2012, 2013, 2014; Mevel et al., 2013; Tomadesso et al., 2015). All participants were aged over 60 years, had at least 7 years of education, and had no history of alcoholism, drug abuse, head trauma, or psychiatric disorder.

HE were recruited from the community and performed within the normal range on all neuropsychological tests in a cognitive battery assessing multiple domains of cognition (verbal and visual episodic memory, semantic memory, language skills, executive functions, visuospatial functions, and praxis). The patients with aMCI or AD were recruited from local memory clinics and selected according to internationally agreed criteria. aMCI patients were selected based on Petersen's criteria for aMCI (Petersen and Morris, 2005) and AD patients fulfilled standard National Institute of Neurological and Communicative Disorders and Stroke, and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) clinical criteria for probable Alzheimer's disease (McKhann et al., 1984). Clinical diagnosis was assigned by consensus under the supervision of a senior neurologist (VdLS) and two neuropsychologists (AP and SE). The majority of participants underwent a florbetapir-PET scan, and the proportions of amyloid-positive scans using previously

TABLE 1 | Demographic information of healthy elders (HE), patients with amnesic mild cognitive impairment (aMCI), and patients with Alzheimer's disease (AD).

	HE	aMCI	AD	p-value			
				Group effect	HE vs. aMCI	HE vs. AD	aMCI vs. AD
F/M ratio	27/16	18/16	12/12	–	0.523	0.448	0.963
Age in years (SD)	68.7 (6.0)	73.4 (6.8)	70.5 (9.4)	0.020	0.022	0.532	0.460
Education in years (SD)	12 (3.5)	10 (3.5)	10 (3.3)	0.116	0.192	0.319	0.999
MMSE (SD)	29.2 (0.8)	26.7 (1.7)	20.8 (4.2)	p < 0.001	p < 0.001	p < 0.001	p < 0.001

The bold values are significant ($p < 0.05$).

published methods (La Joie et al., 2012) were 17.9% (7/39) for HE, 65.6% (21/32) for patients with aMCI, and 100% (23/23) for patients with AD.

The IMAP+ study was approved by a regional ethics committee (Comité de Protection des Personnes Nord-Ouest III) and registered with <http://clinicaltrials.gov> (no. NCT01638949). All participants gave their written informed consent to the study prior to the investigation.

Neuroimaging Data Acquisition

All participants were scanned with the same MRI and PET cameras at the Cyceron Center (Caen, France): a Philips Achieva 3.0 T scanner and a Discovery RX VCT 64 PET-CT device (General Electric Healthcare), respectively. High-resolution T1-weighted anatomical volumes were acquired using a three-dimensional 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).

Resting-state functional volumes were obtained using an interleaved 2D T2* SENSE EPI sequence designed to reduce geometric distortions, with parallel imaging, short echo time, and small voxels (2D-T2*-FFE-EPI axial, SENSE = 2; time repetition = 2382 ms, time echo = 30 ms, flip angle = 80°, 42 slices with no gap, slice thickness = 2.8 mm, field of view = 224 × 224 mm², in plane resolution = 2.8 × 2.8 mm², 280 volumes, acquisition time = 11.5 min). Participants were equipped with earplugs, their head was stabilized with foam pads to minimize head motion, and the scanner room's light was turned off. During this acquisition, which was the last one in the MRI scanning session, participants were asked to relax, lie still in the scanner, and keep their eyes closed, without falling asleep. A subsequent debriefing questionnaire allowed us to ensure that the participants had no difficulty staying awake throughout the duration of the resting-state fMRI scan and that nothing particular had disturbed their attention during the scanning.

Finally, ¹⁸FDG-PET images were acquired with a resolution of 3.76 × 3.76 × 4.9 mm³ (field of view = 157 mm). Forty-seven planes were obtained with a voxel size of 1.95 × 1.95 × 3.2 mm³. A transmission scan was performed for attenuation correction before the PET acquisition. Participants were fasted for at least 6 h before scanning. After a 30-min resting period in a quiet and dark environment, 180 MBq of FDG was intravenously injected as a bolus. A 10-min PET acquisition scan began 50 min after injection.

Neuroimaging Data Preprocessing

Anatomical MRI

MRI data were segmented, normalized to the Montreal Neurological Institute (MNI) template and modulated (nonlinear only) using the VBM5.1 toolbox, and smoothed with an 8-mm Gaussian filter. The resulting gray matter datasets were used in all subsequent analyses.

Resting-State fMRI

Individual datasets were first checked for artifacts by applying the TSDiffAna routines (<http://imaging.mrc-cbu.cam.ac.uk/imaging/DataDiagnostics>), during which a variance volume was created for each participant to check that most of the signal variability was restricted to the cortex. Datasets showing evidence of significant movements (>3 mm translation or 1.5° rotation) associated with image artifacts and/or an abnormal variance distribution were excluded from subsequent analyses. Data were then processed as described in La Joie et al. (2014), including slice timing correction, realignment to the first volume, spatial normalization, smoothing (4 mm), masking to include only gray matter voxels and exclude the cerebellum (based on the T1-weighted and non-EPI-T2* volumes), and temporal bandpass filtering (0.01–0.08 Hz).

The vPCC and dPCC were manually delineated on the normalized anatomical T1-MRI of a representative HE scan using Anatomist (Version 4.0.0) software, based on cytoarchitectural and functional findings (Vogt et al., 2006; Yu et al., 2011). The vPCC included Brodmann areas v23 and 31, and was bordered anteriorly by the ventral branch of the splenial sulcus and posteriorly by the parieto-occipital sulcus. The dPCC included Brodmann areas 23c, 23d, d23, and 31, and was limited anteriorly by the cingulate sulcus and posteriorly by the ventral branch of the splenial sulcus.

The two subregions were then masked using the gray matter mask described above, and used as seeds in subsequent connectivity analyses (Figure 1). Coincidentally, both regions measured 3592 mm³ (449 voxels). We then checked that the vPCC and dPCC locations matched for each participant, by superimposing the regions on each individual normalized scan.

For each of the 101 participants and each seed of interest (transformed using the MarsBar toolbox, Brett et al., 2002), positive correlations were assessed between the mean time course in the seed and the time course of each gray matter voxel. To remove potential sources of spurious variance, the time courses from white matter, cerebrospinal fluid, the whole brain,

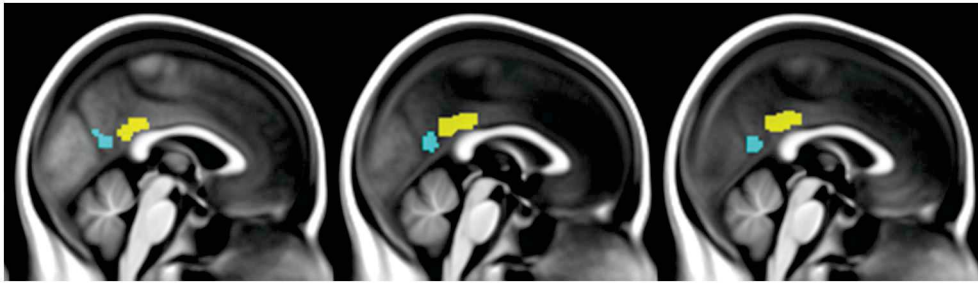


FIGURE 1 | Illustration of the ventral PCC (blue) and dorsal PCC (yellow) seeds manually delineated on the mean normalized anatomical T1-MRI scans of all participants.

their derivatives, and the six movements parameters generated from realignment of head motion were introduced as covariates. Lastly, Fisher's z transform and 6.3 mm full width at half maximum (FWHM) smoothing were applied to the resulting individual connectivity maps, leading to a final smoothness of 8 mm FWHM ($\sqrt{(2.8^2 + 4^2 + 6.3^2)}$).

FDG-PET

^{18}F FDG-PET data were corrected for partial volume effects using a three-compartment method (Giovacchini et al., 2004) with PMOD (PMOD Technologies). Images were then coregistered onto their respective MRIs, spatially normalized to the MNI template using the respective MRI parameters, and scaled using the mean PET value of the cerebellar gray matter. Smoothing kernel of $7.1 \times 7.1 \times 6.3$ mm Gaussian filter was applied so that the final smoothness of the images was the same as for the fMRI data ($8 \times 8 \times 8$ mm).

Statistical Analysis

Between-group differences on demographic variables were assessed with a one-factor (group) analysis of variance (ANOVA) for continuous variables and a chi2 test for categorical variables.

Identification of the vPCC and dPCC Networks in HE

A voxelwise paired t -test was performed on resting-state fMRI scans in HE to identify the brain regions that were significantly more correlated with the dPCC than with the vPCC and vice versa (FWE-corrected $p < 0.05$, $k > 50$), including only regions that were significantly positively correlated with these regions in HE (see details in Figure 2). Binary masks of the ventral and dorsal networks were obtained from this analysis for use in subsequent analyses (Figure 3).

Voxelwise Neuroimaging Analyses in Patients

To assess changes within these networks in patients with aMCI or AD, compared with HE, we ran single factor (group) ANCOVAs using Statistical Parametric Mapping (SPM) software with full factorial designs. More specifically, two ANCOVAs were carried out to assess FC disruption in patients vs. HE within the ventral and dorsal networks, and the same analyses were repeated with maps of gray matter volume and ^{18}F FDG-PET metabolism to assess for atrophy and hypometabolism within

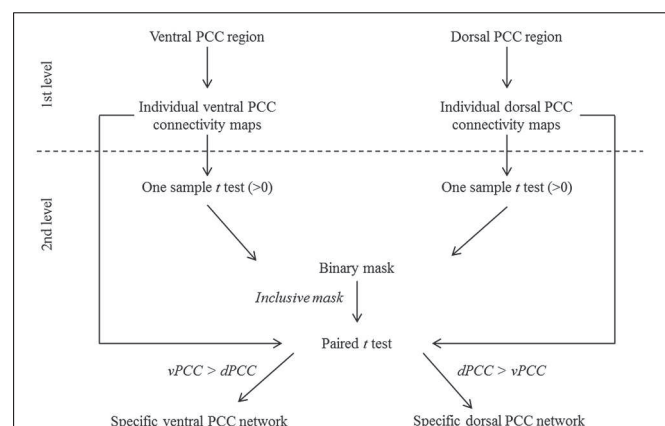


FIGURE 2 | Schematic representation of the procedure for ventral (vPCC) and dorsal (dPCC) PCC connectivity analyses in HE. At the first level, vPCC and dPCC regions were used as seeds to obtain individual vPCC and dPCC connectivity maps. At the second level, one-sample t -tests (>0) were performed on the individual connectivity maps and thresholded at p (FWE-corrected) < 0.01 , $k > 100$ to identify regions positively correlated with the vPCC and dPCC in HE. The resulting maps were binarized and combined to obtain a mask of brain regions that were positively correlated with the ventral or dorsal PCC. This mask was used in a paired t -test comparing the individual vPCC and dPCC connectivity maps to identify, within the regions positively associated with the ventral or dorsal PCC, those more correlated with one or the other. The resulting maps, thresholded at p (FWE-corrected) < 0.05 ($k > 50$) and binarized, were used as the specific ventral and dorsal PCC networks in subsequent analyses.

these same networks. Age, sex, and education were controlled for in all group comparisons, and we used a statistical threshold of p (uncorrected) = 0.001. Cluster extent was determined by Monte-Carlo simulation (AlphaSim program by D. Ward) for each modality and within each network to achieve a multiple comparison-corrected $p < 0.05$ (Table S1). The percentage of alteration within each network was calculated by dividing the total number of disrupted voxels by the total number of voxels in the corresponding network (Table 2). Finally, to assess the links with global cognitive changes, correlations were assessed between atrophy and hypometabolism found in vPCC and dPCC networks in aMCI and AD patients vs. performances at the MMSE using non-parametric Spearman correlation analyses and a $p < 0.05$ (Figure S2).

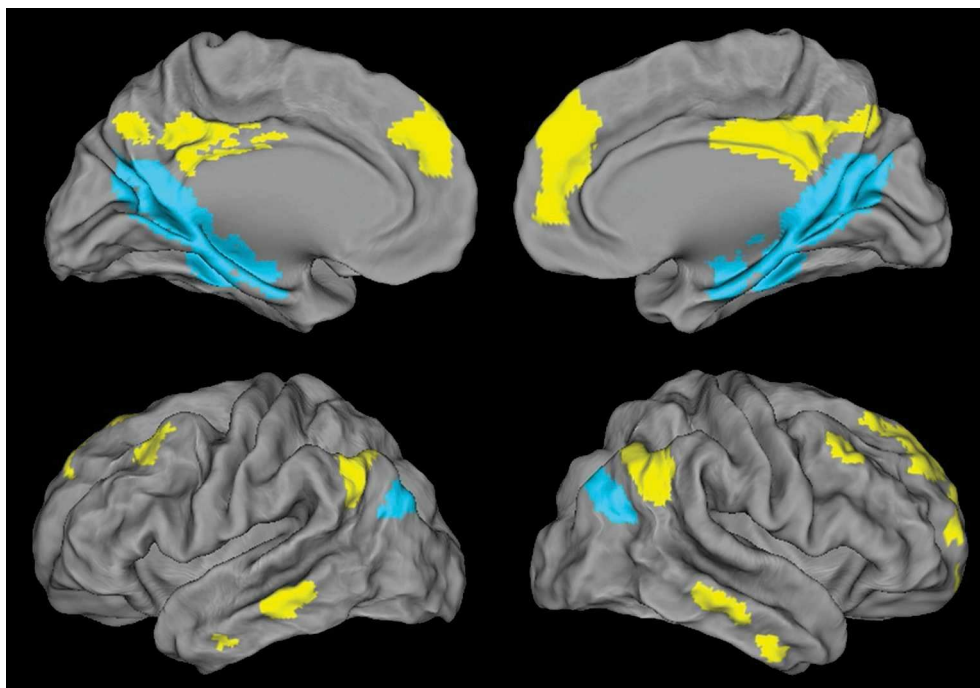


FIGURE 3 | Illustration of the ventral PCC (blue) and dorsal PCC (yellow) networks in HE obtained with a paired *t*-test and thresholded at *p* (FWE-corrected) < 0.05, *k* > 50.

TABLE 2 | Percentage of the volume of the ventral and dorsal networks showing FC disruption, atrophy and hypometabolism in patients compared with HE.

	Ventral Network		Dorsal Network	
	MCI	AD	MCI	AD
FC disruption	1.82	3.17	0.00	0.47
Atrophy	11.42	49.37	0.00	50.23
Hypometabolism	10.09	61.21	28.18	79.24

RESULTS

Demographic Data

The three groups did not differ on either sex or years of education, but the patients with aMCI were significantly older than HE (Table 1).

Identification of the vPCC and dPCC Networks in HE

Regions showing higher connectivity with the vPCC than with the dPCC, and thus constituting the ventral PCC network, included the vPCC region (autocorrelation) extending to the retrosplenial cortex, the medial temporal lobe including the hippocampus and parahippocampal cortex and encroaching on the fusiform and lingual gyri, the ventroposterior part of the precuneus, the cuneus, the most inferoposterior part of the angular gyrus, and the parieto-occipital sulcus (Figure 3). The volume of the vPCC network was 53272 mm³ (6659 voxels).

Regions showing higher connectivity with the dPCC than with the vPCC, and thus constituting the dorsal PCC network, bilaterally included the dPCC region (autocorrelation) extending to the middle cingulate cortex, the dorsomedial prefrontal cortex (encroaching on both the anterior cingulate gyrus and the frontal superior cortex), and the superior frontal gyrus (superolateral part), middle frontal gyrus (superior portion), orbitofrontal cortex, dorsal part of the precuneus, supero-anterior part of the angular gyrus, and middle temporal gyrus (Figure 3). The volume of the dPCC network was 58,968 mm³ (7371 voxels).

We had expected to highlight distinct FC networks for the ventral and dorsal PCC, consistent with previous studies and with the known heterogeneity of the PCC. We did indeed find significant differences between the two networks in HE, with the vPCC being more strongly connected to medial temporal and parieto-occipital brain areas, while the dPCC network mainly involved frontal and lateral temporal brain regions.

Alteration within the vPCC and dPCC Networks in Patients with aMCI or AD, Compared with HE

FC Disruptions

Within the vPCC network, FC was bilaterally reduced in the anterior part of the hippocampus in patients with aMCI compared with HE. Within the dPCC network, no significant difference in FC was found between patients with aMCI and HE.

In AD, FC disruptions within the vPCC network were found in the anterior part of the bilateral hippocampus, as

well as in the left parahippocampal gyrus and left angular gyrus (inferoposterior part). Within the dPCC network, FC was reduced in the anterior part of the right middle temporal gyrus (Figure 4A).

Results therefore showed that FC disruption initially concerned the vPCC network at the aMCI stage. It then extended further within this network and also occurred within the dPCC network at the AD dementia stage.

Atrophy

Within the vPCC network, significant atrophy was found in the bilateral hippocampus and parahippocampal gyrus in patients with aMCI compared with HE. Within the dPCC, no significant atrophy was found in patients with aMCI vs. HE.

In patients with AD, the vPCC network was atrophied in the bilateral hippocampus, parahippocampal and fusiform gyri, bilateral vPCC, cuneus and posterior part of the precuneus,

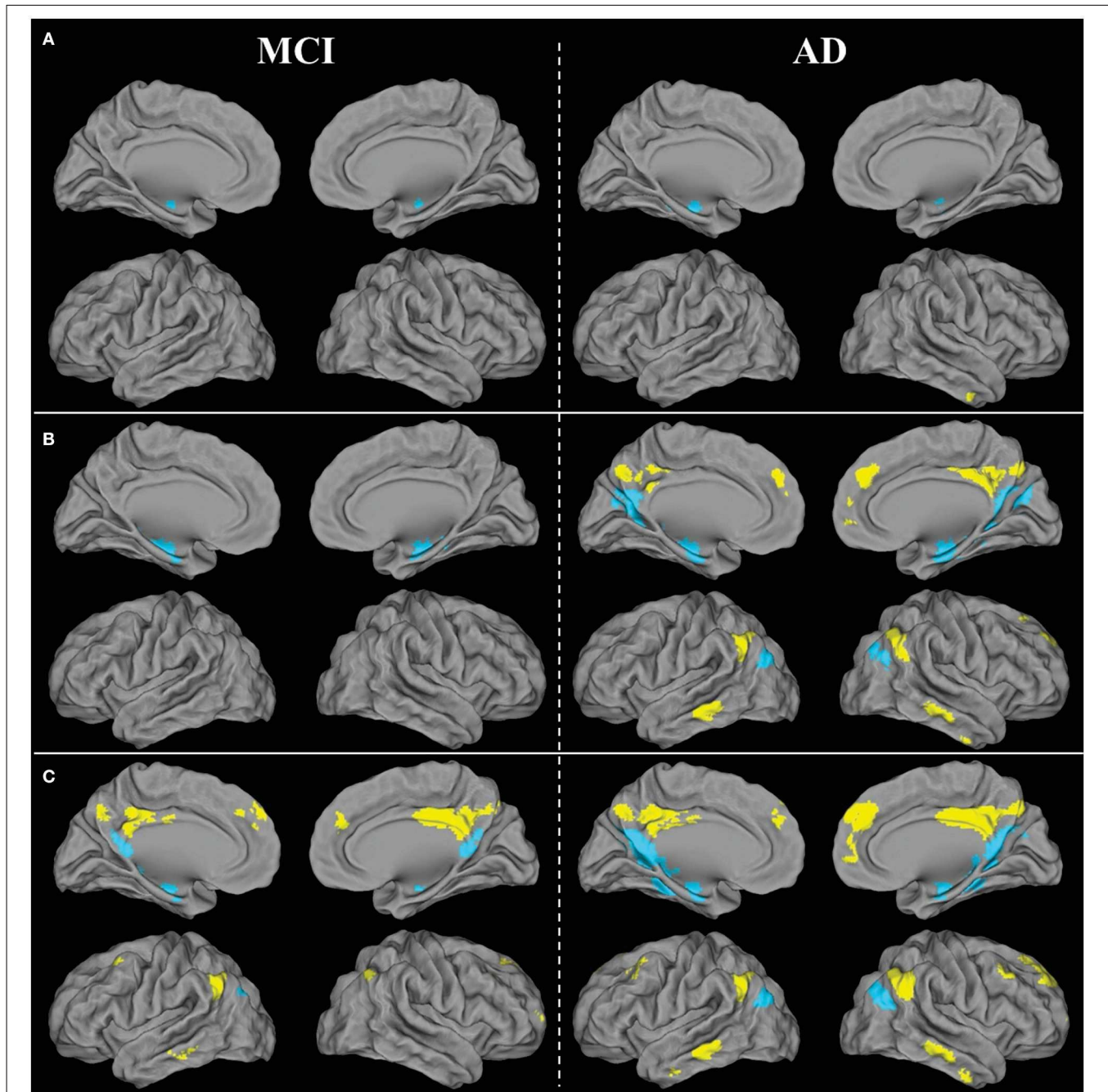


FIGURE 4 | Brain areas showing significant FC disruptions (A), atrophy (B), and hypometabolism (C) within the ventral (blue) and dorsal (yellow) PCC networks of patients with aMCI or AD compared with HE, as revealed by ANCOVAs thresholded at p (uncorrected) < 0.001 .

angular gyrus, and right parieto-occipital sulcus. The dPCC network was also atrophied bilaterally in patients with AD vs. HE in the supero-anterior part of the angular gyrus, dPCC and precuneus, middle temporal gyrus, anterior cingulate gyrus extending to the superior frontal gyrus, and in the right middle frontal gyrus (Figure 4B).

In sum, as with FC disruption, atrophy was initially restricted to the vPCC network at the aMCI stage, before extending further within this network and in the dPCC network as well at the AD dementia stage.

Hypometabolism

Within the vPCC network, significant bilateral hypometabolism was found in the vPCC/precuneus region and hippocampus in patients with aMCI compared with HE. The dPCC network was also hypometabolic in patients with aMCI, in parietal regions encompassing the bilateral dPCC and left angular cortex, as well as in the left inferoposterior temporal, bilateral orbitofrontal and middle frontal cortex.

In patients with AD vs. HE, significant hypometabolism was found in all the regions of the vPCC and dPCC networks (Figure 4C).

Thus, unlike FC disruption and atrophy, hypometabolism was found not to be restricted to the vPCC network at the MCI stage, as it was already present in both networks, and affected the whole of the vPCC and dPCC networks by the AD dementia stage.

Correlations between Atrophy or Hypometabolism and MMSE Score

Atrophy and hypometabolism in MCI and AD in the vPCC and dPCC networks was found to be correlated with the MMSE score either significantly or at a trend level (ρ values between 0.3 and 0.51 and p -values between 0.09 and 0.01; see Table S2 and Figure S2). This suggests that the alterations reflect the evolution of the pathological process associated with global cognitive decline.

DISCUSSION

In the present study, we sought to highlight the distinct FC of the vPCC and dPCC networks in HE, and identify the FC disruptions, atrophy, and hypometabolism within these two networks in patients with aMCI or AD.

Topography of vPCC and dPCC Networks in HE

Direct comparisons between vPCC vs. dPCC connectivity revealed the distinct topography of these networks in HE. The vPCC network mainly included parieto-occipital and medial temporal regions, while the dPCC network was mainly composed of frontal and lateral temporal brain regions. This topography is consistent with previous resting-state FC studies showing that the vPCC is more correlated with hippocampal and parahippocampal networks (Margulies et al., 2009) and the left inferior parietal cortex (Bzdok et al., 2015), while the dPCC is less correlated with the medial temporal lobe but more with the lateral temporal cortex (Margulies et al., 2009) and dorsomedial prefrontal, inferior parietal, posterior middle cingulate and left

dorsolateral prefrontal cortex (Bzdok et al., 2015). These findings were also corroborated by a correlation analysis of resting-state glucose metabolism data showing higher correlations for the vPCC with the temporal and occipital cortices, and higher correlations for the dPCC with parietal areas (Vogt et al., 2006). Despite this overall consistency, there were also subtle differences from previous studies. For example, the prefrontal cortex was described as forming part of the vPCC network in some previous studies (Maddock et al., 2001; Bzdok et al., 2015) but not here, or the parietal cortex has sometimes been found to belong to the dPCC network (Vogt et al., 2006; Beckmann et al., 2009; Bzdok et al., 2015). These discrepancies probably reflect differences in the specific seed of interest, the samples, or other methodological aspects across studies. In line with their cytoarchitectonic and connectivity differences, distinct cognitive roles have been attributed to the ventral and dorsal PCC. Thus, the vPCC has been preferentially associated with tasks involving internally-focused attentional states such as self-reflection (Johnson et al., 2002), episodic (autobiographical) memory retrieval (Nielsen et al., 2005; Sugiura et al., 2005; Vogt et al., 2006; Dastjerdi et al., 2011), planning for the future (Fransson, 2005) and daydreaming (Mason et al., 2007). By contrast, the dPCC has been found to be preferentially involved in more externally-oriented attentional and/or visuospatial tasks (Maguire et al., 1997, 1998; Sugiura et al., 2005; Spreng and Schacter, 2012). The dPCC has also been found to play a role in switching between the DMN (internal focus) and the cognitive control network (external attention; Leech et al., 2011).

Earlier Atrophy and Functional Disruption in the vPCC Network

The vPCC network showed alteration in both FC and gray matter volume, mainly in bilateral hippocampal regions, in patients with aMCI, whereas the dPCC network showed neither FC disruption nor atrophy at the aMCI stage. This early disruption of the vPCC network especially involving the hippocampus, is consistent with previous findings highlighting the particular vulnerability of the PCC-hippocampus axis in the course of AD (Villain et al., 2008, 2010), and studies showing alteration of the caudal part of the cingulum bundle that connects the hippocampus to the PCC (Choo et al., 2010; Villain et al., 2010). This vPCC network alteration may reflect the propagation of tau lesions from early sites of tau deposition, such as the medial temporal areas (Buée and Delacourte, 2006), to the most directly connected brain regions (vPCC network). It may also reflect the fact that the vPCC contains more pyramidal neurons than the dPCC (Vogt et al., 2006), and pyramidal neurons of the CA1 (Braak and Braak, 1997) are particularly vulnerable to tau pathology. Neuropathological examinations in patients with AD have also shown that the IV, Va, and Vb layers of the PCC (Brodmann area 23a) are the most vulnerable to neuronal loss (Vogt et al., 1998). These layers are more extensively represented and contain more densely packed neurons in the vPCC than in the dPCC (Vogt et al., 2006), which may explain the earlier involvement of the vPCC network in the present study.

By the AD dementia stage, the FC disruption and atrophy had extended further within the vPCC network (left fusiform and angular region), and was also present in the dPCC network (right middle temporal region for FC, and bilateral precuneus, frontal and temporal regions for atrophy). These results are consistent with the hypothesis that lesions propagate from the hippocampal-PCC axis within the vPCC network to the dPCC network, resulting in both FC disruption and atrophy, conducting to dementia (see below).

The PCC as a Hub through Which the Pathology Spreads?

Medial temporal atrophy is one of the earliest events in the pathophysiological process of AD, and is thought to reflect neuronal and synaptic loss related to local neurofibrillary tangles (Fukutani et al., 2000; Whitwell et al., 2012). Our findings are consistent with the idea that the pathology (reflected in structural and FC disruptions), is initially restricted to the vPCC network, and subsequently spreads to the dPCC network. The PCC thus appears as a hub through which the pathology progresses. The two PCC subregions are known to be highly interconnected in monkeys (Parvizi et al., 2006) and humans (Leech et al., 2011). This hypothesis is in line with the network degeneration hypothesis whereby neurodegenerative diseases target brain networks (Seeley et al., 2009; Zhou et al., 2013; Raj et al., 2015, 2012) as pathologies progress from neuron to neuron through transneural spread, consistent with *prion-like* spreading (Frost and Diamond, 2009). Thus, misfolded proteins may spread throughout specific neural networks via trans-synaptic transmission pathways. Within this framework, we can hypothesize that the alterations observed within the vPCC network at the aMCI stage spread to the dPCC network in AD via the trans-synaptic connections between the vPCC and the dPCC.

Hypometabolism within vPCC and dPCC

In contrast to the atrophy and connectivity disruptions, hypometabolism was found in both the vPCC and dPCC networks, even in patients with aMCI. Post-mortem studies in patients with AD suggest that PCC hypometabolism may, at least partly, be related to a reduction in the expression of energy metabolism genes in PCC neurons (Liang et al., 2008). Hypometabolism seems not to follow the same progressive involvement of the ventral and dorsal networks, as its progression was not initially restricted to the vPCC network. This may reflect the fact that hypometabolism is due to both local and distant alterations (La Joie et al., 2012), that is, diaschisis due to atrophy in connected brain regions (Chételat et al., 2009). In other words, atrophy within structures of the vPCC network in patients with aMCI may be associated with hypometabolism both in the same regions of the vPCC network and in distant connected areas of the dPCC network.

At the AD dementia stage, the whole vPCC and dPCC networks were hypometabolic. Early hypometabolism is commonly found in the PCC, temporoparietal and frontal areas in patients with AD or aMCI, and is thought to reflect mechanisms of disconnection from the atrophied hippocampus via the cingulum bundle and uncinate fasciculus (Chételat et al.,

2008; Villain et al., 2008, 2010; Fouquet et al., 2009; Yakushev et al., 2011).

LIMITATIONS/PERSPECTIVES

Our study had several strengths and also several limitations. The strengths included a voxelwise multimodal approach that afforded a comprehensive view of the patterns of FC disruption, atrophy and hypometabolism in the vPCC and dPCC networks in patients with aMCI or AD. The limitations included the heterogeneous amyloid status of the patients with aMCI. However, when we repeated our neuroimaging analysis considering just the subgroup of amyloid-positive patients with aMCI ($n = 21$), the results remained essentially unchanged (Figure S1). The only difference was that, while there was no atrophy in the dPCC network for the aMCI group as a whole, atrophy was found in a small cluster located in the dPCC when we only considered the amyloid-positive patients with aMCI. The cross-sectional nature of the present study was a second limitation; further longitudinal studies would allow to demonstrate the spread of lesions from the vPCC to the dPCC networks and to assess the sequence of events and causal relationships between the different biomarkers.

ETHICS STATEMENT

Comite de Protection des Personnes Nord-Ouest III, registered with <http://clinicaltrials.gov> (number NCT01638949). All participants gave written informed consent to the study prior to the investigation. Alzheimer patients were accompanied by a relative who gave also his consent to the study.

AUTHOR CONTRIBUTIONS

JM, GC, VdLS, and FE contributed to the study concept and design. JM, GC contributed to the interpretation of the data and to the drafting of the manuscript. JM, CT, RdF, and FM contributed to the data acquisition. JM, BL, and FM contributed to the data analyses. All the authors revised the work, approved the manuscript to be published, and agreed to be accountable for the work.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary Material

Connectivity disruption, atrophy and hypometabolism within posterior cingulate networks in Alzheimer's disease

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Table S1: Cluster extent for each modality and within each network to achieve a multiple comparison-corrected statistical significance of $p < 0.05$.

	Ventral Network		Dorsal Network	
	k	volume (mm ³)	k	volume (mm ³)
FC	22	176	20	160
Gray Matter Volume	276	276	174	174
Metabolism	22	176	20	160

Table S2: Spearman correlations between atrophy or hypometabolism within vPCC and dPCC networks and MMSE score in patients with aMCI or AD with a significant threshold (*) set to $p < 0.05$.

		vPCC network		dPCC network	
		<i>rho</i>	<i>p</i>	<i>rho</i>	<i>p</i>
aMCI patients	Atrophy	0.39	0.02*	-	-
	Hypometabolism	0.30	0.09	0.36	0.04*
AD patients	Atrophy	0.36	0.09	0.51	0.01*
	Hypometabolism	0.47	0.03*	0.46	0.04*

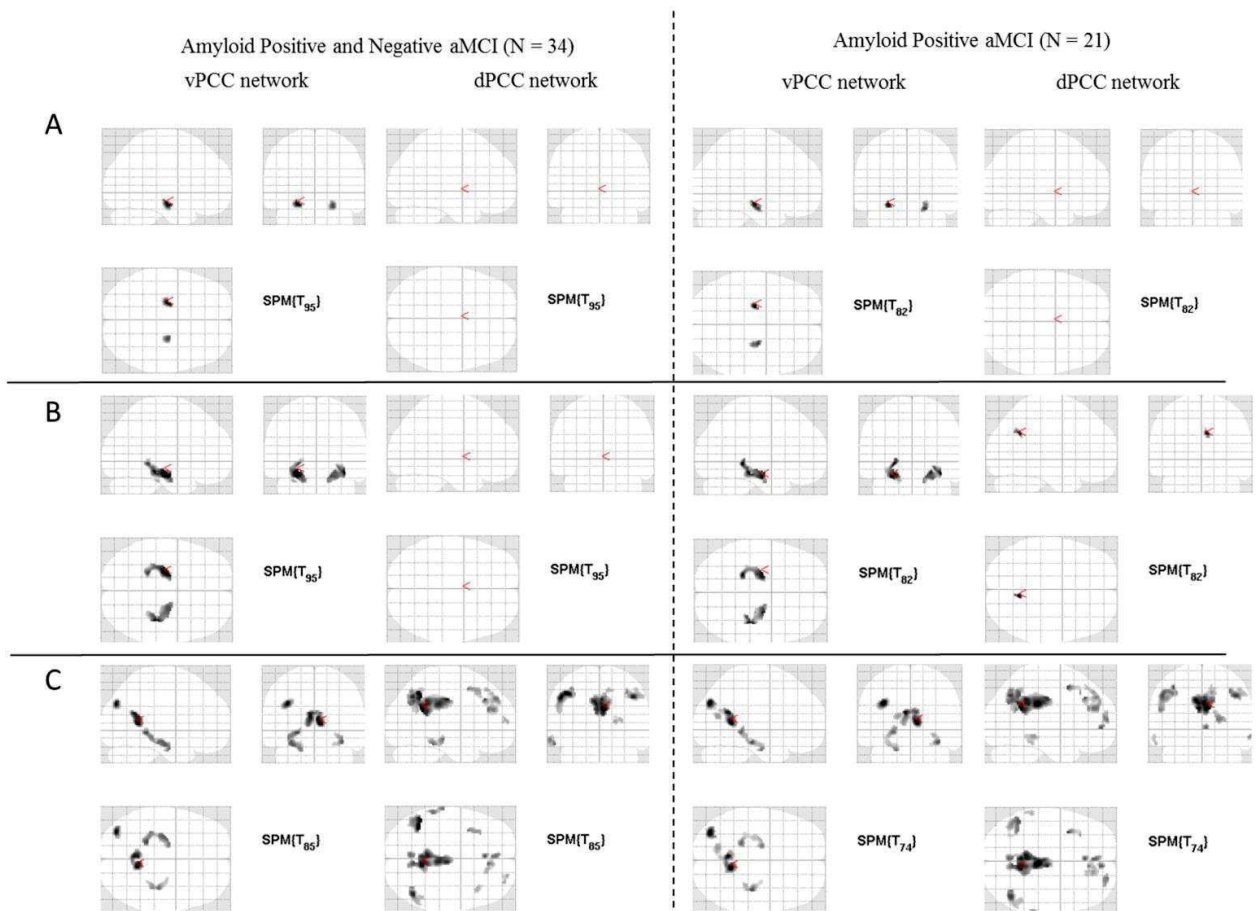


Figure S1: Alterations in the entire aMCI sample (left) versus in the amyloid-positive aMCI subsample (right) compared with HE within the ventral and dorsal PCC networks. The FC disruptions are shown in panel (A), atrophy is shown in panel (B) and hypometabolism in panel (C)

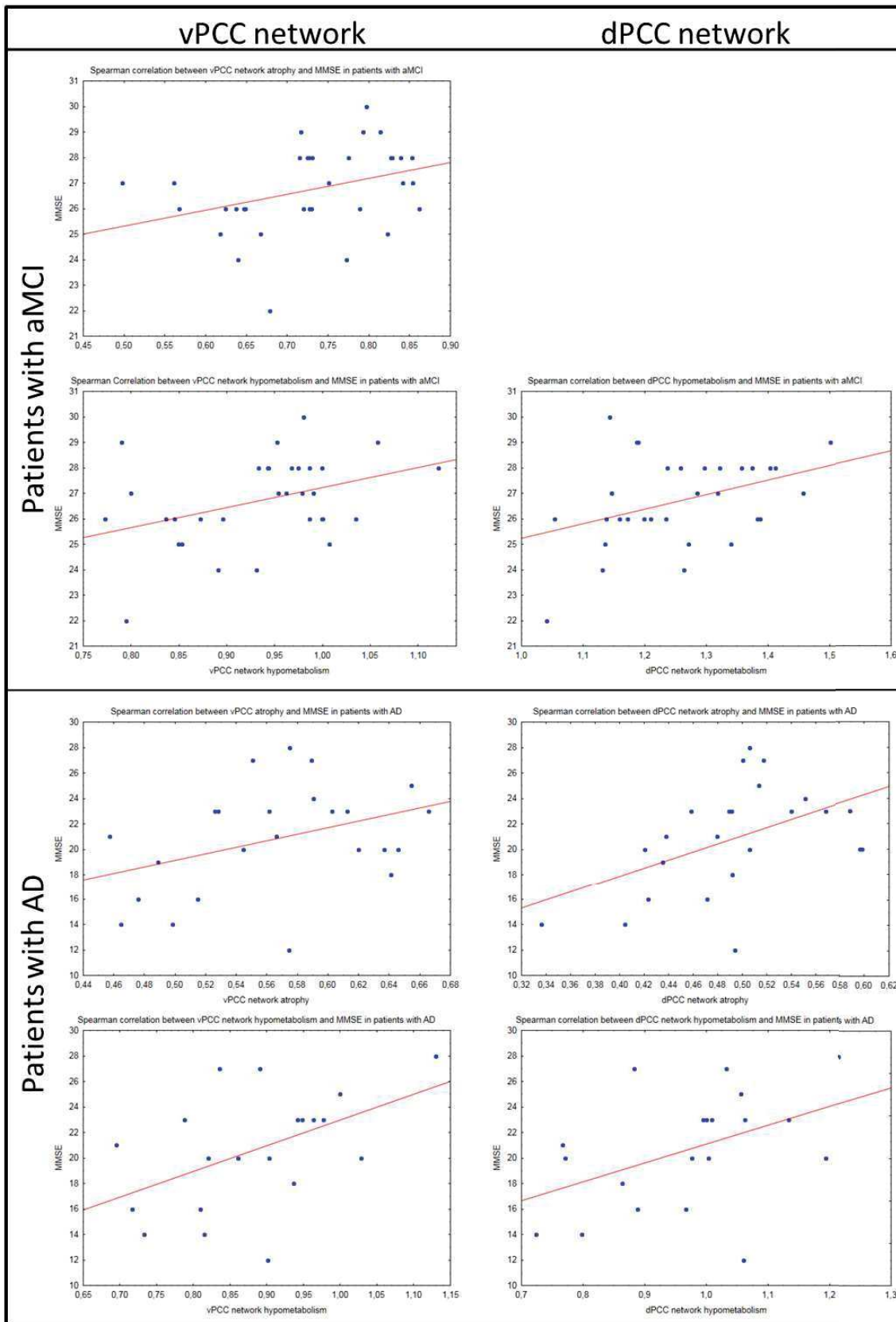


Figure S2: Representation of the Spearman correlations between atrophy or hypometabolism within vPCC and dPCC networks and MMSE score in patients with aMCI or AD

4.4. Etude 2 : *Specific and global connectivity differentially predict Alzheimer's disease lesion topography and spread* (Article en révision dans Brain)

De récents travaux ont montré que la connectivité fonctionnelle pourrait sous-tendre la répartition topographique et la propagation des lésions dans la MA. Certaines régions présenteraient en effet une plus grande vulnérabilité aux altérations survenant dans la MA en raison de leurs propriétés de connectivité fonctionnelle.

D'une part, les régions «hubs», dont les valeurs particulièrement élevées de connectivité globale traduisent le fait qu'elles soient très connectées avec le reste des régions cérébrales, seraient des cibles privilégiées de la MA (Buckner et al., 2009; van den Heuvel et Sporns, 2013). Tout au long de la vie, ces régions sont beaucoup sollicitées et présentent une forte activité métabolique. Dans la MA, ce sont ces mêmes régions qui montrent les taux d'hypométabolisme et d'accumulation amyloïde les plus importants.

D'autre part, la pathologie de la MA s'initie au niveau de régions dites «épices» qui correspondent au point de départ de l'altération considérée, que ce soit l'atrophie, l'hypométabolisme ou l'accumulation amyloïde. Selon l'hypothèse de la dégénérescence transneuronal, les lésions se répandraient au sein de réseaux spécifiques et ainsi, les régions les plus fonctionnellement connectées à l'épicentre (qui ont une forte connectivité spécifique) seraient plus fragiles.

S'il a été mis en évidence que la topographie et la propagation des lésions sont liées à connectivité globale et à la connectivité spécifique, l'influence relative de ces deux dernières sur différents biomarqueurs de neuroimagerie n'a, à notre connaissance, jamais été évaluée. L'objectif de cette étude était donc de répondre à cette question en estimant les connectivités spécifiques et globale chez des participants contrôles afin de prédire la topographie de l'atrophie, de l'hypométabolisme et de l'accumulation amyloïdes chez des patients ainsi que leur propagation en 18 mois.

Pour ce faire, 42 sujets âgés sains (69.6 +/- 6.1) et 35 patients (MCI amnésiques et MA tous amyloïdes positifs) (71.2 +/- 9.5) ont été inclus dans cette étude. Tous les participants ont effectués un examen IRMf au repos, une IRMa et deux TEP marquées au FDG et au

florbetapir pour évaluer l'hypométabolisme et les dépôts A β . Les patients ont repassé ces examens 18 mois plus tard.

Les régions épacentres ont été définies à partir de l'atteinte maximale en atrophie, en hypométabolisme ou en dépôts A β chez les patients comparativement aux sujets sains au temps initial. La connectivité globale et les connectivités spécifiques ont été obtenues chez les sujets sains au temps initial et les cartes d'altération initiale et leur propagation ont été définies chez les patients. Des analyses de régressions dans 239 régions cérébrales obtenues d'après la parcellisation de Power et al. (2011) ont été effectuées pour évaluer les liens entre d'une part, la connectivité spécifique et la connectivité globale estimées chez les sujets sains, et d'autre part, les atteintes initiales ainsi que leur propagation chez les patients.

L'originalité de cette étude réside dans le fait d'estimer l'influence relative de la connectivité globale et spécifique sur les trois principaux biomarqueurs en neuroimagerie que sont l'atrophie, l'hypométabolisme et les dépôts amyloïdes en considérant à la fois les atteintes transversales au temps initial mais aussi longitudinales.

Cette étude a permis de mettre en évidence que les régions hubs seraient plus vulnérables à l'hypométabolisme et aux dépôts A β mais relativement préservés de l'atrophie dont la topographie et la propagation serait déterminées par la connectivité spécifique et non globale. Ces résultats ont montré une influence différentielle des connectivités spécifique et globale sur la topographie et la propagation des lésions apportant ainsi une meilleure compréhension des mécanismes sous-jacents à la propagation des lésions.

Distinct influence of specific versus global connectivity on the different Alzheimer's disease biomarkers

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16 **Running title:** Connectivity to predict Alzheimer's disease biomarkers

17

18 **Abstract**

19 Recent findings suggest that the topography and propagation of lesions in Alzheimer's disease are
20 related to functional connectivity, either showing that hubs (global connectivity) are more vulnerable
21 or that lesions propagate neurons-to-neurons (specific connectivity) from a starting area called the
22 epicenter. However the relative influence of specific and global connectivity and their differential
23 impact on the three main neuroimaging biomarkers of the disease (atrophy, hypometabolism and β -
24 amyloid deposition) have never been investigated to date. Forty-two healthy elders and 35 β -amyloid
25 positive amnesic mild cognitive impairment and Alzheimer's disease patients underwent resting-
26 state functional MRI, anatomical T1-weighted MRI, [18F]-fluorodeoxyglucose-PET and florbetapir-
27 PET scans. All patients also underwent follow-up T1-weighted MRI, [18F]-fluorodeoxyglucose-PET
28 and florbetapir-PET scans 18 months later to assess the lesion propagation over this period. The
29 epicenter was defined per modality as the most altered region at baseline in patients compared to
30 controls. Maps of global and specific functional connectivity were computed from the resting-state
31 functional MRI data of the healthy elders, and maps of baseline alterations and propagation were
32 computed for gray matter atrophy, hypometabolism and β -amyloid deposition in patients. Regression
33 analyses were performed across 238 brain regions from the Power atlas to assess the links between
34 global or specific functional connectivity in healthy elders and Alzheimer's disease-related baseline
35 disruptions or alteration propagation. Atrophy at baseline was predicted by specific connectivity and
36 inversely correlated with global connectivity, while hypometabolism and β -amyloid deposition were
37 positively influenced by both global and specific connectivity. Regarding longitudinal changes,
38 atrophy spread in regions with high specific connectivity while hypometabolism propagated in areas
39 showing high global connectivity. This is the first study to show that global connectivity has an
40 opposite relationships with atrophy versus hypometabolism and β -amyloid deposition, suggesting
41 that the high level of functional connectivity found in hubs exerts a differential influence on these

42 Alzheimer's disease lesions. These results sustain the hypotheses of higher vulnerability of hubs to
43 hypometabolism and β -amyloid deposition versus transneuronal propagation of atrophy from the
44 epicenter to connected regions, in Alzheimer's disease. Global and specific connectivity exert a
45 differential influence on, and provide complementary information to predict, the topography of
46 Alzheimer's disease lesions and their propagation.

47 **Keywords:** resting-state connectivity, amyloid imaging, brain atrophy, Alzheimer's disease, glucose
48 metabolism, longitudinal.

49 **Abbreviation:** DARTEL = Diffeomorphic Anatomical Registration through Exponentiated Lie
50 Algebra.

51

52 **1 Introduction**

53 Alzheimer's disease is the most widespread neurodegenerative disease in the elderly population.
54 Alzheimer's disease is characterized by a progressive decline in cognitive performances typically
55 predominated by episodic memory deficits. The abnormal accumulation of tau-rich neurofibrillary
56 tangles and β -amyloid deposition plaques are both neuropathological hallmarks of the disease. In-
57 vivo neuroimaging biomarkers of the disease include atrophy – predominantly in the hippocampus
58 and temporal neocortex, hypometabolism – mainly in the posterior cingulate and temporoparietal
59 cortex, and A β deposition in medial frontal, parietal and temporoparietal cortical areas (McKhann *et*
60 *al.*, 2011; Winblad *et al.*, 2016).

61 Recent evidences from neuroimaging studies have shown that neurodegenerative diseases in general,
62 and Alzheimer's disease in particular, target specific brain networks, leading to the network
63 degeneration hypothesis (Buckner *et al.*, 2005; Du *et al.*, 2007; Sorg *et al.*, 2007; Seeley *et al.*, 2009;
64 La Joie *et al.*, 2014). Thus, different mathematical modeling approaches have been developed to
65 assess the relationship between healthy brain networks and connectivity on the one hand, and the
66 topography and spread of lesions in dementia on the other hand (Seeley *et al.*, 2009; Raj *et al.*, 2012).
67 More specifically, these studies applied graph theoretical analysis to resting-state functional MRI or
68 diffusion tensor imaging data and showed that the pattern of atrophy or hypometabolism – and their
69 propagation - could be predicted based on functional and/or structural connectivity (Raj *et al.*, 2012;
70 Zhou *et al.*, 2012; Crossley *et al.*, 2014; Raj *et al.*, 2015).

71 Two possible mechanisms might explain the fact that the topography and propagation of lesions are
72 constrained or influenced by brain networks. First, it has been proposed that the most metabolically
73 active brain regions, those with the highest level of neuronal activity and “global connectivity” with
74 the rest of the brain, defined as network “hubs”, are more vulnerable to Alzheimer's disease

75 pathology (Buckner *et al.*, 2009; van den Heuvel and Sporns, 2013). This hub vulnerability
76 hypothesis might notably explain the similarity between the topography of hubs and that of
77 Alzheimer's disease lesions (Buckner *et al.*, 2005). It is further supported by evidences from
78 neuroimaging studies showing a relationship between the level of global connectivity in healthy
79 adults and the level of β -amyloid deposition (Buckner *et al.*, 2005).

80 Alternatively, the fact that lesions are preferentially confined within brain networks might reflect
81 their transneuronal propagation. Thus Alzheimer's disease lesions are thought to propagate neurons-
82 to-neurons through prion-like mechanisms. This view is supported by neuropathological evidence
83 that numerous disease proteins, as alphasynuclein, β -amyloid, tau and trans-activating response
84 DNA/RNA binding protein 43, have the capacity to misfold and propagate via transsynaptic spread
85 (Frost and Diamond, 2009; Palop and Mucke, 2010; Jucker and Walker, 2013). This transneuronal
86 spread hypothesis implies that the brain areas the most connected to the initial site of disruption
87 (called as the "epicenter") are more likely to be progressively involved compared to those less
88 connected to the epicenter. Neuroimaging evidence using connectivity ring or graph theoretical
89 analyses from diffusion tensor imaging or resting-state functional MRI data support this hypothesis
90 by showing a link between the regions connected to the epicenter and the topography or propagation
91 of lesions as reflected in atrophy or hypometabolism (Seeley *et al.*, 2009; Zhou *et al.*, 2012; Mallio *et*
92 *al.*, 2015; Raj *et al.*, 2015).

93 Both global and specific functional connectivity are thus thought to influence the topography and
94 propagation of Alzheimer's disease -related brain alterations respectively via hub vulnerability and
95 transneuronal spread. To our knowledge, only one previous study assessed both connectivity
96 processes to predict atrophy in dementia (Zhou *et al.*, 2012) and highlighted the contribution of both.
97 However, the respective involvement of each of these two factors on the different Alzheimer's
98 disease neuroimaging biomarkers has never been assessed to date.

99 The aim of the present study was to estimate the relative contribution of global and specific
100 functional connectivity, measured in healthy elders, to predict Alzheimer's disease baseline atrophy,
101 hypometabolism and β -amyloid deposition as well as their propagation over 18 months in β -amyloid
102 positive mild cognitive impairment and Alzheimer's disease patients. We expected to show a
103 differential influence of these two connectivity measures on Alzheimer's disease lesions. We
104 hypothesized that atrophy would be mostly influenced by specific connectivity as a reflect of
105 intraneuronal tau propagation while the high activity level in hubs would make them more vulnerable
106 to β -amyloid pathology and hypometabolism.

107 **2 Materials and Methods**

108 An overview of the data processing and analyses is represented in Fig1.

109 **2.1 Participants**

110 Seventy-seven right-handed native French-speaking participants from the « Imagerie Multimodale de
111 la Maladie d'Alzheimer à un stade Précoce » (IMAP+) Study (Caen) were included in the present
112 study: 42 healthy elders, 14 amnesic mild cognitive impairment patients and 21 Alzheimer's disease
113 patients. Demographic data and mini-mental state examination scores are displayed in Table 1. Part
114 of them was included in previous publications from our lab (La Joie *et al.*, 2012, 2013; Mevel *et al.*,
115 2013; La Joie *et al.*, 2014; Tomadesso *et al.*, 2015). All participants were aged over 52 years, had at
116 least 7 years of education and had no history of alcoholism, drug abuse, head trauma, or psychiatric
117 disorder.

118 Healthy elders were recruited from the community and performed in the normal range on all
119 neuropsychological tests from a cognitive battery assessing multiple domains of cognition (verbal
120 and visual episodic memory, semantic memory, language skills, executive functions, visuospatial
121 functions, and praxis). Patients were recruited from local memory clinics and selected according to

122 corresponding internationally agreed criteria. Amnesic mild cognitive impairment patients were
123 selected based on Petersen's criteria for amnesic mild cognitive impairment (Petersen and Morris,
124 2005) and Alzheimer's disease patients fulfilled standard National Institute of Neurological and
125 Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders
126 Association (NINCDS-ADRDA) clinical criteria for probable Alzheimer's disease (McKhann *et al.*,
127 1984). Clinical diagnosis was assigned by consensus under the supervision of a senior neurologist
128 (V.d.L.S.) and neuropsychologists (A.P. and S.E.). All participants had a florbetapir-PET scan to
129 assess β -amyloid deposition. Only patients with a positive florbetapir-PET scan using previously
130 published methods (La Joie *et al.* 2012) were included in this study. In healthy elders, the proportion
131 of β -amyloid-positive was 19.5 % (8/41).

132 The IMAP+ Study was approved by a regional ethics committee (Comité de Protection des Personnes
133 Nord-Ouest III) and is registered with <http://clinicaltrials.gov> (number NCT01638949). All
134 participants gave written informed consent to the study prior to the investigation.

135 **2.2 Neuroimaging data acquisition**

136 All participants were scanned on the same MRI and PET cameras at the Cyceron Center (Caen,
137 France): a Philips Achieva 3.0 T scanner and a Discovery RX VCT 64 PET-CT device (General
138 Electric Healthcare), respectively. A high-resolution T1-weighted anatomical volume was acquired
139 using a three-dimensional fast-field echo sequence (3D-T1-FFE sagittal; repetition time = 20 ms;
140 echo time = 4.6 ms; flip angle = 10°; 180 slices with no gap; slice thickness = 1 mm; field of view =
141 256 x 256 mm²; in-plane resolution = 1 x 1 mm²). In the present study we used baseline MRI scans
142 of all participants and follow-up scans at 18 months in patients.

143 At baseline, resting-state functional volumes were obtained in healthy elders using an interleaved 2D
144 T2* SENSE EPI sequence designed to reduce geometric distortions using parallel imaging, short

145 echo time, and small voxels (2D-T2*-FFE-EPI axial, SENSE =2; Time Repetition = 2382 ms; Time
146 Echo = 30 ms; flip angle = 80°; 42 slices with no gap; slice thickness = 2.8 mm; field of view = 224 x
147 224 mm²; in plane resolution = 2.8 x 2.8 mm²; 280 volumes, acquisition time = 11.5 min).
148 Participants were equipped with earplugs, their head was stabilized with foam pads to minimize head
149 motion and the scanner room's light was turned off. During this acquisition, which was the last one of
150 the MRI scanning session, participants were asked to relax, lie still in the scanner and keep their eyes
151 closed, without falling asleep. A subsequent debriefing questionnaire allowed us to ensure that the
152 participants had no difficulty staying awake throughout the duration of the resting-state functional
153 MRI scan and that nothing particular had disturbed their attention during the scanning.

154 Both [18F]-fluorodeoxyglucose- and florbetapir-PET scans were acquired in patients at baseline and
155 follow-up with a resolution of 3.76 × 3.76 × 4.9 mm³ (field of view = 157 mm). Forty-seven planes
156 were obtained with a voxel size of 1.95 × 1.95 × 3.2 mm³. A transmission scan was performed for
157 attenuation correction before the PET acquisition. [18F]-fluorodeoxyglucose-PET: the participants
158 were fasted for at least 6 hours before scanning. After a 30 min resting period in a quiet and dark
159 environment, 180 MBq of [18F]-fluorodeoxyglucose was intravenously injected as a bolus. A 10 min
160 PET acquisition scan began 50 min after injection. Florbetapir-PET: each participant underwent a 20
161 min PET scan, beginning 50 min after the intravenous injections of ~4MBq/Kg of florbetapir.

162 **2.3 Neuroimaging data preprocessing**

163 **2.3.1 Anatomical MRI**

164 **2.3.1.1 Baseline**

165 MRI data were segmented, normalized to a customized DARTEL (Diffeomorphic Anatomical
166 Registration through Exponentiated Lie Algebra) template (obtained from healthy volunteers and
167 patients from IMAP), modulated using the SPM12 segmentation procedure and smoothed with an 8

168 mm full-width at half-maximum Gaussian filter. To assess baseline atrophy, W-score maps were then
169 computed for each patient using the healthy elder group as a reference as described in La Joie *et al.*
170 (2012). W-scores are analogous to Z-scores but they are adjusted for specific covariate(s) (Jack *et al.*
171 1997; Jack *et al.* 2008), i.e. age, education and total intracranial volume in the present study. A group
172 level one sample t-test, masked by a gray matter mask obtained from DARTEL normalized gray
173 matter images and excluding the cerebellum (the so-called DARTEL gray matter mask in what
174 follows), was then computed on the atrophy W-score maps of all patients.

175 **2.3.1.2 Longitudinal changes**

176 For each patient, a pairwise longitudinal registration was computed between the baseline and follow-
177 up anatomical MRI resulting in a mid-point average anatomical MRI image (anatomical MRI
178 average) and the jacobian determinants. Negative values of the jacobian determinants reflect
179 contractions and positive values reflect expansions of the tissues. The anatomical MRI average was
180 segmented into gray matter, white matter and cerebrospinal fluid. The resulting gray matter segment
181 was then i) multiplied by the jacobian determinants resulting in the gray matter jacobian image), ii)
182 normalized to the DARTEL template, and the resulting deformation parameters were applied to the
183 gray matter jacobian image. The normalized gray matter jacobian image, smoothed with an 8 mm
184 full-width at half-maximum isotropic Gaussian kernel, was used as a reflect of atrophy propagation
185 over the 18-month follow-up period for each subject. At the group level, a one sample t-test masked
186 by the DARTEL gray matter mask was performed on the atrophy propagation maps of all patients.

187 **2.3.2 PET images**

188 Baseline and follow-up PET images were coregistered on their corresponding anatomical MRI
189 average. PET data were then voxel-wise corrected for partial volume effects using the PMOD
190 software. Then, partial volume effects corrected PET data were normalized to the DARTEL template

191 by applying the deformation parameters from the corresponding anatomical MRI average gray matter
192 segment. Resulting [18F]-fluorodeoxyglucose-PET images were scaled using a metabolically
193 preserved brain region, namely the cerebellar vermis (Mevel *et al.*, 2007), to control for inter- and
194 intra-individual global variations in [18F]-fluorodeoxyglucose-PET signal and florbetapir-PET
195 images were scaled using a reference region including the whole cerebellum, the brainstem/pons and
196 the white matter thresholded at 70% (as recommended for longitudinal florbetapir analyses in
197 Alzheimer's Disease Neuroimaging Initiative (ADNI), see Landau and Jagust, 2011; Landau *et al.*,
198 2015) to control for inter- and intra-individual global variations in florbetapir-PET signal.

199 **2.3.2.1 Baseline**

200 A smoothing kernel of 7.1 x 7.1 x 6.3 mm Gaussian filter was applied to all baseline spatially
201 normalized and scaled PET images so that the final smoothness of PET images was the same as
202 anatomical MRI images (8 x 8 x 8 mm). To assess the baseline hypometabolism or baseline β -
203 amyloid deposition, W-score maps were then computed from the [18F]-fluorodeoxyglucose- and
204 florbetapir-PET images as described for baseline gray matter atrophy, using age and education as
205 covariates. A group-level one sample t-test, masked by the DARTEL gray matter mask, was then
206 computed on the hypometabolism W-score or β -amyloid deposition W-score maps of all patients.

207 **2.3.2.2 Longitudinal changes**

208 To assess propagation of hypometabolism or β -amyloid deposition, PET-percent annual changes
209 maps of [18F]-fluorodeoxyglucose and florbetapir were computed as described in Fouquet *et al.*,
210 2009 to calculate rates of change over the 18-month follow-up period. Briefly, PET-percent annual
211 changes maps were calculated voxelwise using baseline and follow-up normalized and scaled PET
212 data with the following formulae: $[(\text{baseline PET} - \text{follow-up PET}) / \text{baseline PET} \times 100] \times (12/18)$.
213 PET-percent annual changes maps were subsequently smoothed using a Gaussian kernel of 5.8 x 5.8

214 x 4.9 mm so that the final smoothness of the images was the same as anatomical MRI data (8 x 8 x 8
215 mm). Group level one sample t-tests masked by the DARTEL gray matter mask were then computed
216 across the [18F]-fluorodeoxyglucose- and florbetapir-PET-percent annual changes maps of all
217 patients.

218 **2.3.3 Resting-state fMRI**

219 Individual datasets were first checked for artefacts through using the TSDiffAna routines
220 (<http://imaging.mrc-cbu.cam.ac.uk/imaging/DataDiagnostics>), during which a variance volume was
221 created for each subject to check that most signal variability was restricted to the cortex. Datasets
222 showing evidence for significant movements (> 3 mm translation or 1.5 degree rotation) associated to
223 image artefacts and/or an abnormal variance distribution were excluded from subsequent analysis.
224 Data were then processed as described in La Joie *et al.* (2014) with slice timing correction,
225 realignment to the first volume and spatial normalization within the native space in order to correct
226 for the distortion effects (Villain *et al.*, 2010b). EPI volumes were then coregistered on the
227 corresponding anatomical MRI average image, normalized to the DARTEL space using the same
228 deformation parameters as described above, and smoothed with a 4 mm full-width at half-maximum
229 Gaussian kernel. Resulting images were then temporally band pass filtered ($0.01 < f < 0.08$ Hz) and
230 masked to include only gray matter voxels taking into account signal loss in EPI volumes by
231 combining the DARTEL gray matter mask and a mask based on non EPI-T2* volumes (the
232 DARTEL gray matter-T2* mask).

233 **2.3.3.1 Global Connectivity**

234 Global connectivity was assessed in healthy elders as in Xia *et al.* (2013). For this purpose, we used
235 the atlas of Power *et al.* (2011) defining 264 putative areas based on a metaanalysis of functional
236 MRI data. The coordinates of the center of the 264 putative areas were used to create spheres of 10

237 mm of diameter in the MNI space that were transformed to the DARTEL space. The spheres were
238 then masked by the DARTEL gray matter-T2* mask, and spheres lower than 10 voxels were
239 excluded, resulting in 239 gray matter areas. The mean time course of the resting-state functional
240 MRI was extracted at the individual level in each of the 239 gray matter areas and used to compute a
241 239 x 239 correlation matrix of Pearson's correlation coefficients between all possible connections of
242 node pairs. At the group level, a one-sample t-test was then performed on the correlation matrix
243 across the 42 healthy elders and the resulting matrix of t-values were thresholded at family-wise error
244 Bonferroni corrected $p < 0.05$ to select only the significant positive correlations. The functional
245 connectivity strength for each region corresponded to the sum of the t-values of the specific region
246 correlation with all other brain regions. These values were then standardized, i.e. transformed to z-
247 scores with the following formulae: [functional connectivity strength of the region minus mean
248 functional connectivity strength of the 238 brain regions divided by standard deviation of the
249 functional connectivity strength of the 238 brain regions)]. The resulting regional standardized
250 functional connectivity strength was used as a measure of global connectivity in what follows, with
251 regions with highest values being considered as hubs.

252 **2.3.3.2 Specific Connectivity**

253 Firstly, we identified the epicenter for each neuroimaging biomarker (i.e. for atrophy,
254 hypometabolism and β -amyloid deposition) as the gray matter area of the Power's atlas showing the
255 highest alteration in the corresponding one-sample t-tests performed on the W-score maps of all
256 patients. The epicenters of atrophy, hypometabolism and β -amyloid deposition corresponded to the
257 left hippocampus, the left angular gyrus and the right frontal gyrus, respectively. Secondly, we
258 obtained the Pearson's correlation coefficients between each epicenter and all other regions of the
259 Power's atlas for each healthy elder, which were averaged across subjects and transformed to z-
260 scores.

261 **2.4 Statistical analyses**

262 Between-group differences in demographic variables were assessed with one-factor ANOVAs
263 (analysis of variance) (Group) for continuous variables and chi2 tests for categorical variables.

264 For all the neuroimaging analyses, age and education were entered as nuisance covariates and total
265 intracranial volume served additionally as a global correction factor for voxel-based morphometry
266 analyses.

267 Baseline and propagation data of atrophy, hypometabolism and β -amyloid deposition in patients were
268 extracted from the SPM-T maps of the corresponding analyses within these 239 regions. Correlation
269 analyses were then performed across brain regions between global or specific functional connectivity
270 in healthy elders and baseline or propagation of atrophy, hypometabolism or β -amyloid load in
271 patients. Multiple regressions and forward stepwise regression analyses were also conducted,
272 including, for each baseline or propagation biomarker entered as the dependent variable, both global
273 and specific functional connectivity as independent variables to identify their relative contribution.

274 The region corresponding to the epicenter used to obtain the specific connectivity was removed from
275 all correlation and regression analyses and Bonferroni correction was applied to control for multiple
276 comparisons, so that a threshold of $p < 0.008$ ($0.05/6$) was required for results to be considered as
277 significant.

278 **3 Results**

279 Healthy elders and patients did not differ in gender and age but healthy elders had a significantly
280 higher education level than patients (Table1).

281 **3.1 Neuroimaging biomarker alterations at baseline and their propagation in patients**

282 In patients, the regions atrophied at baseline were located in the bilateral medial temporal cortex
283 (including the left hippocampus (autocorrelation), right hippocampus, parahippocampi and
284 amygdala), bilateral thalami, bilateral inferior temporal gyrus, right postcentral and supramarginal
285 gyri and left superior parietal cortex. The hypometabolic regions at baseline were mainly located in
286 bilateral posterior and lateral parietal areas including the precuneus and posterior cingulate cortex,
287 bilateral inferior temporal cortex, left thalamus and parahippocampus, bilateral postcentral, middle
288 frontal gyri and right superior frontal gyrus. Unsurprisingly (patients were selected to be β -amyloid-
289 positive and most of the controls were β -amyloid-negative), high degree of β -amyloid increase was
290 found at baseline in patients in almost the entire gray matter, with highest accumulation located in the
291 frontal cortex (Fig. 2).

292 In longitudinal analyses, the hippocampi showed the highest rate of atrophy over the 18-month
293 follow-up period in patients. Atrophy spread also extended to other medial temporal areas such as the
294 parahippocampal cortex, amygdala, fusiform and lingual gyri, the lateral temporal neocortex,
295 occipital regions and parietal areas (including lateral parietal gyri, bilateral angular gyri, bilateral

296 precuneus and posterior cingulate cortex), the basal ganglia (including the left putamen and
297 dorsomedial thalamic nucleus) and left middle frontal and anterior cingulate gyri. Hypometabolism
298 propagation predominated in the left middle temporal gyrus, posterior cingulate cortex and left
299 angular gyrus. β -amyloid deposition spread in the right inferior and middle frontal regions (Fig. 2).

300 **3.2 Topography of global and specific connectivity networks in healthy elders**

301 The brain areas showing the highest values of global functional connectivity (corresponding to hubs)
302 were mainly located within the dorso-medial prefrontal cortex, left middle temporal gyrus, posterior
303 cingulate cortex / precuneus, and the temporal-parietal cortex (angular / supramarginal gyri) (Fig.
304 3A).

305 The brain regions with the strongest specific functional connectivity with the epicenter of atrophy
306 (the left hippocampus) encompassed the bilateral medial temporal cortex (including the left
307 hippocampus, right hippocampus, bilateral parahippocampi, amygdala and fusiform cortex), middle
308 temporal gyrus, ventral posterior cingulate cortex, rectus gyrus and frontal pole (Fig. 3B).

309 The brain regions with the strongest specific functional connectivity with the epicenter of
310 hypometabolism (the left angular gyrus) included bilateral posterior medial and lateral parietal areas,
311 and the inferior frontal, precentral and inferior temporal cortex (Fig. 3C).

312 The brain regions with the strongest specific functional connectivity with the epicenter of $A\beta$
313 deposition (the right inferior frontal gyrus) included the bilateral inferior frontal, middle and inferior
314 temporal and angular cortex (Fig. 3D).

315 **3.3 Correlations between connectivity in healthy elders and disruptions in patients**

316 Baseline atrophy and its propagation positively correlated with atrophy specific connectivity, and
317 baseline atrophy also tended to negatively correlate with global connectivity. Multiple and stepwise
318 regression analyses showed that specific connectivity was the strongest predictor for baseline atrophy
319 and its propagation. Global connectivity provided an additional contribution to the model for baseline
320 atrophy with regions of highest global connectivity being less atrophied (Table 2, top panel).

321 Baseline hypometabolism and its propagation positively correlated with global connectivity, and
322 baseline hypometabolism also tended to positively correlate with hypometabolism specific
323 connectivity. Multiple and stepwise regression analyses revealed that, for baseline hypometabolism,
324 global connectivity was the strongest predictor and specific connectivity provided an additional
325 contribution to the model, while hypometabolism propagation was only predicted by global
326 connectivity (Table 2, middle panel).

327 Baseline β -amyloid deposition positively correlated with both global and specific connectivity while
328 no correlation was found for β -amyloid propagation. Multiple and stepwise regression analyses
329 revealed that both predictors independently contributed to the model with specific connectivity being
330 the strongest predictor and global connectivity providing an additional contribution (Table 2, bottom
331 panel).

332 **4 Discussion**

333 Here we highlighted that hubs, defined as regions showing high level of global connectivity in
334 healthy elders, were particularly sensitive to hypometabolism and β -amyloid deposition at baseline
335 and hypometabolism propagation. Moreover, we showed that global connectivity was a better
336 predictor of hypometabolism alterations than specific connectivity. These results support the

361 findings suggest that the topography reflects both the preferential involvement of hubs and the fact
362 that β -amyloid lesions contaminate functionally connected areas. Note that we did not find β -amyloid
363 propagation to be predicted by neither global nor specific connectivity. This might reflect the fact
364 that only β -amyloid-positive patients with high level of baseline β -amyloid deposition were enrolled
365 in our study and the rate of β -amyloid accumulation in most of these patients might be close to
366 plateau (Villemagne *et al.*, 2011; Villain *et al.*, 2012). This is consistent with the fact the longitudinal
367 changes in β -amyloid deposition were found to be less significant than those observed for atrophy or
368 hypometabolism (Fig. 2).

369 Contrastingly, we found that atrophy topography and propagation were better predicted by specific,
370 instead of global, connectivity. This finding supports the transneuronal propagation hypothesis
371 according to which Alzheimer's disease pathology would start in an epicenter region (here the left
372 hippocampus) from which it would then spread neurons-to-neurons through prion-like mechanism
373 (Seeley *et al.* 2009; Zhou *et al.* 2012). This transneuronal propagation process has been especially
374 demonstrated for intra-neuronal tau-rich aggregates that spread from one region to the other in a very
375 stereotyped manner following neuroanatomy connections (Braak and Braak, 1991; Duyckaerts *et al.*,
376 1998; Braak and Del Tredici, 2011; de Calignon *et al.*, 2012; Ahmed *et al.*, 2014). Histopathological
377 studies have shown for instance that Alzheimer's disease-related tau pathology would begin within
378 the locus coeruleus and then spread to the transentorhinal region, which receives axonal projections
379 from the locus coeruleus (Braak and Del Tredici, 2011; Duyckaerts, 2013). We think that, in the
380 context of Alzheimer's disease (which we increased the probability in our sample as only β -amyloid
381 positive patients were included), atrophy mainly reflects tau pathology (Whitwell *et al.* 2008). Thus,
382 atrophy propagation can reflect tau propagation which would be rather linked to synaptic
383 connectivity via network-dependent spread than global functional connectivity reflected in hubs.
384 Note that, in addition to specific connectivity, we found atrophy topography to be also negatively

337 hypothesis of higher vulnerability of hubs according to which Alzheimer's disease pathology would
338 preferentially occurs or accumulates in brain areas with high level of neuronal and metabolic activity,
339 i.e. highly connected network hubs (Drzezga *et al.* 2011). These network hubs typically involve
340 multimodal brain regions including components of the default mode network and the cognitive
341 control system such as the medial frontal and parietal areas and temporo-parietal regions (Buckner *et*
342 *al.*, 2009; Cole *et al.*, 2010; Tomasi and Volkow, 2011; Jagust and Mormino, 2012). The higher
343 vulnerability of hubs might reflect the fact that protracted exposure to upregulation of cellular
344 activity throughout life would cause or contribute to pathologies later in life (Buckner *et al.*, 2009;
345 Jagust and Mormino, 2012; Vlassenko and Raichle, 2015). It has been proposed for instance that the
346 glyceraldehyde-3-phosphate dehydrogenase (GAPDH), a key enzyme of glycolysis, would promote β -
347 amyloid aggregation (Itakura *et al.* 2015), or that excessive neuronal activity would increase the
348 production of β -amyloid from the amyloid precursor protein (Cirrito *et al.* 2005). Alternatively, it is
349 also possible that brain disorders that are associated with metabolic distress will selectively manifest
350 network abnormalities in high-cost components such as hubs (Bullmore and Sporns, 2012). In other
351 words, driven by economical load, Alzheimer's disease pathology would attack the most expensive
352 (hub) nodes of a brain network. Here we showed that hypometabolism (at baseline and over time)
353 and β -amyloid deposition (at baseline), but not atrophy, seem to follow this rule of affecting
354 predominantly the most expensive (metabolically active and functionally connected) brain regions.

355 Both hypometabolism and β -amyloid deposition at baseline were also predicted by their respective
356 specific connectivity, suggesting that, in addition to hub vulnerability, the topography of these
357 processes is also influenced by their specific functional connectivity to the epicenter. This is in line
358 with the idea that hypometabolism not only reflects alterations but might also result from
359 disconnection processes, i.e. occurs as a reflect of alterations in connected brain regions (Villain *et*
360 *al.*, 2008, 2010a; Choo *et al.*, 2010; Teipel and Grothe, 2016). As for β -amyloid deposition, our

385 predicted by global connectivity suggesting that regions with low global connectivity are more
386 vulnerable to AD-related atrophy than hubs. This is the first study to report such a negative
387 relationship between atrophy and hubs, which might reflect the fact that this relationship is only
388 evidenced when taking both specific and global connectivity into account, and/or that no previous
389 study investigated the relationships between atrophy and global functional connectivity throughout
390 all putative functional areas. Pending replication, this finding has important implication as it indicates
391 that tau pathology accumulation is driven by different factors compared to hypometabolism and β -
392 amyloid deposition that showed an inverse (positive) relationship to global functional connectivity.

393 Several brain regions, mainly within the ventral posterior cingulate, medial frontal, angular and
394 inferior temporal cortex are included in both global and specific connectivity networks. Interestingly,
395 these regions were also those showing the most important rates of change, i.e. the inferior temporal,
396 angular and posterior cingulate cortex for atrophy and posterior cingulate cortex for hypometabolism.
397 We think that, given their pivotal position at the crossroad between the specific and global
398 connectivity networks, the involvement of these brain regions represents a critical step in the
399 evolution of the disease. They might represent convergent points between AD lesions (e.g. tau and β -
400 amyloid), promoting their synergistic deleterious effects (Gotz *et al.* 2004; Mormino *et al.* 2009;
401 Ittner and Götz 2011; Chételat and Fouquet 2013; Wirth *et al.* 2013; Villeneuve *et al.*, 2015). This
402 amplification process might thus reflect the facts that i) tau and β -amyloid lesions are thought to
403 interact to promote the pathological process either via dual pathways (Small and Duff, 2008) and/or
404 via synergistic effect (Rhein *et al.* 2009); and/or ii) the propagation of lesions is heightened once they
405 reach these crossroad regions as they are major hubs characterized by particularly dense
406 interconnection and rich-club organization (van den Heuvel and Sporns, 2013).

407 Here we studied the relative impact of what we called specific and global connectivity on different
408 neuroimaging modalities supposed to reflect different pathological processes of the disease. This is a

409 first step through an overall understanding of the pathology propagation processes. Complementary
410 approaches to assess specific and global connectivity could be explored, other potential determinants
411 of lesion topography and spread could be tested (e.g. Euclidian distance, structural connectivity, etc.),
412 and other neuroimaging markers (such as tau-PET imaging) could be used. Further studies are thus
413 needed so that we get a more complete understanding of the main determinants of the lesions and
414 their propagation rules that would help to develop therapeutic strategies.

415 **Table 1: Demographic information of healthy elders and patients**

	Healthy elders	Patients	p-value
Ratio F/M	26/16	17/18	$\chi^2(1)$ 0.5
Age (SD)	69.6 (6.1)	71.2 (9.5)	0.37
Education (SD)	12.8 (3.9)	10.9 (3.7)	0.03
MMSE (SD)	29.1 (1.9)	24 (3.6)	$p < 0.001$

416 F /M = Female/Male; MMSE = Mini-Mental State Examination; SD = Standard Deviation

417

418 **Table 2: Regression analyses between global or specific connectivity and AD baseline**
 419 **disruptions and their propagation.**

	Simple regressions		Multiple regressions		Stepwise regression	
	Global connectivity	Specific connectivity	Global connectivity	Specific connectivity		
Baseline atrophy	$p = 0.016$	$p = 0.007$	$p = 0.006$	$p = 0.003$	1 Specific connectivity	$p = 0.0027$ $b = 0.192$
	$r = -0.157$	$r = 0.175$	$b = -0.175$	$b = 0.192$	2 Global connectivity	$p = 0.0062$ $b = -0.175$
Atrophy propagation	NS	$p < 0.0001$ $r = 0.256$	NS	$p < 0.0001$ $b = 0.255$	1 Specific connectivity	$p < 0.0001$ $b = 0.256$
Baseline hypometabolism	$p = 0.001$	$p = 0.011$	$p = 0.0001$	$p = 0.0014$	1 Global connectivity	$p = 0.0001$ $b = 0.245$
	$r = 0.211$	$r = 0.165$	$b = 0.245$	$b = 0.205$	2 Specific connectivity	$p = 0.001$ $b = 0.205$
Hypometabolism propagation	$p = 0.0003$ $r = 0.234$	NS	$p = 0.0003$ $b = 0.236$	NS	1 Global connectivity	$p = 0.0003$ $b = 0.234$
Baseline β amyloid deposition	$p = 0.0009$	$p < 0.0001$	$p = 0.0028$	$p < 0.0001$	1 Specific connectivity	$p < 0.0001$ $b = 0.413$
	$r = 0.213$	$r = 0.429$	$b = 0.175$	$b = 0.413$	2 Global connectivity	$p = 0.0025$ $b = 0.175$
β-amyloid propagation	NS	NS	NS	NS	—	

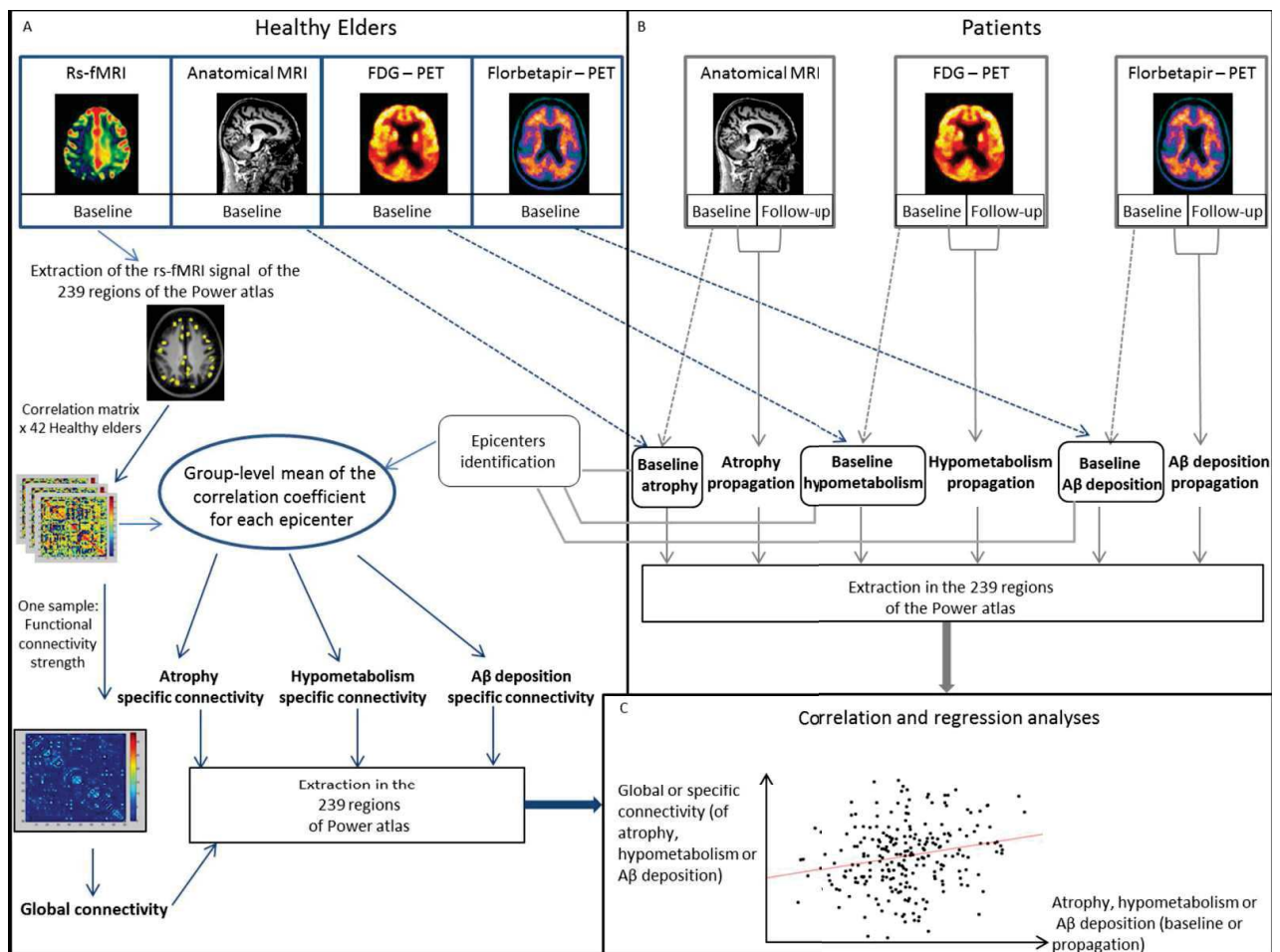
420 Bonferroni correction was applied to control for multiple comparisons, so that a threshold of
421 $p < 0.008$ ($0.05/6$) was required for results to be considered as significant (bold). NS: non-significant.

422 Trends are in *italic*

423

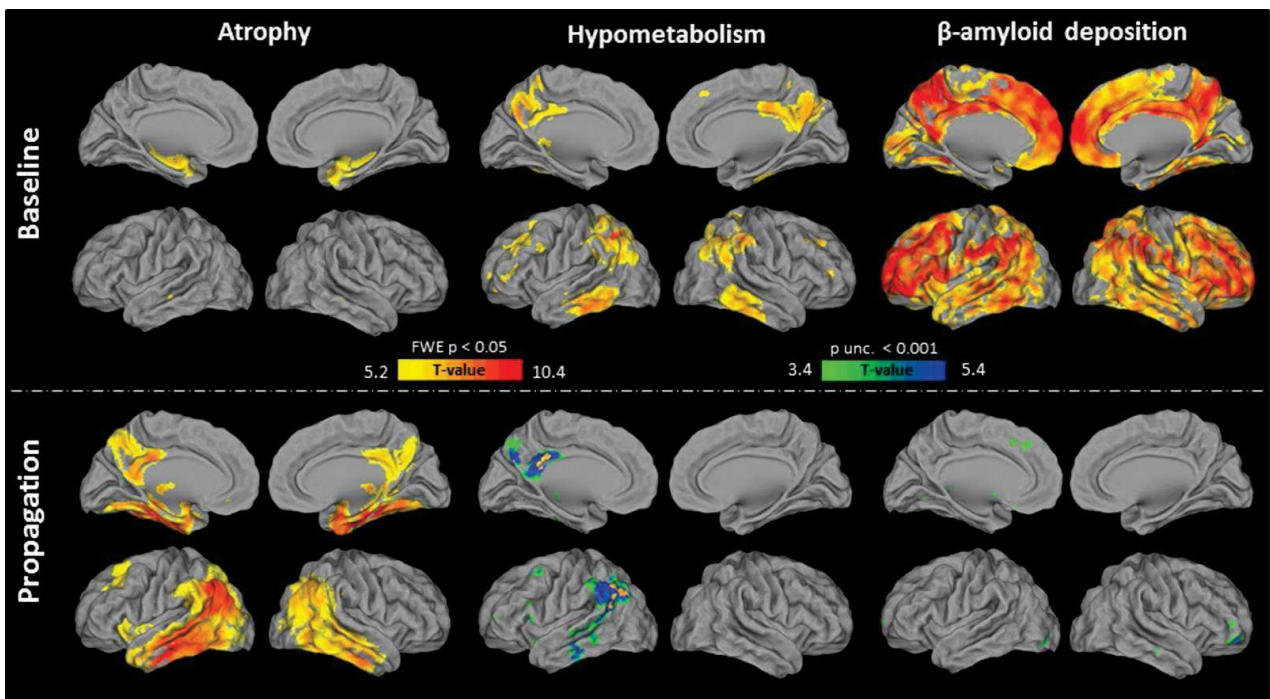
424 Figure legends

425



426 Figure 1: Overall schematic representation of data processing and analyses. Patients underwent
427 anatomical MRI, [18F]-fluorodeoxyglucose (FDG)-PET and florbetapir-PET at baseline and follow-
428 up (18 months later) to assess baseline and propagation of atrophy, hypometabolism and Aβ
429 deposition (B). The three regions of the Power atlas corresponding to the clusters showing the most

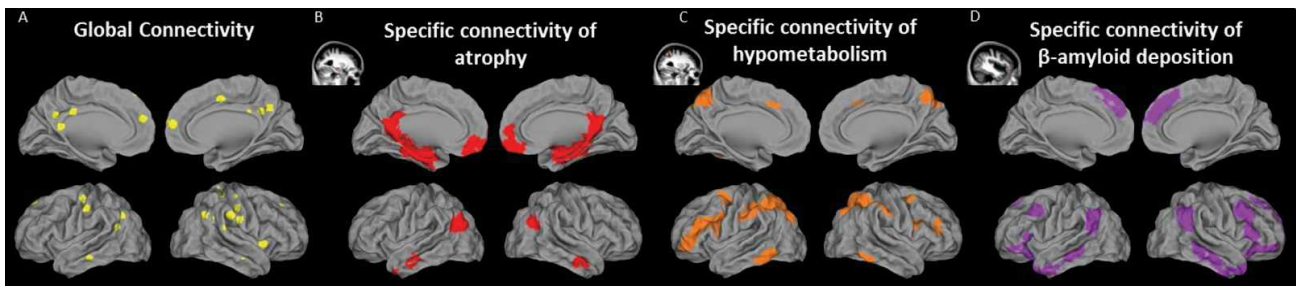
430 significant alteration at baseline (W-scores) were isolated as epicenters of atrophy, hypometabolism
 431 or β -amyloid ($A\beta$) deposition respectively, and the specific connectivity of these three regions was
 432 extracted from the correlation matrix performed in healthy elders (A). Healthy elders underwent
 433 anatomical MRI, FDG-PET and florbetapir-PET at baseline to assess baseline disruption in patients
 434 (W-scores) and resting-state functional MRI (rs-fMRI) from which global and specific functional
 435 connectivity were assessed. All data values were extracted in the 239 regions of the Power atlas.
 436 Correlation and stepwise regression analyses were carried out to assess the relationships between
 437 global or specific connectivity and baseline or propagation of atrophy, hypometabolism or $A\beta$
 438 deposition.



439
 440 Figure 2: Atrophy, hypometabolism and β -amyloid deposition at baseline (top line) and their
 441 propagation over the 18-month follow-up period (bottom line). Results are shown at family-wise
 442 error-corrected $p < 0.05$ and cluster extent $k > 50$ voxels (yellow-red scale bar) and

443 p (uncorrected) < 0.001 and cluster extent $k > 50$ voxels (blue-yellow scale bar) as well for
444 hypometabolism and β -amyloid propagation.

445



446

447 Figure 3: Global (A; yellow) and specific (B; red) functional connectivity of atrophy (B; red),
 448 hypometabolisms (C; orange) and β -amyloid deposition (D; purple) in healthy elders. For global
 449 connectivity, only the nodes with a Z-score value higher than 1, considered as the main network
 450 hubs, are displayed. To illustrate specific connectivity, the mean time course was extracted in the
 451 epicenter seed for each of the 42 healthy elders and positive correlations were assessed voxelwise
 452 between the mean time course in the seed and the time course of each gray matter voxel using
 453 SPM12. To remove potential sources of spurious variance, the time courses from the white matter,
 454 the cerebrospinal fluid, the whole brain, their derivatives, and the six movement parameters
 455 generated from realignment of head motion were introduced as covariates. A Fisher's z transform, as
 456 well as a 6.3 mm full-width at half-maximum Gaussian kernel smooth, were then applied to the
 457 individual connectivity maps, resulting in a final smoothness of 8 mm full-width at half-maximum. A
 458 group-level one sample t-test masked by the DARTEL gray matter-T2* mask was performed across
 459 the resulting functional connectivity maps of the 42 healthy elders. The SPM-T map resulting from
 460 this analysis was used to illustrate the regional values of specific functional connectivity. All results
 461 are presented at family-wise error-corrected $p < 0.05$ and cluster extent $k > 50$ voxels.

462

463 **5 Conflict of Interest**

464 The authors declare that the research was conducted in the absence of any commercial or financial
465 relationships that could be construed as a potential conflict of interest.

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5. Discussion générale

Cette thèse visait à apporter une meilleure compréhension des liens entre la connectivité fonctionnelle et la topographie et la propagation des atteintes cérébrales survenant dans la MA que sont l'atrophie, l'hypométabolisme et les dépôts A β . Dans cette optique, deux études ont été menées à l'aide de techniques de neuroimagerie multimodale transversales ou longitudinales alliant l'IRMf au repos, l'IRM structurale et la TEP marquée au FDG et au florbetapir. Dans un premier temps, nous nous sommes intéressés à caractériser les atteintes structurales, fonctionnelles et métaboliques au sein de deux sous-réseaux du CCP dans le MCI et la MA. Dans un second temps, nous avons évalué l'influence de la connectivité fonctionnelle sur la topographie et la propagation des lésions en distinguant la connectivité spécifique d'une région initialement atteinte (en atrophie, hypométabolisme ou dépôts A β) de la connectivité globale qui reflète la connectivité d'une région avec le reste du cerveau. Après un bref rappel des études menées dans cette thèse, nous confronterons les résultats de manière plus intégrée puis nous terminerons par l'évocation des perspectives qui découlent de ces travaux.

5.1. Vers une meilleure compréhension de la topographie et de la propagation des atteintes cérébrales dans la MA

La première étude visait à mieux caractériser les atteintes survenant dans deux réseaux fonctionnels du CCP, qui est une région clé dans la MA. En effet, cette région présente une vulnérabilité particulière à la MA qui se traduit par un hypométabolisme précoce mais aussi par des atteintes de sa connectivité fonctionnelle au repos. En se basant sur des arguments structuraux, métaboliques et fonctionnels, nous avons étudié le CCP en deux sous-parties ventrale et dorsale à partir desquelles nous avons identifié deux réseaux fonctionnels distincts. Le réseau ventral du CCP était constitué des régions pariéto-occipitales et temporales médianes tandis que le réseau dorsal du CCP comprenait principalement des régions frontales et latérales. L'étude de ces deux réseaux dans la pathologie a montré une plus grande vulnérabilité du réseau ventral dès le stade de MCI en connectivité fonctionnelle et en atrophie, atteintes qui s'étendaient à davantage de régions dans le stade de MA. Le réseau dorsal semblait être préservé chez les MCI et ne présentait une diminution de la connectivité fonctionnelle et une atrophie que chez les patients MA. L'hypométabolisme était quant à lui présent dans les deux réseaux et ce dès le stade MCI. Cette étude suggère ainsi que les mécanismes sous-jacents à l'hypométabolisme diffèrent de ceux de l'atrophie

et de la connectivité fonctionnelle. De plus, le fait que la diminution de connectivité fonctionnelle et l'atrophie ne concernent que le réseau ventral chez les MCI et que ces atteintes soient présentes dans les réseaux ventral et dorsal chez les MA peut laisser penser à l'existence d'une dynamique spatio-temporelle de la propagation de ces lésions. Cependant, cette première étude ne peut que suggérer la propagation des lésions au sein de ces deux réseaux mais en aucun cas l'affirmer du fait de sa nature transversale.

Notre deuxième étude, qui s'est appuyée sur un suivi longitudinal de 18 mois, a justement amélioré la compréhension des liens entre la connectivité fonctionnelle et l'apparition et la propagation des lésions dans la MA. Ces travaux nous ont permis d'évaluer l'influence de deux types de connectivité fonctionnelle sur la topographie et la propagation de l'atrophie, l'hypométabolisme, et les dépôts A β . Le premier type de connectivité est représenté par la connectivité globale, c'est-à-dire la connectivité de chaque région avec le reste du cerveau et dont les valeurs les plus fortes sont considérées comme des hubs. Le second type est la connectivité spécifique de l'épicentre, qui est défini comme étant la région la plus atteinte initialement par l'atrophie, l'hypométabolisme ou les dépôts A β . Ainsi, au sein de notre population, nous avons identifié les épicentres de l'atrophie, de l'hypométabolisme et des dépôts A β respectivement au niveau de l'hippocampe gauche, du gyrus angulaire gauche et du gyrus frontal droit. Cette étude a montré d'une part, que la topographie et la propagation de l'atrophie se ferait préférentiellement par la connectivité fonctionnelle spécifique de l'hippocampe et la corrélation négative entre la topographie de l'atrophie et la connectivité globale suggère que l'apparition de l'atrophie se ferait dans des régions à faible connectivité globale. D'autre part, les résultats ont mis en évidence que les topographies de l'hypométabolisme et des dépôts A β étaient corrélées à la fois à la connectivité spécifique et à la connectivité globale et que la propagation de l'hypométabolisme était seulement prédite par la connectivité globale. Cette étude a ainsi mis en évidence que l'atrophie apparaissait et se propagerait selon la connectivité spécifique de la région la plus atrophiée initialement, tandis que l'hypométabolisme et les dépôts A β cibleraient davantage les régions hubs. Ces résultats suggèrent donc qu'en fonction du biomarqueur considéré, les règles de propagation diffèrent, avec une implication différentielle de la connectivité globale *versus* spécifique.

5.2. Les biomarqueurs en imagerie de la MA suivent des règles de propagation différentes

La première étude a révélé une topographie distincte de l'atrophie et des perturbations de la connectivité fonctionnelle d'un côté et de l'hypométabolisme de l'autre côté. En effet, les MCI présentaient une atrophie et une diminution de la connectivité fonctionnelle dans le réseau ventral du CCP, principalement au niveau des hippocampes bilatéraux, alors que l'hypométabolisme concernait les réseaux ventral et dorsal du CCP. Les patients MA montraient quant à eux des atteintes dans les deux réseaux de la connectivité fonctionnelle, l'atrophie et de l'hypométabolisme. Ces résultats suggèrent donc que les mécanismes sous-jacents à ces lésions seraient distincts et auraient pour conséquence de guider la topographie et la propagation différemment en fonction des caractéristiques fonctionnelles des régions cérébrales. La première supposition peut être étayée par le fait que la connectivité fonctionnelle et l'atrophie seraient le reflet de la mort neuronale et synaptique causées notamment par la propagation des lésions tau du site de l'atteinte initiale (le lobe temporal interne qui contient l'hippocampe) vers les régions auxquelles il est le plus connecté, situées au sein du réseau ventral (Buée et Delacourte, 2006). En effet, des études ont montré que l'atrophie hippocampique mesurée en IRMa serait liée à la quantité des DNF évaluée par des analyses immuno-histologiques *post-mortem* (Burton et al., 2009; Csernansky et al., 2004; Silbert et al., 2003; Whitwell et al., 2008) suggérant ainsi que l'atrophie hippocampique serait le reflet des pertes neuronales et synaptiques causées par les DNF (Fukutani et al., 2000; Whitwell et al., 2012). De plus, la partie ventrale du CCP contient davantage de neurones pyramidaux que la partie dorsale du CCP (Vogt et al., 2006) et les neurones pyramidaux hippocampiques, notamment localisés au niveau de CA1 sont particulièrement sensibles à la pathologie tau (Buée et Delacourte, 2006). Ceci pourrait donc expliquer la vulnérabilité plus précoce du réseau ventral en atrophie et en connectivité fonctionnelle comparée au réseau dorsal du CCP. L'hypométabolisme quant à lui, serait sous-tendu par des mécanismes différents de ceux de la connectivité fonctionnelle et de l'atrophie et pourrait ainsi refléter à la fois des altérations locales et à distance (La Joie et al., 2012). En effet, la présence de l'hypométabolisme au sein des deux réseaux du CCP dans les stades MCI et MA est en accord avec l'idée que l'hypométabolisme reflète également le phénomène de diaschisis. Ainsi, l'hypométabolisme serait en partie causé par la déconnexion progressive entre l'hippocampe atrophié (appartenant au réseau ventral) et le

CCP, via le cingulum et le faisceau unciné notamment (Chételat et al., 2009; Fouquet et al., 2009; Villain et al., 2008, 2010; Yakushev et al., 2011). Aussi, il a été montré qu'au stade préclinique de la MA, l'hypométabolisme du CCP reflèterait les altérations à distance dont l'atrophie hippocampique que nous avons mentionnée précédemment. Cependant, à un stade plus avancé, l'hypométabolisme du CCP ferait davantage écho aux altérations locales d'atrophie et de la pathologie amyloïde notamment du fait de la diminution de la connectivité entre l'hippocampe et le CCP (Teipel et Grothe, 2016). Ainsi, au stade de MCI, l'hypométabolisme du réseau ventral et du réseau dorsal du CCP traduirait surtout les altérations à distance de l'atrophie hippocampique. Au stade de MA, l'hypométabolisme ayant atteint presque l'intégralité des 2 réseaux, serait davantage le reflet des atteintes locales en atrophie qui, comme nous l'avons vu, concernait à ce stade les deux réseaux. La deuxième supposition qui découle de ces travaux est que les différences de topographie entre l'atrophie, la connectivité fonctionnelle et l'hypométabolisme dans le MCI et la MA suggèrent que ces lésions ne se propageraient pas de la même manière.

Des travaux récents ont montré que la connectivité fonctionnelle pourrait avoir une influence sur la propagation des lésions dans la MA. D'une part, Seeley et al., (2009) ont mis en évidence que les profils d'atrophie de 5 maladies neurodégénératives différentes (MA, démence fronto-temporale (DFT) comportementale, démence sémantique (DS), aphasia primaire progressive non fluente et dégénérescence cortico-basale) correspondaient chacun à un réseau fonctionnel spécifique identifié chez des individus sains. Cette observation a abouti à l'hypothèse d'une propagation transneuronal des lésions de la MA, qui s'effectuerait de manière analogue à la propagation des lésions survenant dans les maladies à prions. D'autre part, la connectivité fonctionnelle pourrait exercer un autre type d'influence sur la topographie et la propagation des lésions dans la MA. En effet, les réseaux fonctionnels cérébraux sont organisés de sorte à optimiser l'intégration des informations tout en minimisant le coût énergétique nécessaire à cette communication efficace (Bullmore et Sporns, 2012). Ainsi, les régions hubs, qui présentent une forte connectivité globale, jouent un rôle central dans la communication avec les autres régions et sont donc continuellement très sollicitées. Il a été mis en évidence que la pathologie de la MA apparaissait préférentiellement dans les régions hubs car ces régions présentent des niveaux d'activité neuronale et métabolique élevés tout au long de la vie (Drzezga et al., 2011) qui

pourraient causer ou du moins contribuer à l'apparition de pathologies (Buckner et al., 2009; Jagust et Mormino, 2012; Vlassenko et Raichle, 2015). L'accumulation amyloïde dans ces régions pourrait être favorisée par un excès de l'activité neuronale (Cirrito et al., 2005) ou de la GAPDH (Glyceraldehyde-3-Phosphate Deshydrogénase) qui est une enzyme de la glycolyse permettant le métabolisme du glucose mais également impliquée dans l'agrégation de la protéine amyloïde (Itakura et al., 2015). Une autre explication possible à la vulnérabilité des régions hubs serait qu'en condition non-pathologique, ces régions sont de fortes consommatrices d'énergie et lorsque la pathologie de la MA survient et conduit à la diminution du métabolisme du glucose, les régions les plus sévèrement touchées par cette réduction sont les régions hubs (Bullmore et Sporns, 2012). En effet, en raison d'une diminution du métabolisme, la pathologie de la MA ciblerait, au sein des réseaux cérébraux, les régions les plus coûteuses d'un point de vue énergétique.

En somme, la connectivité globale et la connectivité spécifique pourraient donc influencer la topographie et la propagation des lésions de la MA différemment. Nos travaux menés dans la deuxième étude de cette thèse ont confirmé que la topographie et la propagation de l'atrophie étaient plus importantes dans les régions les plus connectées fonctionnellement à l'hippocampe, région initialement la plus atrophiée. Ainsi, la propagation de l'atrophie se ferait bien selon l'hypothèse de la neurodégénérescence transneuronale. Comme nous l'avons vu précédemment, l'atrophie mesurée en IRM anatomique reflète notamment la pathologie tau et les DNF. Or, des travaux ont montré que la protéine tau, tout comme la protéine A β , partageraient des propriétés relatives à leur transmission d'une région à une autre communes à celles des protéines à prions dont la propagation transneuronale a été mise en évidence (Alonso et al., 2016; Eisele et Duyckaerts, 2016; Frost et Diamond, 2009a; Goedert et al., 2010). Outre le fait que nous ayons confirmé la vulnérabilité préférentielle des régions les plus connectées à la région initialement atrophiée, nous avons également observé une relation négative entre la topographie de l'atrophie et la connectivité globale. Ce dernier constat suggère que l'atrophie (et donc en partie les DNF) aurait tendance à être plus importante dans les régions peu connectées, et moins importante dans les régions à forte connectivité globale, *i.e.* les hubs. Cette caractéristique des hubs n'a, à notre connaissance, jamais été rapportée dans la littérature. Nos travaux ont également montré que la topographie de l'accumulation de la protéine A β était encore plus fortement

influencée par la connectivité fonctionnelle de la région la plus chargée en dépôts A β initialement que par la connectivité globale. Ce résultat rejoint les hypothèses d'accumulation de la protéine A β selon le même mécanisme que les protéines à prions cité ci-dessus. La propagation de la protéine A β n'a pas été retrouvée comme étant liée à la connectivité fonctionnelle ou globale. Ceci peut s'expliquer par le fait que l'accumulation de la protéine A β est un processus très lent, dont la progression ralentit fortement dans les stades les plus tardifs de la MA (Villain et al., 2012; Villemagne et al., 2011). Seuls des patients A β -positifs ont été inclus dans nos analyses et ont en effet montré un taux de changement de l'accumulation de la protéine A β en 18 mois beaucoup plus faible que ceux de l'atrophie ou de l'hypométabolisme. Concernant la propagation de l'hypométabolisme, nos résultats ont clairement montré qu'elle était exclusivement influencée par la connectivité globale. Ceci souligne la plus forte propension des hubs à être hypométaboliques et rejoint l'hypothèse que la MA aurait de plus fortes répercussions sur les régions coûteuses énergétiquement (Bullmore et Sporns, 2012).

Ainsi, différentes règles de propagation des lésions régissent la progression de la MA avec d'un côté une influence majeure de la connectivité fonctionnelle spécifique sur la topographie et la propagation de l'atrophie et d'un autre côté une forte influence de la connectivité globale sur la topographie des dépôts amyloïdes et de l'hypométabolisme ainsi que sur la propagation de l'hypométabolisme.

5.3. Le CCP, une région clé de la propagation des lésions dans la MA ?

L'atteinte du réseau dorsal en connectivité fonctionnelle et en atrophie, n'apparaissant qu'au stade de MA, suggère que les altérations présentes dans le réseau ventral du CCP se propageraient au réseau dorsal de manière concomitante à la progression de la maladie. Les parties ventrale et dorsale du CCP, bien que différentes sur plusieurs aspects (fonctionnel, cytoarchitectonique), appartiennent à la même structure et entretiennent de fortes connexions (Parvizi et al., 2006). Ainsi, nous supposons que l'atrophie initialement confinée au sein du réseau ventral, pourrait se propager au réseau dorsal par l'intermédiaire des connexions entre les parties ventrale et dorsale du CCP. Le fait que le réseau dorsal ne soit atteint en atrophie et connectivité fonctionnelle qu'au stade de MA nous laisse supposer que la propagation de ces atteintes au réseau dorsal pourrait signer le passage à la démence.

Ainsi, l'hypothèse de la propagation des lésions d'un réseau à l'autre *via* le CCP chez les patients MA suggère que le CCP jouerait un rôle clé dans la progression de la MA.

De plus, la deuxième étude a montré que les lésions apparaissaient et se propageaient dans des régions spécifiques en fonction des propriétés de connectivité fonctionnelle de ces dernières. Les régions hubs ont ainsi été identifiées comme étant plus vulnérables à l'hypométabolisme et aux dépôts A β qu'à l'atrophie. Cependant, avec l'avancée de la maladie, ces régions sont également touchées par l'atrophie, probablement sous l'influence de la connectivité spécifique. Nous pouvons supposer que leur atteinte marquerait alors l'amplification de la propagation des lésions car les hubs ont la particularité d'être très fortement connectés entre eux avec une organisation en « *rich-club* » (van den Heuvel et Sporns, 2013). Les hubs sont en effet, de par leur nature, très fortement connectés avec un ensemble de régions et ils entretiennent également une communication privilégiée entre eux. Ceci pourrait suggérer qu'une fois les hubs atteints, la propagation de la pathologie serait amplifiée par l'intermédiaire de toutes ces connexions. Le fait que la connectivité globale et la connectivité spécifique influencent la propagation des lésions peut laisser à penser que les régions qui présentent à la fois une forte connectivité globale (hub) mais également une forte connectivité spécifique pourraient être impliquées dans l'amplification de la propagation des lésions. Nous avons ainsi, dans le cadre de notre deuxième étude, identifié quelques régions aux fortes connectivités globale et spécifique, dont nous pouvons citer le cortex angulaire mais également la partie ventrale du CCP (Figure 19). En étant le point de convergence entre ces deux types de connectivité fonctionnelle, le CCP pourrait donc être une région clé dans la propagation des lésions de la MA. En effet, comme il présente une forte connectivité spécifique, il serait donc préférentiellement atteint par l'atrophie qui reflète la pathologie tau. De plus, sa valeur élevée de connectivité globale le rendrait plus vulnérable aux dépôts A β . Ainsi, nous pouvons supposer que l'influence concomitante de la connectivité spécifique et de la connectivité globale sur le CCP sous-tendrait le fait que cette région soit le point de rencontre entre les pathologies tau et amyloïde. Il a été mis en évidence que les pathologies tau et amyloïde pouvaient interagir en synergie et amplifier les processus délétères dans la MA (Chételat et Fouquet, 2013; Gotz et al., 2004; Ittner et Götz, 2011; Mormino et al., 2009; Villeneuve et al., 2015; Wirth et al., 2013). Le CCP jouerait donc un rôle majeur dans l'amplification de la propagation des lésions

dans la MA en étant situé à la fois à l'interface entre les réseaux ventral et dorsal et en étant le point de convergence de la connectivité spécifique et de la connectivité globale.

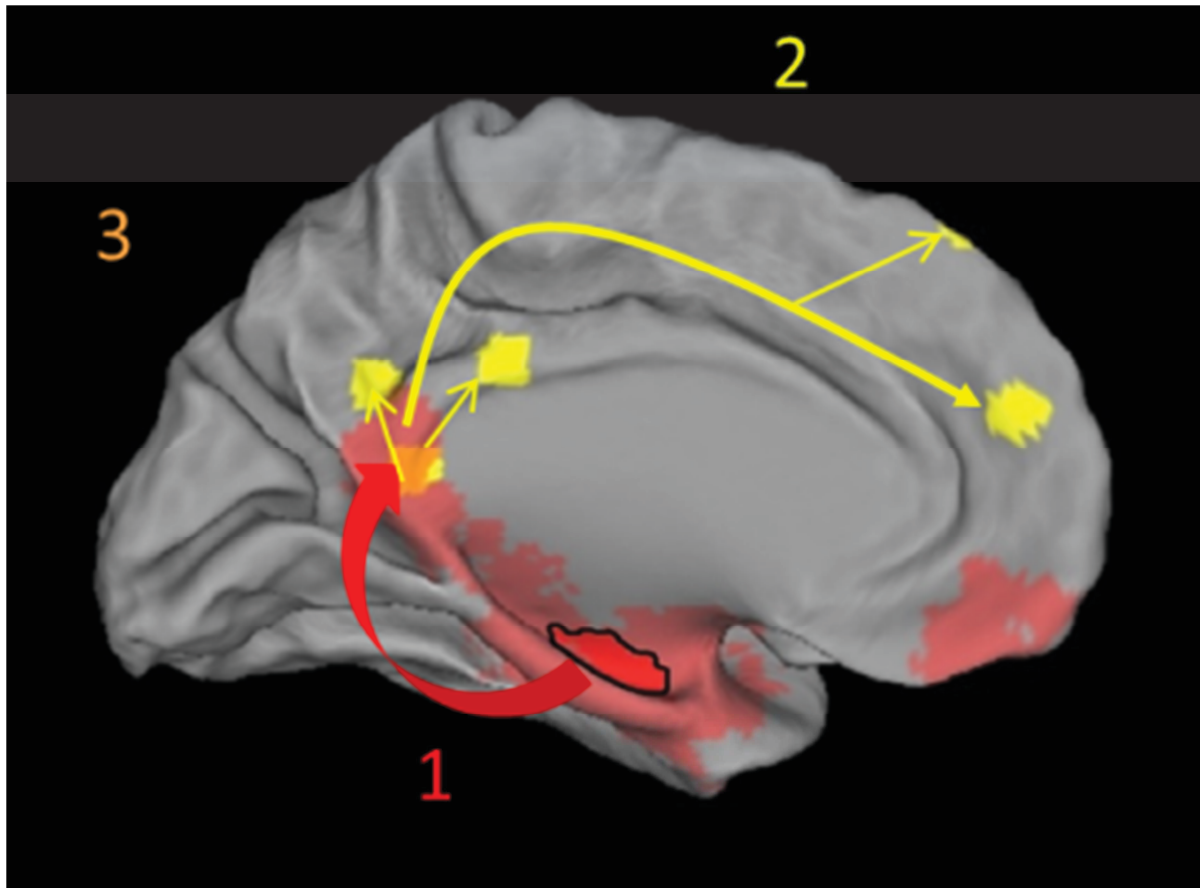


Figure 19 : Schéma de synthèse. L'atrophie s'accumule au niveau de l'épicentre (hippocampe gauche encadré en noir) et se propage via la connectivité spécifique (flèche rouge) au sein du réseau de l'épicentre (en rouge pâle) qui présente de fortes similitudes avec le réseau du CCP ventral (1). Parallèlement, les dépôts amyloïdes et l'hypométabolisme s'accumulent dans les régions hubs (en jaune) et l'hypométabolisme progresse via la connectivité globale (2). Le CCP (orange) est une région avec à la fois une forte connectivité spécifique de l'atrophie et globale ce qui suggère son implication dans l'amplification de la propagation de la pathologie. Cette supposition est renforcée par la haute valeur prédictive de son hypométabolisme initial dans la vitesse de propagation de l'atrophie (3).

5.4. Limites et perspectives

Au cours de cette thèse, nous avons pu étudier les liens entre la connectivité fonctionnelle au repos et l'atrophie, l'hypométabolisme et les dépôts A β concernant leur topographie et leur propagation. Le taux de propagation de l'atrophie a été utilisé ici comme un reflet de la pathologie tau. Cependant, il serait intéressant d'évaluer la topographie et la propagation de la pathologie tau directement à l'aide de l'imagerie tau dont la mise au point est de plus en plus optimale. Nous pourrions ainsi mettre ses résultats en lien avec la topographie et la propagation des altérations structurales (atrophie), métaboliques (hypométabolisme), moléculaires (pathologie amyloïde) et fonctionnelles (troubles de la connectivité). Ceci

permettrait peut-être une meilleure mise en évidence des régions clés de l'amplification de la MA où plusieurs altérations sont présentes de manière simultanée.

D'après les résultats de notre première étude, nous avons supposé que l'atteinte du réseau dorsal en atrophie et en connectivité fonctionnelle pourrait correspondre à l'expression de la démence. Afin de vérifier cette hypothèse, nous avons tenté d'établir des liens entre les performances cognitives des patients et les atteintes cérébrales que nous avons mesurées dans les deux réseaux fonctionnels du CCP. Malheureusement, ces travaux ont conduit à des résultats inconsistants et n'ont donc pas été mentionnés dans le présent manuscrit. Cependant, nous aurions pu nous attendre à trouver des relations entre les atteintes cérébrales des réseaux du CCP et le déclin cognitif étant donné le rôle majeur que joue le CCP dans les processus d'introspection et de mémoire épisodique, en lien avec l'hippocampe, qui sont deux fonctions fortement altérées dans la MA.

De plus, cette thèse a tenté d'apporter quelques éléments de réponse quant à l'influence relative de la connectivité spécifique et de la connectivité fonctionnelle sur la topographie et la propagation des atteintes survenant dans la MA. Cependant, il serait intéressant d'évaluer, au-delà de la connectivité fonctionnelle, d'autres facteurs qui pourraient potentiellement prédire l'évolution de la propagation de l'atrophie, de l'hypométabolisme et des dépôts A β . En effet, la connectivité structurale pourrait influencer la propagation des lésions dans la MA, indépendamment de la connectivité fonctionnelle. Des études menées en imagerie en tenseur de diffusion (DTI) ont mis en évidence une altération des faisceaux de substance blanche dans la MA, qui pourrait notamment être à l'origine du phénomène de diaschisis (Yakushev et al., 2011). En outre, il a été montré que la connectivité structurale individuelle pourrait prédire l'évolution individuelle vers la démence (Shao et al., 2012) et aurait une influence sur la relation qu'entretiennent les différents biomarqueurs en imagerie dans la MA (Pandya et al., 2016). Enfin, un modèle mathématique, basé sur l'hypothèse de la neurodégénérescence transneuronal, a utilisé le connectome de sujets sains dérivé de la connectivité structurale pour prédire la propagation de l'atrophie et de l'hypométabolisme dans la MA (Raj et al., 2015). Ainsi, tous ces éléments nous laissent penser que la connectivité structurale pourrait elle aussi influencer la propagation des lésions dans la MA. Une perspective pourrait donc être d'évaluer la contribution de la connectivité structurale et fonctionnelle, mais aussi d'autres facteurs potentiels comme l'effet de proximité (distance euclidienne par exemple), sur la propagation des lésions.

Une autre perspective découle de ce travail et consisterait à améliorer les connaissances relatives à la prédiction de la vitesse de propagation des lésions. En effet, il a été mis en évidence que le taux de propagation de la pathologie est un bon indicateur de l'évolution clinique des patients (Fox et al., 1999; Jack et al., 2004; Risacher et al., 2010). Ceci confère donc une importance particulière à l'identification des facteurs qui pourraient accélérer la propagation des lésions dans la MA. Nos travaux ont soulevé l'existence de régions qui pourraient être responsables de l'amplification de la pathologie. De nombreuses études ont montré que la progression de la MA n'était pas linéaire et que certains patients progressaient plus rapidement que d'autres (Cerami et al., 2015; Jack et al., 2004; Sluimer et al., 2008). L'identification des facteurs pouvant accélérer la progression de la maladie constitue un enjeu majeur pour l'élaboration d'une stratégie thérapeutique efficace qui permettrait de stopper, ou du moins, de ralentir la progression de la pathologie.

En conclusion, cette thèse a mis en évidence que la topographie et la propagation de l'atrophie, de l'hypométabolisme et des dépôts amyloïdes étaient différemment influencées par la connectivité spécifique et la connectivité globale. De plus, nos travaux ont suggéré que l'amplification de la propagation des lésions pourrait se faire au travers de régions clés comme le CCP, qui se trouve être à l'interface de plusieurs réseaux fonctionnels et de la connectivité globale et spécifique.

6. Bibliographie

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7. Annexes

7.1. Collaborations à des études publiées dans des revues internationales

Fauvel *et al.* (2014)

Tomadesso *et al.*, (2015)

Perrotin *et al.*, (2016)

Branger *et al.*, (2016)

7.1.1. Fauvel *et al.*, (2014)



Musical practice and cognitive aging: two cross-sectional studies point to phonemic fluency as a potential candidate for a use-dependent adaptation

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Because of permanent use-dependent brain plasticity, all lifelong individuals' experiences are believed to influence the cognitive aging quality. In older individuals, both former and current musical practices have been associated with better verbal skills, visual memory, processing speed, and planning function. This work sought for an interaction between musical practice and cognitive aging by comparing musician and non-musician individuals for two lifetime periods (middle and late adulthood). Long-term memory, auditory-verbal short-term memory, processing speed, non-verbal reasoning, and verbal fluencies were assessed. In Study 1, measures of processing speed and auditory-verbal short-term memory were significantly better performed by musicians compared with controls, but both groups displayed the same age-related differences. For verbal fluencies, musicians scored higher than controls and displayed different age effects. In Study 2, we found that *lifetime period* at training onset (childhood vs. adulthood) was associated with phonemic, but not semantic, fluency performances (musicians who had started to practice in adulthood did not perform better on phonemic fluency than non-musicians). *Current frequency* of training did not account for musicians' scores on either of these two measures. These patterns of results are discussed by setting the hypothesis of a transformative effect of musical practice against a non-causal explanation.

Keywords: cognitive aging, brain reserve, musical practice, cognitive transfer, verbal functions

INTRODUCTION

Normal brain and cognitive aging are challenging to study, as advancing age is often associated with various pathologies that compromise cognition. However, there are accumulating evidences suggesting that, even in pathology-free conditions, normal aging is associated with changes in the neural basis of cognition (Hedden and Gabrieli, 2004; Kalpouzos et al., 2009). Cognitive functions are disproportionately impacted by aging, the earliest and most concerned are processing speed, working memory, spatial ability, reasoning, and long-term memory (Hedden and Gabrieli, 2004; Salthouse, 2010). By contrast, measures of semantic knowledge and verbal abilities are relatively stable across the lifespan (Park et al., 2002).

Studies have reported that the brain retains its dynamic properties in aging, with structural and functional rearrangements allowing for new learning and skills improvements (Draganski and May, 2008). It has been suggested that all lifelong environmental features and demands contribute to the establishment of a cognitive reserve, thereby partly counteracting the age-related cognitive decline (Foubert-Samier et al., 2010). Therefore, besides genetic dispositions, both former and current individuals'

experiences may influence the quality of cognitive aging (Hultsch et al., 1999; Wilson et al., 2005; Stern, 2012), raising hopes for therapeutic interventions and/or daily lifestyle recommendations (Green and Bavelier, 2008). Epidemiological works have shown that, in addition to education (Evans et al., 1993) and occupational activity (Adam et al., 2013), the degree of individuals' engagement in leisure activities covaries with cognitive functioning in old age (Wang et al., 2012). For instance, Christensen and Mackinnon (1993) found a positive statistical link between mental, social, and physical activities and the cognitive performances of a large sample of participants aged 70–89 years. Longitudinal studies have confirmed that practicing leisure activities in later life is linked to increases in cognitive reserve (Schooler and Mulatu, 2001).

Regarding musical practice, cross-sectional works in children and young adults have reported an association with better performances across a wide range of cognitive domains. Individuals who practice music in their spare time have been found to significantly outperform matched non-musicians on verbal memory (Chan et al., 1998; Brandler and Rammsayer, 2003; Ho et al., 2003; Franklin et al., 2008; Jakobson et al., 2008), vocabulary

(Forgeard et al., 2008), spatial ability (Brochard et al., 2004), non-verbal reasoning (Forgeard et al., 2008), short-term memory (Huntsinger and Jose, 1991; Tierney et al., 2008), and working memory (Franklin et al., 2008).

It has been hypothesized that music training has transformative effects on specific cognitive functions because they share mechanisms (e.g., auditory processes involved both in music and in language; Patel and Iversen, 2007; Fauvel et al., 2013; Dawson, 2014). Another claim is that music lessons, being scholar-like activities, instead of leading to specific cognitive improvements, result in a small general gain in Intelligent Quotient (IQ; Schellenberg, 2004), possibly through the potentiation of executive functions (Hannon and Trainor, 2007; Schellenberg and Peretz, 2008; but see Schellenberg, 2011).

However, environmental factors influencing human cognition are challenging to study as well, and previous positive results from quasi-experimental studies should be interpreted with caution regarding the direction of the causality (e.g., high-functioning people are more likely to take music lessons; Schellenberg, 2011). Moreover, a recent well-controlled (random assignment) longitudinal study observed that visual art or music preschool instruction did not influence children's cognitive development (Mehr et al., 2013).

In seeking for potential factors that could promote successful cognitive aging, cross-sectional studies have revealed that both past and recent musical training are associated with better cognitive performances in later life (Hanna-Pladdy and MacKay, 2011; Hanna-Pladdy and Gajewski, 2012). A study conducted in older musicians (60–83 years) with two levels of expertise (high activity (>10 years) vs. low activity (<10 years) found that they scored higher than non-musicians on the delayed recall of a geometric shape (visual long-term memory), a verbal naming task, and Parts A and B of the Trail Making Test (TMT A and B), which measures processing speed (Hanna-Pladdy and MacKay, 2011). Although the performances of the low-activity musicians were halfway between those of the controls and high-activity musicians, suggesting a causal explanation, the differences were not significant. Moreover, those musicians who were still actively engaged in music at the time of the study did not perform better than those who had ceased.

In another study (Hanna-Pladdy and Gajewski, 2012) where general lifestyle activities were controlled for, findings were replicated for visuospatial judgment, verbal memory, verbal working memory, planning functions (non-musicians made more rule violations in an executive function-related task), and phonemic fluency. Statistical analyses revealed that the musicians' visuospatial ability was predicted by recent musical engagement, whereas auditory-verbal memory seemed to be influenced by the early age of musical acquisition. The authors suggested that it could reflect differences in use-dependent adaptation periods depending on cognitive domain.

ISSUES

In their investigation of the association between musical practice and late-life cognition, already published works have focused on musicians who started their training around 10 years old, while quasi-experimentally manipulating the current engagement

(active vs. inactive), and by implication, the total duration of training (more or less than 10 years; Hanna-Pladdy and MacKay, 2011; Hanna-Pladdy and Gajewski, 2012). Therefore, the question of whether old musicians who started practicing music in adulthood also display better cognitive performances remains unanswered.

Moreover, any differences uncovered by comparing musicians and non-musicians at a single point in time are of a *quantitative* nature, and do not inform about the cognitive aging *quality* of these two populations (i.e., is musical practice associated with better performances in old age *and* weaker cognitive decline).

The first aim of the present work was to confirm that individuals practicing music since childhood display better cognitive performances than non-musicians. Then, we wanted to explore whether these two populations differ in terms of aging-related performances evolution. Finally, we looked at whether two different characteristics of practice (age at training onset and current frequency of training) account for older musicians.

Indeed, in the perspective that musical training influences the aging of cognitive abilities by stimulating them, we hypothesized that:

- (i) Some tests' results would be higher in musically-trained participants *and* display weaker age-related differences between middle-aged and older participants compared with non-musicians.
- (ii) For cognitive functions displaying this pattern, at least one of the two characteristics of musical practice (age at onset and/or current frequency of training) would be associated with the musicians' performances.

Therefore, in Study 1, we assessed several cognitive functions in middle-aged and older musicians (all having started in childhood), and compared their cognitive performances, together with the age-dependent differences, with those of middle-aged and older non-musicians (cf. **Figure 1**).

In Study 2, we wanted to explore whether two variables of practice (i.e., lifetime period at training onset and current frequency of training) could explain the older musicians' higher scores. We therefore included a sample of older individuals who had started music later in life (mean age at training onset = 42.7 years, $SD = 11$), and measured their cognitive performances on tests having revealed significant interactions in Study 1. In addition, we ran a correlation analysis between these test scores and all the older musicians' current frequency of training.

STUDY 1: MATERIALS AND METHODS

PARTICIPANTS

This study was made according to the ethical recommendations of Helsinki agreements for human researches and cognitive investigations. Sixty-eight individuals were included. All were informed about the study's details and gave their consent for participation.

Thirty-four were amateur musicians recruited from several French conservatories or music schools (no self-educated musicians were included). They were required to have an uninterrupted time of practice of at least 4 years at the time of the study, and for a frequency of training of more than 2 h a week during

the last 6 months. To make sure that the musicians had an “active” practice, rather than a routinized one, a further inclusion requirement was that they had to have learned at least two new music pieces in the course of the previous year. They played various musical instruments (piano, guitar, trumpet, etc.). Overall, the mean training duration was 38.12 years ($SD = 17.7$), with a mean age at training onset of 9.54 years ($SD = 4.14$), and a frequency of current training of 12.6 h per week ($SD = 10.7$) (cf. **Table 1**). This sample was divided into a middle-aged group (19 participants, mean age = 40.7 years, $SD = 9.6$, min = 21, max = 55) and an

older group (15 participants, mean age = 67.1 years, $SD = 5.2$, min = 60, max = 78).

The 34 control participants were recruited from the general population. This sample was also divided into a middle-aged group (14 participants, mean age = 38.86 years, $SD = 15.9$, min = 22, max = 55) and an older group (20 participants, mean age = 67 years, $SD = 4.4$, min = 60, max = 79) (cf. **Table 1**).

The cut-off ages (middle-aged ≤ 55 –60 \leq older) were chosen because of works showing that cognitive performances fall significantly below the mean of the general population at around this age (Salthouse, 2010).

All participants were given a semi-structured questionnaire that had been specially designed for the study in order to rate demographic data (gender, age, education, and occupation) (cf. **Table 1**). The stimulating quality of the participants’ occupations was rated as follows: a value of 1 was attributed for jobless individuals; 2 for manual workers; 3 for office workers, public-sector workers, tradespeople, and storekeepers; 4 for the self-employed, executive managers, and students; and 5 for physicians and company directors. The musicians were also asked to evaluate their age at training onset, and its average frequency for the last 6 months. Based on this questionnaire, the groups of participants were matched on gender, age, education, and occupational level. Moreover, middle-aged and older musician groups differed only marginally on age at training onset as well as frequency of practice (cf. **Table 1**).

NEUROPSYCHOLOGICAL ASSESSMENT

The neuropsychological assessment was made of 8 tests that are classically used in a clinical context (cf. **Table 2**). The entire test battery was administered in a single session which lasted about 90 min, and took place in a quiet room conducive to concentration. As the whole recruitment extended through 3 years and was shared between master’s degree students in psychology, eight different experimenters were trained to run the tests in the most

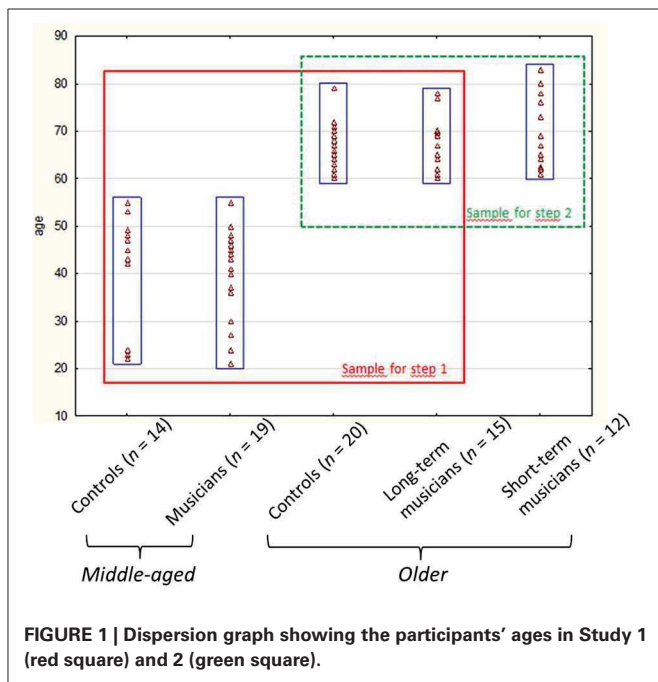


Table 1 | Means (SDs) and inferential statistics for demographic data and characteristics of musical practice (trend/significance p -values: $^{\$}p \leq 0.1$).

	Middle-aged controls (n = 14)	Older controls (n = 20)	Middle-aged musicians (n = 19)	Older musicians (n = 15)	F/ χ^2	p
ANOVAs/χ^2						
Sex ratio (M/F)	5/9	7/13	10/9	8/7	2.15	0.54
Education (years)	13.6 (3.5)	13 (2.5)	14.6 (2.1)	14 (2.5)	1.3	0.28
Occupation	2.6 (0.7)	3.1 (1)	3.2 (0.4)	3 (0.5)	2.2	0.1
	Middle-aged controls	Older controls	Middle-aged musicians	Older musicians	t/ χ^2	P
TWO-SAMPLE t-TESTS/χ^2						
Sex ratio (M/F; collapsed across age)	12/22		18/16		2.15	0.14
Education (collapsed across age)	13.2 (2.9)		14.3 (2.3)		1.76	0.08 ^{\$}
Occupation (collapsed across age)	2.9 (0.9)		3.1 (0.4)		1.26	0.21
Age (middle-aged)	38.9 (12.9)		40.7 (9.7)		-0.48	0.25
Age (older)	67 (4.4)		67.1 (5.2)		-0.09	0.93
Frequency of training			15.3 (12.6)		1.71	0.1 ^{\$}
Age at onset of training			8.4 (3.7)		-1.84	0.07 ^{\$}

Table 2 | List of the tests used, the cognitive functions they assess, and the scores retained.

Psychometric tests	Dependent variables (outcomes)	Cognitive functions assessed
Delayed recall of the Signoret BEM-144's 12 words (Signoret, 1991)	Number of words recalled.	Verbal long-term memory, free recall.
Doors test (Baddeley et al., 1994)	Number of doors properly recognized.	Visual long-term memory, recognition.
Delayed recall of Rey–Osterrieth complex figure (Rey, 1959)	Recall fidelity (number of details, their completeness, and location).	Visual long-term memory, free recall.
Forward digit span (Godefroy et al., 2008)	Highest number of digits properly recalled in 2/3 trials.	Auditory-verbal short-term memory.
Digit-symbol coding subtest of the WAIS-III (Wechsler, 2000)	Number of digits paired with their proper symbol in 2 min.	Processing speed, visual scanning.
d2 test (Brickenkamp, 1981)	Sum of the number of items processed per line in 15 s.	Processing speed, visual discrimination.
Semantic and phonemic fluency tasks (Cardebat et al., 1990)	Number of words enunciated in 2 min.	Verbal functions.
Raven's progressive matrices test (Wechsler, 2000)	Number of matrices properly completed.	Non-verbal reasoning.

possible standardized form. In line with previous studies in the field, we focused on 6 cognitive domains (cf. **Table 2**).

We probed the verbal component of long-term memory using the delayed free recall of the 12 words from the Signoret BEM-144 (Signoret, 1991). (1) This test is taken from the French Batterie d'Efficienc e Mnésique, and requires participants to recall verbal information after a delay of approximately 7 min. Long-term memory's visual component was assessed by combining the two versions of Baddeley's Doors test (Baddeley et al., 1994), and with the delayed recall of the Rey-Osterrieth complex figure (Rey, 1959). (2) These two tests asked, respectively, to recognize 12 previously encoded pictures of doors, and to redraw an abstract geometrical shape copied approximately 3 min earlier. They are both standardized tests of visual memory with good face validity and available normative data. Auditory-verbal short-term memory was evaluated using the size of the forward digit span (Godefroy et al., 2008) (3), which requires participants to immediately recall the highest number of digits in the order they were presented. This task is also part of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; Wechsler, 2000). Processing speed was measured with the digit-symbol coding subtest of the WAIS-III (Wechsler, 2000), and with the number of items processed in the d2 test (Brickenkamp, 1981). (4) In these two tests, the subject is asked to associate or to discriminate visual stimuli as quickly as possible. The digit-symbol coding is part of the WAIS-III (Wechsler, 2000), and the d2 test is a valid measure of attention and processing speed based on German and American normative samples. The d2 is a time-restricted pencil-and-paper test that asks participants to cross out as many letter "d"s with two marks above or below them, in any order. The surrounding distractors are relatively similar to the target stimulus (a "p" with two marks or a "d" with one or three marks). We administered the non-verbal Raven's progressive matrices test (Wechsler, 2000) to estimate participants' non-verbal reasoning skills. This test is also a good proxy for Spearman's general intelligence (g) factor. (5) In this test, participants are presented with an unfinished matrix of drawings, and have to choose which of the proposed answers logically completes the matrix. Finally (6), phonemic and semantic verbal fluency tasks (Cardebat et al., 1990) were administered to assess participants' verbal functions.

These time-restricted tasks ask to recite as many words beginning with a given letter (phonemic) or belonging to a given semantic category (semantic) as possible. They are frequently used to assess cognition after neurological damage (Henry and Phillips, 2006). Performances on these tests can be improved by applying strategies (clustering by- and switching between-phonemic or semantic word categories).

STATISTICAL ANALYSES

All the statistical analyses were performed with STATISTICA software (StatSoft, 2011). STATISTICA (data analyses software), 10th version (www.statsoft.fr). The weakest significance threshold was set at $p = 0.05$, uncorrected for multiple comparisons.

Two chi-square tests of independence were run to attest that the musician and non-musician groups did not differ significantly in gender frequencies. The first compared all four groups (middle-aged controls, middle-aged musicians, older controls, and older musicians), and the second tested the musician and non-musician groups, collapsed across age (cf. **Table 1**).

Two analyses of variance (ANOVAs) were conducted to attest that the four groups did not differ significantly on education and occupation level (cf. **Table 1**). For these variables, we also ran two *t*-tests, where the musician and non-musician groups were collapsed across age. Moreover, two-sample *t*-tests were run to confirm that there was no statistical difference in age between the middle-aged musicians and non-musicians, and the older musicians and non-musicians. Finally, two-sample *t*-tests were run on the middle-aged and older musicians' age at training onset and frequency of training (cf. **Table 1**).

For informative purposes, a correlation analysis was performed between all the outcome measures (cognitive scores) of all the participants (cf. **Table 3**).

To seek for between-group differences regarding cognitive performances, we designed Two-Way ANOVAs specifying each cognitive score as the dependent variable, and age (middle-aged vs. older) and group (musicians vs. non-musicians) as independent factors. Each time, the Two-Way ANOVAs tested for the main effects of group and age, as well as for the Age*Group interaction effect (cf. **Table 4**).

Table 3 | Pairwise correlations among the outcome measures (trend/significance p -values: $^{\$}p < 0.1$; $^*p < 0.05$; $^{}p < 0.01$; $^{***}p < 0.001$).**

	8	9	7	6	5	4	3	2
	Phonemic fluency	Semantic fluency	d2 test	Digit-symbol coding	Raven's matrices	Forward digit span	Rey-Osterrieth complex figure	Doors test
1	0.43***	0.31*	0.22 ^{\$}	0.37**	0.14 ^{ns}	0.1 ^{ns}	0.18 ^{ns}	0.17 ^{ns}
2	0.1 ^{ns}	0.05 ^{ns}	0.28*	0.16 ^{ns}	0.33**	0.01 ^{ns}	0.38**	
3	0.16 ^{ns}	0.05 ^{ns}	0.35**	0.44***	0.35**	0.2 ^{ns}		
4	0.27*	0.43***	0.4**	0.41**	0.46***			
5	0.19 ^{ns}	0.3*	0.31*	0.55***				
6	0.47***	0.31*	0.61***					
7	0.26*	0.22 ^{\$}						
9	0.48***							

Squares featuring tests meant to measure the same cognitive domain are shaded.

1, Delayed recall of the Signoret BEM-144's 12 words; 2, Doors test; 3, Delayed recall of Rey-Osterrieth complex figure; 4, Forward digit span; 5, Raven's progressive matrices; 6, Digit-symbol coding; 7, d2 test; 8, Phonemic fluency; 9, Semantic fluency.

Table 4 | Means (SDs) for neuropsychological Z scores, as well as F -values resulting from the Two-Way ANOVAs (trend/significance p -values: $^{\$}p < 0.1$; $^*p < 0.05$; $^{}p < 0.01$; $^{***}p < 0.001$).**

	Middle-aged controls	Middle-aged musicians	Older controls	Older musicians	F		
					Age	Group	Age*Group
1	-0.06 (0.8)	0.09 (1.2)	-0.14 (1)	0.13 (1)	0.005	0.69	0.07
2	-0.13 (1.1)	0.21 (1.1)	0.07 (0.9)	-0.24 (1)	0.23	0.004	1.8
3	0.3 (0.9)	0.21 (1.1)	-0.4 (0.9)	0.01 (1)	3.61 ^{\$}	0.46	1.18
4	0.09 (1)	0.4 (0.9)	-0.72 (0.9)	0.38 (0.9)	3.6 ^{\$}	10.43**	3.29 ^{\$}
5	0.56 (0.7)	0.41 (0.9)	-0.66 (1.1)	-0.16 (0.6)	17.1***	0.65	2.2
6	0.53 (0.7)	0.63 (1.2)	-0.76 (0.7)	-0.28 (0.4)	30.3***	2	0.9
7	-0.23 (1)	0.7 (1.12)	-0.38 (0.7)	-0.1 (0.8)	4.1*	6.7*	1.92
8	-0.32 (0.8)	0.1 (0.5)	-0.5 (1.13)	0.9 (0.9)	1.83	17.9***	5.2*
9	0.1 (0.7)	0.08 (1.18)	-0.5 (0.9)	0.48 (0.8)	0.18	4.18*	4.67*

1, Delayed recall of the Signoret BEM-144's 12 words; 2, Doors test; 3, Delayed recall of Rey-Osterrieth complex figure; 4, Forward digit span; 5, Raven's progressive matrices; 6, Digit-symbol coding; 7, d2 test; 8, Phonemic fluency; 9, Semantic fluency.

STUDY 1: RESULTS

DEMOGRAPHIC MATCHING

The two chi-square tests of independence showed that the four groups did not differ on gender frequencies [$\chi^2_{(3, N=68)} = 2.15$, $p = 0.54$], and nor did the musician and non-musician groups collapsed across age, [$\chi^2_{(1, N=68)} = 2.15$, $p = 0.14$].

No significant difference was revealed by the ANOVAs run on the mean years of education [$F_{(3, 64)} = 1.29$, $p = 0.28$], and professional occupation stimulating quality [$F_{(3, 64)} = 2.19$, $p = 0.1$]. There was also no significant difference when comparing the musician and non-musician groups (collapsed across age) on professional occupations [$t_{(66)} = 1.26$, $p = 0.21$], but the musicians tended to be more highly educated than the non-musicians [$t_{(66)} = 1.76$, $p = 0.08$].

T -tests confirmed that there was no difference in age between musicians and non-musicians, be they middle-aged [$t_{(31)} = 0.48$, $p = 0.63$], or older [$t_{(33)} = -0.09$, $p = 0.93$].

Finally, t -tests comparing the middle-aged and older musicians on frequency of training [$t_{(32)} = 1.71$, $p = 0.1$], and age

at onset of practice [$t_{(32)} = -1.84$, $p = 0.07$], revealed trends toward significance, as the middle-aged musicians tended to have started musical training earlier and to have practiced more frequently than the older musicians ($p \leq 0.1$).

BETWEEN-GROUP DIFFERENCES IN THE AGE EFFECT ON COGNITION

To explore whether musical practice interacted with the age effect, each cognitive score was entered in a Two-Way ANOVA, with group and age as explanatory variables (cf. Table 4).

Verbal long-term memory

The delayed recall of the 12 words taken from the BEM-144 yielded no main effect of either group, [$F_{(1, 64)} = 0.69$, $p = 0.41$], or age, [$F_{(1, 64)} = 0.005$, $p = 0.94$], and no interaction effect [$F_{(1, 64)} = 0.07$, $p = 0.8$].

Visual long-term memory

Performances on Baddeley's Doors test revealed no main effect of either group [$F_{(1, 64)} = 0.004$, $p = 0.95$]; or age [$F_{(1, 64)} = 0.23$,

$p = 0.63$]; and no Group*Age interaction effect [$F_{(1, 64)} = 1.83$, $p = 0.18$]. Regarding the delayed recall of the Rey–Osterrieth complex figure, results indicated no main effect of group [$F_{(1, 64)} = 0.46$, $p = 0.5$]; a trend toward significance for the main effect of age [$F_{(1, 64)} = 3.6$, $p = 0.06$]; and no interaction effect [$F_{(1, 64)} = 1.2$, $p = 0.3$].

Auditory-verbal short-term memory

The Two-Way ANOVA conducted on the auditory forward digit span scores revealed a main effect of group [$F_{(1, 64)} = 10.43$, $p < 0.01$], and trends toward significance for the main effect of age [$F_{(1, 64)} = 3.55$, $p = 0.06$], and the interaction effect [$F_{(1, 64)} = 3.29$, $p = 0.07$].

Non-verbal reasoning

Raven's progressive matrices' scores revealed a significant main effect of age, $F_{(1, 64)} = 17.1$, $p < 0.0001$, but no significant effect of group [$F_{(1, 64)} = 0.65$, $p = 0.42$], or the Group*Age interaction [$F_{(1, 64)} = 2.2$, $p = 0.14$].

Processing speed

Performances on the digit–symbol coding test showed no significant group effect [$F_{(1, 64)} = 1.98$, $p = 0.16$]; a significant “age” effect [$F_{(1, 64)} = 30.3$; $p < 0.001$]; and no significant interaction [$F_{(1, 64)} = 0.88$, $p = 0.35$].

Regarding the d2 test, analysis revealed significant effects of group, [$F_{(1, 64)} = 6.7$, $p < 0.05$], and age [$F_{(1, 64)} = 4.1$, $p < 0.05$], but no significant interaction effect [$F_{(1, 64)} = 1.93$, $p = 0.17$].

Verbal fluencies

The number of words provided during the phonemic fluency task showed a significant effect of group [$F_{(1, 64)} = 17.9$, $p < 0.001$], no age effect [$F_{(1, 64)} = 1.83$, $p = 0.18$], and a significant interaction effect [$F_{(1, 64)} = 4$, $p < 0.05$].

Post hoc analysis showed that the middle-aged and older controls had very similar performances ($p = 0.5$), whereas the older musicians performed significantly better than the middle-aged musicians ($p < 0.05$). It resulted in a difference in performances

between the older musicians and non-musicians ($p < 0.001$). The performances of the middle-aged musicians and non-musicians were the same ($p = 0.18$) (cf. **Figure 2**).

Regarding semantic fluency, the Two-Way ANOVA revealed a significant effect of group [$F_{(1, 64)} = 4.19$, $p < 0.05$], no effect of age [$F_{(1, 64)} = 0.18$, $p = 0.67$], and a significant interaction [$F_{(1, 64)} = 4.67$, $p < 0.05$].

Post-hoc analysis revealed that the older controls tended to perform worse than their middle-aged counterparts ($p = 0.07$), but there was no difference between the older and middle-aged musicians ($p = 0.22$). Again, there was a significant difference between older controls and older musicians ($p < 0.01$); and no difference between middle-aged controls and musicians ($p = 0.93$) (cf. **Figure 2**).

STUDY 1: DISCUSSION

In order to explore whether regular engagement in musical activities is associated with a decrease in the age effect on some cognitive functions, we studied the cognitive performances of middle-aged and older musicians in comparison with control participants. In line with the literature, results were as follows:

NO MAIN EFFECT OF MUSICAL PRACTICE

We found no musical practice-related difference on the verbal and visual modalities of long-term memory. Hanna-Pladdy and MacKay (2011) had previously found that musical engagement in older individuals was linked to better performances in visual memory. This finding was not replicated here, despite using a virtually identical test (delayed visual figure reproduction).

We also found that musical practice was not associated with better performances on Raven's progressive matrices, suggesting that there is no link between engagement in musical activities and non-verbal reasoning skills. Correlational studies regarding musical training and non-verbal reasoning skills (assessed using virtually similar tests) have sometimes reported positive findings (e.g., Forgeard et al., 2008; Bailey and Penhune, 2012), but not always (e.g., Franklin et al., 2008; Schellenberg and Moreno, 2009). The null finding of the present study adds to the uncertainty about the

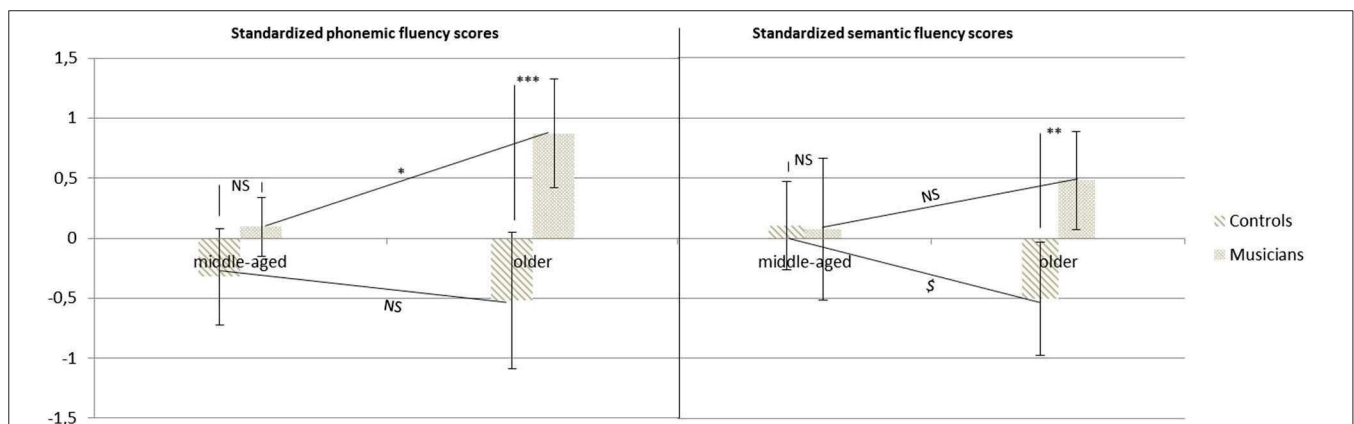


FIGURE 2 | Phonemic and semantic fluency z scores as a function of age for middle-aged and older musicians and controls ($^{\$}p < 0.1$; $^*p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$).

association between musical training and non-verbal reasoning skills.

In the same vein, digit-symbol coding was not performed better by musician participants of our sample. Individualized music lessons (learning to play the piano) given to 16 older non-musicians were shown to increase performances on this measure (Bugos et al., 2007). Here, we found that older musicians who had been practicing music since childhood were no better at this test.

AN EFFECT OF MUSICAL PRACTICE THAT DOES NOT INTERACT WITH AGE

For processing speed, as assessed with the d2 test, we found significantly better performances for musician individuals compared with non-musicians, but differences between middle-aged and older participants were the same for both groups. The literature investigating musical practice during old age had already reported a trend toward significance for difference on the TMT A (Hanna-Pladdy and MacKay, 2011). This finding was replicated here with a different test, and with the precision that age-related differences were the same for both musicians and non-musicians.

Regarding the size of the digit span, we found that musicians performed significantly better than their non-musician counterparts. This result goes against Hanna-Pladdy et al.'s two cross-sectional studies (2011, 2012), which did not report such findings even though they used the same test. In addition, we showed a trend toward significance for the interaction with age, but which was not significant. That meant, again, that the age-related differences in performances were not significantly different between the groups.

These patterns of results did not match our first hypothesis, and were likely to reflect a predisposition in musicians for learning/practicing music, rather than a stimulation of learning/practicing music. Nevertheless, it is also conceivable that features of musical practice (e.g., score reading, typing, and auditory attention) lead to an increase in neural resources for processing speed and auditory-verbal short-term memory, endowing musicians with an advantage of a quantitative nature, with no further particular change.

AN EFFECT OF MUSICAL PRACTICE THAT INTERACTS WITH AGE

For the two verbal fluency tests (phonemic and semantic), results showed that musicians produced significantly more correct words than non-musicians. This was only partially in agreement with Hanna-Pladdy and Gajewski (2012), as they found the same effect for phonemic, but not semantic fluency. Therefore, we confirmed that older individuals who practice music score higher on a test measuring verbal skills.

In addition, significant interactions with age indicated that performances were relatively similar between middle-aged and older individuals of the control groups (with a trend toward reduced semantic fluency for older participants), but increased significantly in musicians for phonemic fluency.

The semantic and phonemic fluency tasks were therefore the only measures that confirmed our hypothesis of different age-related changes for musicians compared with non-musicians. However, we did not find significant effect of age on these measures, making them less interesting in the framework of cognitive reserve. Moreover, it is important to point out that for these

two tests, no difference was found between musicians and non-musicians of the middle-age groups. This did not really suggest a transformative effect of musical practice, because in the case of an actual *stimulation*, one would have expected musicians to outperform non-musicians from middle age onwards.

STUDY 2: MATERIALS AND METHODS

STUDY 2: PARTICIPANTS

In this second step, we sought for a link between the characteristics of the musicians' practice and their performances on tests having revealed significant interactions in Study 1 (i.e., phonemic and semantic fluencies). To probe the age at training onset effect, we added a sample of older musicians who had started music in adulthood (called "short-term musicians"), and compared their performances with those of the age-matched participants of Study 1 (the older "long-term musicians" and older controls). We also questioned the influence of a characteristic of current practice by running a correlation analysis between the older musicians' frequency of training and their performances.

Twelve older amateur musicians (mean age = 70.04 years, $SD = 7.7$, min = 61, max = 83) who had started music at a mean age of 42.7 years ($SD = 11$) were recruited from French conservatories or music schools. As for Study 1, no self-educated musicians were included, they had learned at least 2 new pieces during the last year, and they had an uninterrupted time of practice of at least 4 years at the time of the study (mean training duration = 25.8 years, $SD = 12.38$, min = 6, max = 40), with at least 4 h practicing a week (mean frequency = 8.08 h, $SD = 7.24$, min = 4, max = 30) (cf. Table 5).

STUDY 2: NEUROPSYCHOLOGICAL ASSESSMENT

Study 2's neuropsychological battery was exactly the same as the one used in Study 1. It comprised the same tests and was administered in an identical way by the same experimenters. Z score values were computed based on the entire Study 2's sample.

STUDY 2: STATISTICAL ANALYSES

A Chi-Square test of independence was run on the between-group gender frequencies to attest that the male/female ratios did not differ significantly. Three ANOVAs were conducted on the means for age, education, and occupation, to attest that the three groups of participants were similar on these measures.

To locate the short-term musician group's performances relative to the long-term musician and the control groups, we conducted ANOVAs on the cognitive scores having revealed interaction effects in Study 1 (i.e., the two verbal fluency tasks). Then, if the ANOVAs led to a significant effect of group, we ran *post-hoc* analyses (Least Square Deviation LSD) for pairwise comparisons.

Finally, to see whether the musicians' frequency of training explained their number of recalled words, we conducted a non-parametric correlation analysis (Spearman's rho) between these variables for all the musicians of the Study 2's sample.

STUDY 2: RESULTS

DEMOGRAPHIC MATCHING

The chi-square test of independence showed no between-group difference for gender frequencies [$\chi^2_{(2, N=47)} = 1.7, p = 0.43$].

The One-Way ANOVAs ran on age [$F_{(2, 44)} = 1.3, p = 0.28$], education [$F_{(2, 44)} = 1.71, p = 0.19$] and occupation [$F_{(2, 44)} = 0.36, p = 0.7$], confirmed that the groups did not differ on these measures (cf. **Table 5**).

The two-sample *t*-tests comparing the practice characteristics of the two musician groups revealed significantly different ages at training onset [$t_{(25)} = -10.26, p < 0.001$], but similar training frequencies [$t_{(25)} = 0.41, p = 0.74$] (cf. **Table 5**).

BETWEEN-GROUP DIFFERENCES FOR PHONEMIC FLUENCY

Phonemic fluency scores showed a significant main effect of group ($F_{(2, 44)} = 7.51, p < 0.05$). *Post-hoc* analysis revealed that the long-term musicians scored significantly higher than the short-term musicians ($p < 0.05$), the latter being no different from control participants ($p = 0.46$) (cf. **Figure 3**).

BETWEEN-GROUP DIFFERENCES FOR SEMANTIC FLUENCY

Semantic fluency scores revealed a significant effect of group ($F_{(2, 44)} = 6.43, p < 0.01$). *Post-hoc* analysis indicated that there

was no difference in the performances of the two groups of musicians ($p = 0.23$), and that the short-term musician group also performed better than control participants ($p < 0.05$) (cf. **Figure 3**).

CORRELATION ANALYSIS

Results of the correlation analysis between the musicians' semantic and phonemic fluency scores and their frequency of training revealed no significant relation (cf. **Table 6**).

STUDY 2: DISCUSSION

To seek for a link between practice characteristics and older musicians' superior performances, we conducted a second study (Study 2), in which we included a sample of different older musicians (they had begun practicing music 30 years later on average than the musicians in Study 1). Results indicated that there was no link between frequency of training and verbal fluency performances. Moreover, because the two musician groups (long-term and short-term) had identical performances on the

Table 5 | Means (SDs) and inferential statistics for demographic data and practice characteristics of short-term and long-term musicians (trend/significance *p*-values: * $p < 0.001$).**

	Controls (n = 20)	Long-term musicians (n = 15)	Short-term musicians (n = 12)	F/χ^2	<i>p</i>
ANOVAs/χ^2					
Sex ratio (M/F)	7/13	8/7	7/14	1.7	0.43
Age (years)	67 (4.4)	67.1 (5.2)	70 (7.7)	1.3	0.28
Education (years)	13 (2.5)	14 (2.5)	14.6 (3.6)	1.7	0.19
Occupation	3.1 (1)	3 (0.5)	3.2 (1.1)	0.4	0.7
	Long-term musicians (n = 15)		Short-term musicians (n = 12)	<i>t</i>	<i>p</i>
TWO-SAMPLE <i>t</i>-TESTS					
Training onset (age)	11.2 (4.5)		42.7 (11)	-10.26	0.000***
Training frequency (h/week)	9.2 (6.6)		8.1 (7.2)	0.41	0.74

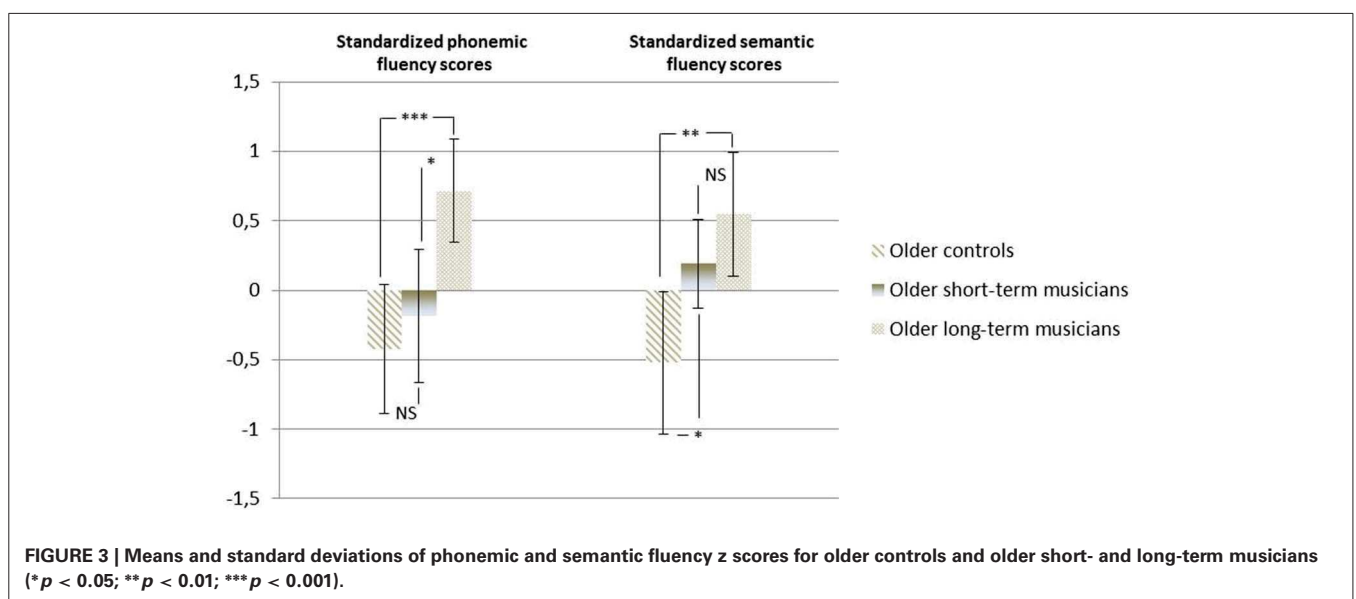


Table 6 | Spearman's rank correlation coefficients between older musicians' frequency of training and their phonemic and semantic fluency scores.

	Phonemic fluency	Semantic fluency
Frequency of training (h/week)	0.29 ($p = ns$)	0.19 ($p = ns$)

semantic version, we concluded that the older musicians' better ability in this test was not explained by their practice, and probably constituted a confounding factor.

For phonemic fluency, results showed another pattern, indicating that musicians who had started their musical training during adulthood did not differ from controls. This could be in line with works showing that practice-related brain or cognitive differences are more pronounced when training starts at an early age (Elbert et al., 1995; Schlaug et al., 1995; Amunts et al., 1997; Steele et al., 2013). As verbal fluency assesses mainly verbal functions, our results also corroborated studies reporting better performances across a wide variety of language-related tests for children who have learned to play music (e.g., vocabulary; Forgeard et al., 2008; Moreno et al., 2009). In line with a previous investigation (Hanna-Pladdy and Gajewski, 2012), the present study showed that musical training in childhood is also associated with better literacy in old age, regardless of current musical engagement. The long-term influence of early environmental factors on brain and cognition has already been attested in animal studies (Fernández-Teruel et al., 1997). Moreover, in humans, educational attainment is known to be a major factor in determining individuals' cognitive reserve later in life (Stern, 2012), even when occupation is controlled for. In the field of music, Gooding et al. (2013) found that the amount of musical engagement from childhood until adulthood explained older individuals' verbal fluency and long-term memory performances. Therefore, it could be that the cognitive advantage we observed in the older musicians was linked to the musical education they had received during the sensitive period of childhood. From this perspective, music lessons would act as an environmental enrichment which endows people who benefit it with better verbal skills in later life. Then again, given that our two studies had a cross-sectional design, our results may also indicate that individuals whose verbal skills are particularly good in old age are also those who were most likely to come to music early, and to continue their musical training lately.

GENERAL DISCUSSION

To sum up, our cognitive investigation of musicians yielded little evidence of reduced age-related changes owing to musical training. In line with this work's hypotheses, phonemic fluency was the only cognitive variable that potentially exemplified a positive use-dependent effect in aging. Hanna-Pladdy and Gajewski (2012) had previously reported better phonemic fluency performances in older individuals who had practiced music in childhood, and the current status of training (active vs. inactive) was not linked with performances (Hanna-Pladdy and MacKay, 2011). This is in agreement with the absence of an association with frequency of training in the present study. In addition, we showed that

the period at training onset seems to matter, as older musicians who had started musical practice in adulthood were no different from controls. This could be because there is a sensitive period for brain and cognitive plasticity (Penhune, 2011). The possibility that musical instruction in childhood could have a long-lasting influence on cognition in later life fits in with the definition of reserve, and the notion that "sensitive periods are epochs in development where specific experiences have enhanced and long-lasting effects on behavior and the brain" (Knudsen, 2004).

We found that only a verbal domain-related task fulfilled our criteria to be qualified as "stimulated by musical practice in aging." This could be viewed as an additional argument in favor of the existence of a special link between musical practice and verbal skills (Chan et al., 1998; Ho et al., 2003; Forgeard et al., 2008). Explanations for this presumed use-dependent enhancement of speech fluency include the processing of common auditory features in music and language (Patel and Iversen, 2007), and the strengthening of the auditory-motor neural coupling that serves both in music and in language production and perception (Bangert et al., 2006).

However, as already stated, phonemic fluency was not better performed by musicians compared with non-musicians for the middle-aged period of life. This is not really what we would expect in the case of actual stimulation. Moreover, in this work, many factors that are known to be associated with cognitive functioning and musical engagement were not controlled for, including the early sociocultural environment (family income, parental first language, parental education, etc.; Elpus, 2013). The first step of the present study investigated older people who had an ongoing musical training since childhood until late-life. Ecologically, such individuals are scarce, and they probably have particular personality traits that prompt them not only to play music, but also to engage in other behaviors that may help them to develop a cognitive reserve (healthy diet, moderate smoking/drinking, and other physical, social, and intellectual activities). Even more important, in this study, none of the IQ scores (verbal or performance) was assessed, but they are important determinants of individuals' cognitive reserve and the likelihood of their taking up music lessons (Schellenberg, 2011). Indeed, if music lessons do lead to improvements in IQ (Schellenberg, 2004), a comprehensive work has rigorously highlighted that children with a high IQ are more inclined than children with a lower IQ to attend music lessons (Schellenberg, 2011).

In the present study, a proxy for performance IQ (Raven's matrices test) showed no between-groups difference, but we found that the semantic fluency task was performed better by musicians, regardless the life period at training onset and the current frequency of training. This result could reflect a tendency of high verbal IQ people (or with a large vocabulary) to come up with—and pursue—music training later in life. However, only the musicians since childhood displayed better performances on phonemic fluency. Therefore, as in Hanna-Pladdy and Gajewski's study (2012), it could suggest that old musician individuals who started practicing music in their childhood display better verbal functions beyond what could be explained by their initially higher verbal IQ.

To conclude, the quality of people's cognitive reserve depends on many intricate factors. It is highly conceivable that people who keep good cognitive functioning in old age are also those who are likely to pursue or expand their daily-life activities. In turn, maintaining these activities may certainly help to *keep their cognition young*. However, in our work ($N = 79/5$), which did not control for such selection bias-related confounding factors, we found that highly trained and active musicians (mean training duration = 38 years; mean frequency of training = 10.86 h/week) did not perform any better than control participants on long-term memory (verbal and visual), non-verbal reasoning, and visual scanning (digit-symbol coding). For processing speed and auditory-verbal short-term memory, musicians scored higher but displayed no weaker age-related difference, thus ruling out a *protective effect* of practice (although both processing speed and auditory short-term memory are highly solicited in musicians). Playing music, as speaking, are auditory-motor behaviors, and there are reports that some individuals own predisposing functional brain organization to learn faster in these abilities (Zatorre, 2013). It is therefore conceivable that some people keep disposing neural substrates that prompt them to pursue music later in life.

Only for phonemic fluency was musical practice associated with a different age-related change in performances, depending on the period at training onset (musicians who started in adulthood performed identically to controls). Therefore, according to us, this test was the solely potential candidate for a use-dependent adaptation interacting with musicians' cognitive aging.

Acquiring an expertise through deliberate practice leads to automation and to strategic processes that allow performances to be improved in a cost-effective way (neural efficiency; Kelly and Garavan, 2005). Other styles of behavior, such as exposure to novelty, may be more efficient in increasing old individuals' cognitive reserve.

AUTHOR CONTRIBUTIONS

Baptiste Fauvel was actively involved in this study from design to drafting. He greatly contributed to participant recruitment and data acquisition. Finally, he conducted all the statistical analyses, produced the figures, participated in the interpretation of the results, and played a central role in revising the article in the wake of the reviewing process. Justine Mutlu made a substantial contribution to this study at every stage. Her assistance was particularly invaluable during revisions, when she participated in the supplementary statistical data analyses, the interpretation of the new results, the rational organization of the ideas, and the design of the figures. Moreover, she revised the manuscript many times in order to eliminate English grammatical mistakes and improve wording. At the outset, Eider M. Arenaza-Urquijo had provided invaluable ideas for interpreting the results. These ideas more or less vanished from the first version of the paper, but became central in the revised one. Moreover, she proved to be a huge help with the statistical data analyses. Finally, she was always generous with her advice, and shared many of her ideas during the revision process. Mathilde Groussard played an active part in this study from beginning to end. She helped in the design and the data acquisition coordination, and brought her theoretical knowledge to bear in the interpretation of the results. Finally, she revised

the manuscript several times, allowing essential improvements to be made. As director of the laboratory, Francis Eustache ensured that we had all the material resources we needed to bring this study to a successful conclusion. His experience and knowledge in neuropsychology were essential for conceiving and designing the study, setting out the issues, and interpreting the results. Finally, he revised the manuscript, and provided relevant advice regarding the rational organization of the ideas. Béatrice Desgranges contributed her extensive experience to this study. Her knowledge in the field of cognitive aging proved essential to the study design, the interpretation of the results, and the drafting of the manuscript. Several of her ideas lie at the very core of the final version. Even more important, she highlighted several methodological problems—and how to solve them. Hervé Platel was the person behind this whole research project, and he coordinated the teamwork from start to finish. On many occasions during the design of the study and the interpretation of the results, his theoretical knowledge about music cognition saved us a huge amount of time. Moreover, his knowledge regarding the state of the art helped us to exploit the data in the most relevant way.

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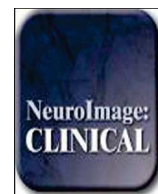
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7.1.2. Tomadesso *et al.*, (2015)



Brain structural, functional, and cognitive correlates of recent versus remote autobiographical memories in amnesic Mild Cognitive Impairment



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ABSTRACT

Deficits in autobiographical memory appear earlier for recent than for remote life periods over the course of Alzheimer's disease (AD). The present study aims to further our understanding of this graded effect by investigating the cognitive and neural substrates of recent versus remote autobiographical memories in patients with amnesic Mild Cognitive Impairment (aMCI) thanks to an autobiographical fluency task. 20 aMCI patients and 25 Healthy elderly Controls (HC) underwent neuropsychological tests assessing remote (20-to-30 years old) and recent (the ten last years) autobiographical memory as well as episodic and semantic memory, executive function and global cognition. All patients also had a structural MRI and an FDG-PET scan. Correlations were assessed between each autobiographical memory score and the other tests as well as grey matter volume and metabolism. Within the aMCI, performances for the remote period correlated with personal semantic memory and episodic memory retrieval whereas performances for the recent period only correlated with episodic memory retrieval. Neuroimaging analyses revealed significant correlations between performances for the remote period and temporal pole and temporo-parietal cortex volumes and anterior cingulate gyrus metabolism, while performances for the recent period correlated with hippocampal volume and posterior cingulate, medial prefrontal and hippocampus metabolism. The brain regions related with the retrieval of events from the recent period showed greater atrophy/hypometabolism in aMCI patients compared to HC than those involved in remote memories. Recall of recent memories essentially relies on episodic memory processes and brain network while remote memories also involve other processes such as semantic memory. This is consistent with the semanticization of memories with time and may explain the better resistance of remote memory in AD.

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1. Introduction

Autobiographical memory is a multifaceted concept which concerns information and experiences of one's personal life and gives a sense of self-continuity (Conway, 2001; Piolino et al., 2009). The disturbance of autobiographical memory is well known in Alzheimer's disease (AD) (Addis et al., 2009; Addis and Tippett, 2004; Greene et al., 1995;

Ivanoiu et al., 2004; Kopelman et al., 1989; Leyhe et al., 2009; M. Irish et al., 2011; Piolino et al., 2003) and has been described in patients with Mild Cognitive Impairment (MCI) as well (Irish et al., 2010; Leyhe et al., 2009; Murphy et al., 2008).

Interestingly, all memories are not affected in the same way in AD: recent memories are impaired first, whereas remote ones resist longer (Leyhe et al., 2009; Irish et al., 2010; Murphy et al., 2008). This is called the amnesic temporal gradient of Ribot or Ribot's law (Ribot, 1881). While the mechanisms underlying this gradient are not fully understood, it is thought to be related to the "semanticization" of episodic memories with time (Cermak, 1984; Eustache and Desgranges, 2008). Thus, remote

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autobiographical memories would tend to depend less on episodic memory function and related brain substrates and more on semantic memory compared to recent memories. As AD primarily affects episodic memory function and brain substrates, this may explain why recent autobiographical memories are more sensitive and remote ones more resistant, especially in the earliest (predementia) stages where structural and functional brain changes are mainly confined to brain regions that belong to the episodic memory network such as the hippocampus and posterior cingulate cortex (Chételat et al., 2002, 2003; Stoub et al., 2006). A study assessing the brain substrates of autobiographical memory in AD tends to confirm this view, showing a relationship with the hippocampus for the recent, but not for the remote memories (Eustache et al., 2004) although conflicting findings have also been reported (Gilboa et al., 2005; Philippi et al., 2012). In patients with MCI, the results are inconclusive as the only study in MCI did not report any relationships with the hippocampus (Bastin et al., 2013).

The main objective of this study was thus to further our understanding of the gradient of Ribot in MCI patients, when brain changes are expected to be mainly confined to the episodic memory network. MCI represents a transitional state between the cognitive changes of normal aging and very early dementia and is recognized as a risk factor for AD. Epidemiologic studies have reported the annual progression rates of clinically diagnosed MCI to dementia to be in the 15–25% range (Petersen et al., 2009). This population is, therefore, particularly well-suited to assess the predementia stage of AD, although all MCI patients will not develop AD. For this purpose, the relationships between remote and recent autobiographical memory performances on the one hand, and cognitive and brain structural and functional measurements, on the other hand, were assessed in patients with MCI. We hypothesized that (i) MCI patients would have predominant deficits in recent episodic memory retrieval; (ii) these predominant recent memory deficits in MCI would reflect the involvement of cognitive processes and brain regions that are more sensitive to AD and (iii) remote episodic memory retrieval would be less affected as it would further depend on brain regions involved in semantic processing that are more preserved, as a reflect of the “semanticization” of episodic memories with time.

2. Methods

2.1. Participants

Forty five right-handed native French-speaking participants from the IMAP project (La Joie et al., 2013, 2012; Mevel et al., 2013) were included in the present study, including 20 patients with amnesic MCI (aMCI) and 25 Healthy elderly Controls (HC) matched for age, gender and education level (Table 1). All participants were aged over

50 years, had at least 7 years of education, had no clinical evidence of psychiatric or neurological disorders, no severe brain lesions on T2-weighted or FLAIR MRI images, no history of alcoholism or drug abuse, were free of medication that could affect cognitive functioning and reported being in good health. aMCI patients were recruited from local memory clinics and had memory complaint for less than 2 years. They were selected according to Petersen’s criteria for aMCI (Petersen and Morris, 2005): isolated episodic memory deficits (1.5 SD of the normal mean for age and education notably for the Free and Cued Selective Recall Reminding Test), normal performances in other areas of cognition, in global cognition (assessed with MMSE and Mattis scales) and preservation of independence in functional abilities (see Fouquet et al., 2009, for further details). Clinical diagnosis was assigned by consensus under the supervision of senior neurologists and neuropsychologists. To further characterize the MCI patients included in this study, we assessed their profile of atrophy and hypometabolism compared to age- and education-matched controls with whole brain comparison analyses. MCI patients showed hippocampal atrophy and hypometabolism in the precuneus–posterior cingulate cortex and temporo-parietal areas. This profile is consistent with the pattern of alterations described in the literature in MCI patients as well as in the predementia stage of AD (Atiya et al., 2003; Chételat et al., 2002, 2003; Nestor et al., 2003a, 2003b).

HC participants were recruited from the community and performed in the normal range on a neuropsychological examination assessing multiple domains of cognition including episodic and semantic memory, executive and visuo-spatial functions, language and praxis.

Within a few days from recruitment, each participant underwent: 1) a detailed experimental neuropsychological battery, 2) a structural magnetic resonance imaging (MRI) study, and 3) a positron emission tomography (PET) study using [¹⁸F] fluoro-2-deoxy-D-glucose (¹⁸FDG).

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

2.2. Neuropsychological assessment

The task of interest in this study was an episodic autobiographical memory fluency task, inspired from Dritschel et al. (1992); see also Chételat et al. (2005), assessing two periods of life (recent and remote). The recent period corresponded to the 10 last years without the last year (to avoid very recent events – e.g. 1 h/day ago for the sake of comparativeness) while the remote period corresponded to the period when the participant was 20–30 years old. In this task, patients were given instructions to recall as many personal events of their life as possible for each period, during 2 min. The instructions were to recall

Table 1
Demographic and neuropsychological performances of the aMCI and control groups.

	aMCI (n = 20)	HC (n = 25)	Group effect
Age: years ± SD (range)	72.3 ± 7.2 (64–86)	70.5 ± 5.4 (61–81)	ns
Women /men	11/9	14/11	ns
Education: years ± SD (range)	10.0 ± 3.5 (7–20)	10.5 ± 3.2 (7–17)	ns
MMSE: score ± SD (range)	26.9 ± 1.5 (29–24)	28.9 ± 0.9 (30–27)	*
Mattis: score ± SD	135.1 ± 4.1	142.36 ± 1.9	*
Episodic memory :			
Recognition after superficial encoding ± SD	9.9 ± 2.9	13.4 ± 1.8	*
Free recall after deep encoding ± SD	5.15 ± 2.0	8.68 ± 2.3	*
Autobiographical memory remote period ± SD	3.05 ± 2.31	5.08 ± 2.99	*
Autobiographical memory recent period ± SD	2.00 ± 1.35	4.52 ± 2.21	*
Semantic memory :			
Category word fluency ± SD	23.8 ± 5.8	31.8 ± 7.3	*
Semantic autobiographical memory ± SD	14.8 ± 9.6	24.56 ± 8.7	*
Executive functions :			
Trail making test (B–A) ± SD	79.09 ± 54.2	55.36 ± 34.4	ns

Standard deviation appears in brackets. All variables were compared using t-tests. ns = non-significant.

*p < 0.001.

events situated in time and space, which lasted less than a day and happened only once, and to provide as many details as possible. An illustrative event with a set of examples of episodic details (e.g. time and place details, people, activities, conversations, emotion and thoughts) was given. In the first part of the trial, which was time-constrained, participants had to remind as many events as possible that they just had to name in a few words. Predefined cues (e.g. a wedding, a birth or a Christmas day) were given to the participants if they stayed over 20 s without saying anything. In the second part of the test, participants were asked to provide as many details as possible for each event they mentioned in the first part. At the end of the task, the experimenter ensured with the participant that each event could be specifically re-experienced with details, assessing the specificity of the content (single or repeated event), the time and spatial location, and the presence of details (perception, thoughts or feelings) (Baddeley and Wilson, 1986). The rater quoted each event on a 5-point scale (single event = 1 point; lasting less than a day = 1 point; located in time = 1 point; situated in space = 1 point and at least 2 specific details = 1 point). Only specific events rated 5 were counted as an episodic event. For example “Every Wednesday with my grandmother we cooked cakes that we ate for afternoon snacks” is an event considered as a semantic event, whereas, “When I was 12 years old with my grandmother we had forgotten the cake in the oven, it was burnt and a lot of smoke spread in the house. My grandfather who was upstairs detected the burning smell, get off at full speed and tumbled in the stairs. I relive the scene as if I was there” is an event considered as an episodic event scored 5 in our scale. The number of episodic events within each period was used as “recent” and “remote” autobiographical episodic memory scores. The neuropsychological battery included 6 tests or subtests that evaluated a set of cognitive, mainly memory, functions. The battery is fully described in Mevel et al. (2013). The total score at the Mattis dementia rating scale (Mattis, 1976) was used to assess global cognitive function. Verbal episodic memory was assessed using the ‘Encoding, Storage, Retrieval’ (ESR) paradigm fully described elsewhere (Chételat et al., 2005). Briefly, participants had to recall as many words as possible from 2 distinct 16-word lists after either a superficial or a deep encoding phase. Performances in recognition after superficial encoding (maximum score = 16) are considered to reflect encoding capacity (and thus referred to as the encoding subtest in what follows), while free recall performances after deep encoding is thought to reflect retrieval capacity (and is thus referred to as the retrieval subtest in what follows). Semantic memory was assessed with the category word fluency task where patients were given instructions to list in 2 minutes as many words as possible which complied with the ‘animals’ semantic criteria (Cardebat et al., 1990). Personal semantic memory was evaluated with a semantic autobiographical fluency task similar to that described above for episodic autobiographical memory, but using names of individuals (excluding family members) that participants have personally met during each of the two periods of life instead of events (Dritschel et al., 1992). The sum of the number of names given for the two periods was used as a measure of personal semantic memory capacity. Finally, the Trail Making Test was used to assess executive functions (Greenlief et al., 1985) (Table 1). All resulting neuropsychological scores were transformed in z-scores [(aMCI value – average scores of controls) / standard deviation of controls] to be used in subsequent analyses. Z-scores were used so that the two scores of episodic autobiographical memory were expressed in a same scale and could be compared (as we were interested in comparing the degree of impairment between remote and recent memories).

2.3. Neuroimaging procedure

2.4.1. MRI and PET data acquisition

For each participant, a high-resolution T1-weighted anatomical image was acquired on a Philips Achieva 3T scanner using a three-dimensional fast-field echo sequence (sagittal; repetition time =

20 ms; echo time = 4.6 ms; flip angle = 20°; 170 slices; slice thickness = 1 mm; field of view = 256 × 256 mm²; matrix = 256 × 256).

¹⁸FDG-PET images were acquired using the Discovery RX VCT 64 PET-CT device (GE Healthcare) with a resolution of 3.76 × 3.76 × 4.9 mm³ (field of view = 157 mm). Forty-seven planes were obtained with a voxel size of 1.95 × 1.95 × 3.2 mm³. A transmission scan was performed for attenuation correction before the PET acquisition. Participants were fasted for at least 6 h before scanning. After a 30 min resting period in a quiet and dark environment, 180 MBq of FDG was intravenously injected as a bolus. A 10 min PET acquisition scan began 50 min after injection.

2.4.2. MRI and PET data handling

MRI data were segmented, normalized and modulated using the VBM5.1 toolbox (<http://dbm.neuro.uni-jena.de>) implemented in the Statistical Parametric Mapping 5 software (SPM5; Wellcome Trust Center for Neuroimaging, Institute of Neurology, London, England). To blur individual variations in gyral anatomy and to increase the signal-to-noise ratio, the spatially normalized GM data sets were smoothed with a 10 mm Gaussian filter. The resulting smoothed and spatially normalized GM data sets were used in the following analyses and processing.

¹⁸FDG-PET data were first corrected for partial volume effects using the three-compartment method described by Giovacchini et al. (2004) and implemented in the PMOD software (PMOD Technologies). This method uses gray matter, white matter, and cerebrospinal fluid segments obtained from the VBM procedure to correct for both spill-in and spill-out effects. Resultant images were then coregistered onto corresponding MRI, normalized using the deformation parameters defined from the VBM procedure performed on the corresponding MRI and scaled using the mean PET value of the cerebellar gray matter. Resultant images were finally smoothed using a 12 mm FWHM Gaussian kernel.

2.4. Statistical analyses

2.5.1. Behavioural analyses

First, a one sample t-test was performed to compare each of the two episodic autobiographical memory z-scores (recent and remote) of aMCI patients to zero, to test whether aMCI performances significantly differed from those of the HC. Second, a paired t-test with the two z-scores of aMCI patients was performed to compare their degree of deficits in remote versus recent episodic autobiographical memory. Finally, to assess, within the aMCI, the cognitive correlates of these measures, the episodic autobiographical memory z-score for each period was entered as a dependent variable in separate partial correlation models with each z-score of the neuropsychological battery as an independent variable, correcting for age. Bonferroni correction was applied to control for multiple comparisons, so that a threshold of $p < 0.008$ (0.05/6) was required for results to be considered as significant.

2.5.2. Imaging analyses

Firstly, a multiple regression analyses were performed within the aMCI group, for each period of life and each neuroimaging modality with the autobiographical z-score as the variable of interest and age as a nuisance variable (4 models were performed). To address the issue of multiple comparisons, for each period and each imaging modality a cluster size was determined (Supplementary Table 1) combined with a voxel-level p (uncorrected) < 0.005 threshold to achieve a corrected statistical significance for multiple comparisons of $p < 0.05$ (as determined through Monte Carlo simulations using the AlphaSim program).

The significant clusters from these 4 regression analyses were defined as the clusters of interest in what follows, to be used in further analyses. In each of these clusters of interest, the corresponding values (mean grey matter volume or cerebral metabolism) were extracted and compared between HC and patients using a two sample t-test.

3. Results

3.1. Behavioural results

Firstly, within the HC, 80% of the remote events and 84.55% of the recent ones were considered as episodic, whereas within the aMCI, the proportions were 75.6% and 68.8%, respectively. aMCI patient z-scores were significantly lower than zero (i.e. significantly lower than the HC) for both the remote ($t(19) = -3.94$; $p < 0.001$) and the recent ($t(19) = 8.42$; $p < 0.001$) periods (Fig. 1). Moreover, the comparison between both z-scores revealed significantly greater deficits in aMCI patients for the recall of events from the recent period than from the remote period ($t(19) = -2.60$; $p = 0.02$).

The correlations between each episodic autobiographical z-score and each of the other cognitive z-scores from the neuropsychological battery showed a significant relationship between performances for the remote period and semantic autobiographical fluency, verbal episodic memory retrieval, and a trend was found for the Mattis (Table 2). For the recent period, a significant correlation was found only for verbal episodic memory retrieval.

3.2. Correlations between autobiographical memory and brain imaging data (grey matter volume and metabolism)

Significant correlations between episodic autobiographical memory z-score for the remote period and normalized grey matter volume were found in the left temporal pole, inferior temporal neocortex and fusiform gyrus (cluster 1_MRI_remote), and in a right temporo-parietal area encompassing the angular and middle occipital cortices (cluster 2_MRI_remote; Fig. 2). For the recent period, significant correlations with grey matter volume were found in anterior medial temporal structures, including the anterior hippocampus and parahippocampal gyrus and the amygdala, in both right (cluster 1_MRI_recent) and left (cluster 2_MRI_recent) hemispheres.

The correlations with FDG-PET data revealed significant association between episodic autobiographical memory z-scores for the remote period and metabolism in the left anterior cingulate gyrus (cluster 1_FDG_remote; Fig. 3). Autobiographical z-scores for the recent period correlated with metabolism in four clusters, including the medial orbitofrontal, ventro-lateral prefrontal cortex and hippocampal region (i.e. hippocampus, amygdala, parahippocampal and fusiform gyrus extending to the temporal neocortex) in the left (cluster 1_FDG_recent) and right (cluster 2_FDG_recent) hemispheres, the posterior cingulate cortex (cluster 3_FDG_recent) and a small cluster encroaching the anterior parahippocampal, fusiform and inferior temporal gyrus (cluster 4_FDG_recent). Table 3 summarizes the coordinates of the peak voxels within each significant cluster as well as the corresponding statistics.

Note that the findings remained essentially unchanged when including as an additional covariate in the model either the score for the other period (i.e. the remote score for the recent one and reversely), or another fluency score, to account for global generative search capacity.

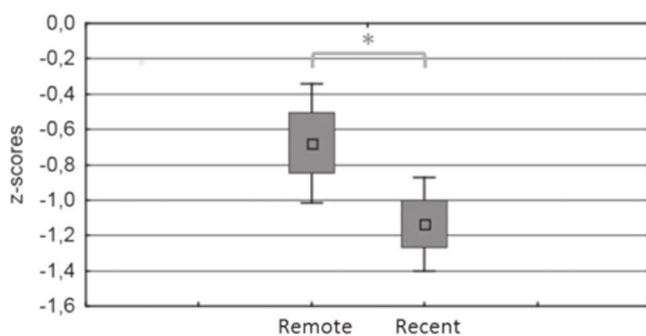


Fig. 1. Autobiographical memory performances in aMCI patients expressed in z-scores using the matched controls as reference.

Table 2

Results of the partial correlation analyses between neuropsychological measures (z-scores) and episodic autobiographical memory z-scores for the two time periods, correcting for age.

Episodic autobiographical memory	Neuropsychological measures	R	p
Remote period	Verbal episodic memory retrieval	0.62	0.004
	Verbal episodic memory encoding	0.27	0.25
	Semantic memory	0.26	0.29
	Personal semantic autobiographical memory	0.76	0.002
	Executive functions	0.50	0.08
Recent period	Global cognitive function	0.50	0.03
	Verbal episodic memory retrieval	0.59	0.008
	Verbal episodic memory encoding	0.29	0.23
	Semantic memory	0.07	0.77
	Personal semantic autobiographical memory	0.26	0.29
	Executive functions	0.09	0.71
	Global cognitive function	0.36	0.13

* Correlations are considered as significant at $p < 0.008$ to account for multiple testing.

3.3. Comparison between HC and aMCI patients in grey matter volume and metabolism in the clusters of interest

The comparison of the grey matter volume between HC and aMCI patients revealed no significant difference in the two clusters from the remote period (left temporal cortex – cluster 1_MRI_remote: $t(43) = 1.44$, $p = 0.16$; right temporo-parietal cortex – cluster 2_MRI_remote: $t(43) = -0.62$, $p = 0.54$). In contrast, a significant decrease was found in aMCI compared to HC in both clusters from the recent period (right medial temporal lobe – cluster 1_MRI_recent: $t(43) = 2.32$, $p = 0.03$; left medial temporal lobe – cluster 2_MRI_recent: $t(43) = 2.52$, $p = 0.02$; see Fig. 2).

As for the comparison of FDG metabolism, no difference was found between HC and aMCI patients in the left anterior cingulate gyrus (cluster 1_FDG_remote: $t(43) = 0.44$, $p = 0.44$). By contrast a significant decrease in aMCI compared to controls was found in two out of the four clusters for the recent period (right fronto-hippocampal region – cluster 2_FDG_recent: $t(43) = 4.84$, $p > 0.001$; posterior cingulate cortex – cluster 3_FDG_recent: $t(43) = 2.40$, $p = 0.02$; see Fig. 3).

4. Discussion

In the present study, we aimed at assessing the cognitive and neural correlates of remote versus recent episodic autobiographical memory so as to better understand the gradient of Ribot in early AD. In patients with aMCI, we found that the performances for the remote period correlated with i) personal semantic performances, verbal episodic memory retrieval (and global cognition as a trend); ii) temporo-parietal and temporal pole volumes and anterior cingulate metabolism, which were all found to be preserved in MCI compared to HC. By contrast, performances for the recent memories only correlated with anterograde episodic memory performances, and the neural substrates included medial temporal (including hippocampal), medial and lateral prefrontal and posterior cingulate areas, most of which being significantly impaired in MCI patients compared to HC.

4.1. Recent autobiographical memory correlates

The involvement of the hippocampal volume and metabolism in recent episodic autobiographical memories is consistent with three previous studies in AD that reported a link with hippocampal (or medial temporal lobe) volume (Gilboa et al., 2005; Philippi et al., 2012) and metabolism (Eustache et al., 2004) for recent periods. The hippocampus is known as a key region for episodic memory processing (Squire and Zola-Morgan, 1991) and also as the main structural substrate for episodic memory deficits in AD (Desgranges et al., 2002; Eustache et al.,

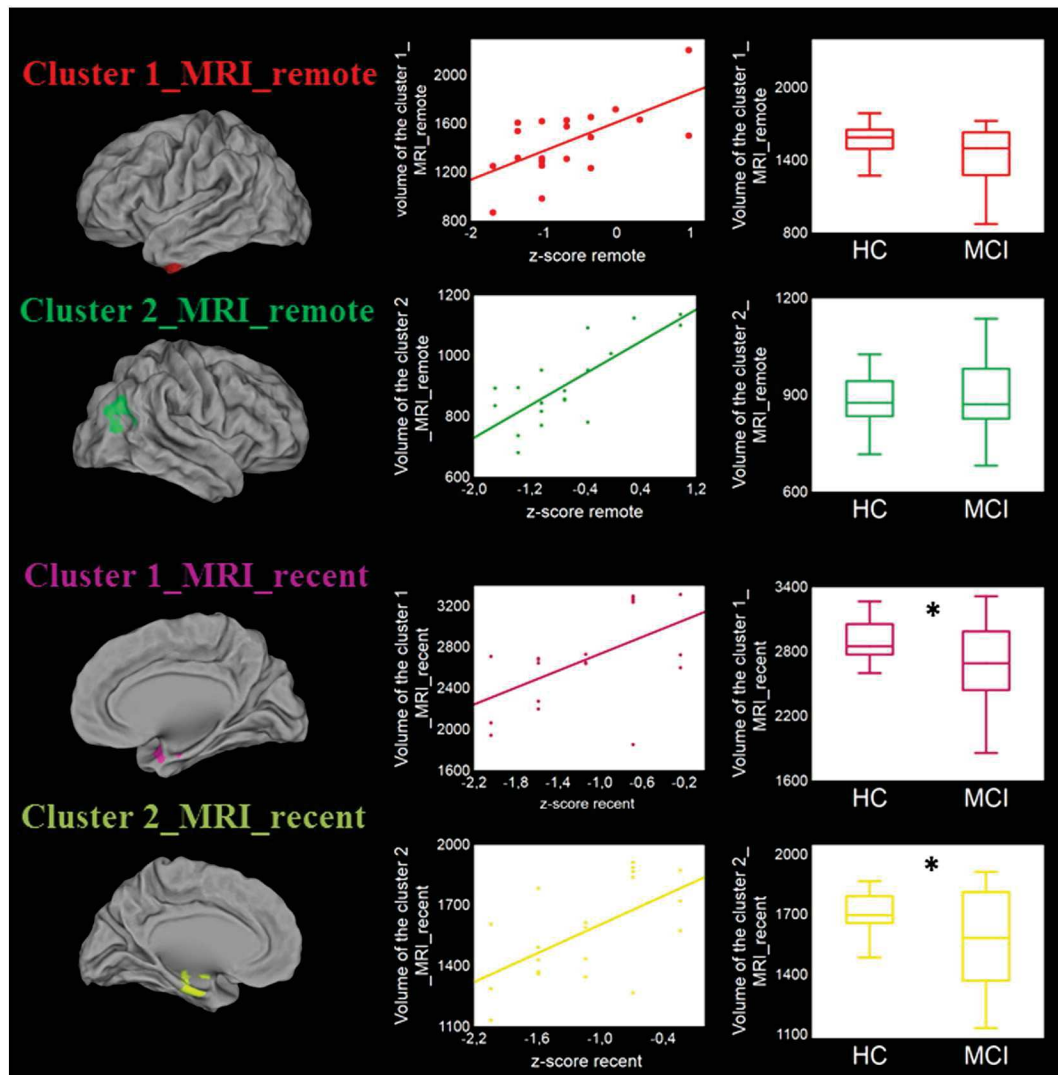


Fig. 2. Positive correlations between remote versus recent episodic autobiographical memory z-scores and grey matter volume, and boxplots of the comparison of grey matter volumes in each corresponding cluster between healthy controls and aMCI patients.

2001) and even in aMCI patients (Chételat et al., 2003; Fouquet et al., 2012; Stoub et al., 2006). Its implication here thus suggests that recent autobiographical memory retrieval mainly relies on episodic memory processes, consistently with the results of the correlation analyses with neuropsychological performances. Note that the only study that assessed this question in patients with aMCI did not find an association with hippocampal volume or metabolism (Bastin et al., 2013). The specific reason for this discrepancy is difficult to identify as there are many differences between this previous paper and ours. Indeed, the autobiographical task (they assessed the degree of episodicity while we assessed the number of episodic events, and the periods differed), and neuroimaging data processing (in our study we applied PVE correction of FDG-PET data and performed cerebellum instead of proportional scaling, two factors known to have a strong influence on the results especially for hippocampal metabolism measurement in early AD; see Mevel et al. 2007) are different.

Beyond the hippocampus, our analyses demonstrated the involvement of other brain areas in recent memories, such as the amygdala (both in terms of volume and metabolism), and the posterior cingulate, medial orbitofrontal, ventrolateral prefrontal and inferior temporal cortex. The amygdala as well as the orbitofrontal cortex are well-known for their role in the processing of emotional information notably in relation with memory (LeDoux, 1998; Roberts et al., 2004); our finding may thus

reflect the emotional content associated with vivid recent memories, and its contribution to the retrieval of these memories. The posterior cingulate cortex is described as a part of the core autobiographical network [for review Svoboda et al., 2006]; it is also known to have a role in episodic memory processes, and to be at least partly responsible for early anterograde episodic memory deficits in AD and aMCI (Bastin et al., 2010; Chételat et al., 2003). The ventrolateral prefrontal activity has been associated with strategic retrieval, monitoring, and selection of relevant information from posterior cortical association areas (Fletcher and Henson, 2001; Henson et al., 1999; Petrides, 2002). Finally, the inferior temporal cortex is part of the “semantic system” (Binder et al., 2009) known to be involved in semantic memory. More specifically, it is considered as an area of high-level integration that stores abstract representations of entity and event knowledge (Binder and Desai, 2011).

Interestingly, all of these regions are part of the Default Mode Network (DMN), a set of brain regions that are consistently more activated during a resting or passive baseline condition than during active, goal-directed analyses of environmental stimuli (Raichle et al., 2001). Some of these regions, such as the posterior cingulate, medial orbitofrontal and ventrolateral prefrontal cortex, are DMN hubs, while others are not always included in the DMN, but all are often co-activated and show correlated activity (Buckner et al., 2009; Tomasi et al., 2010).

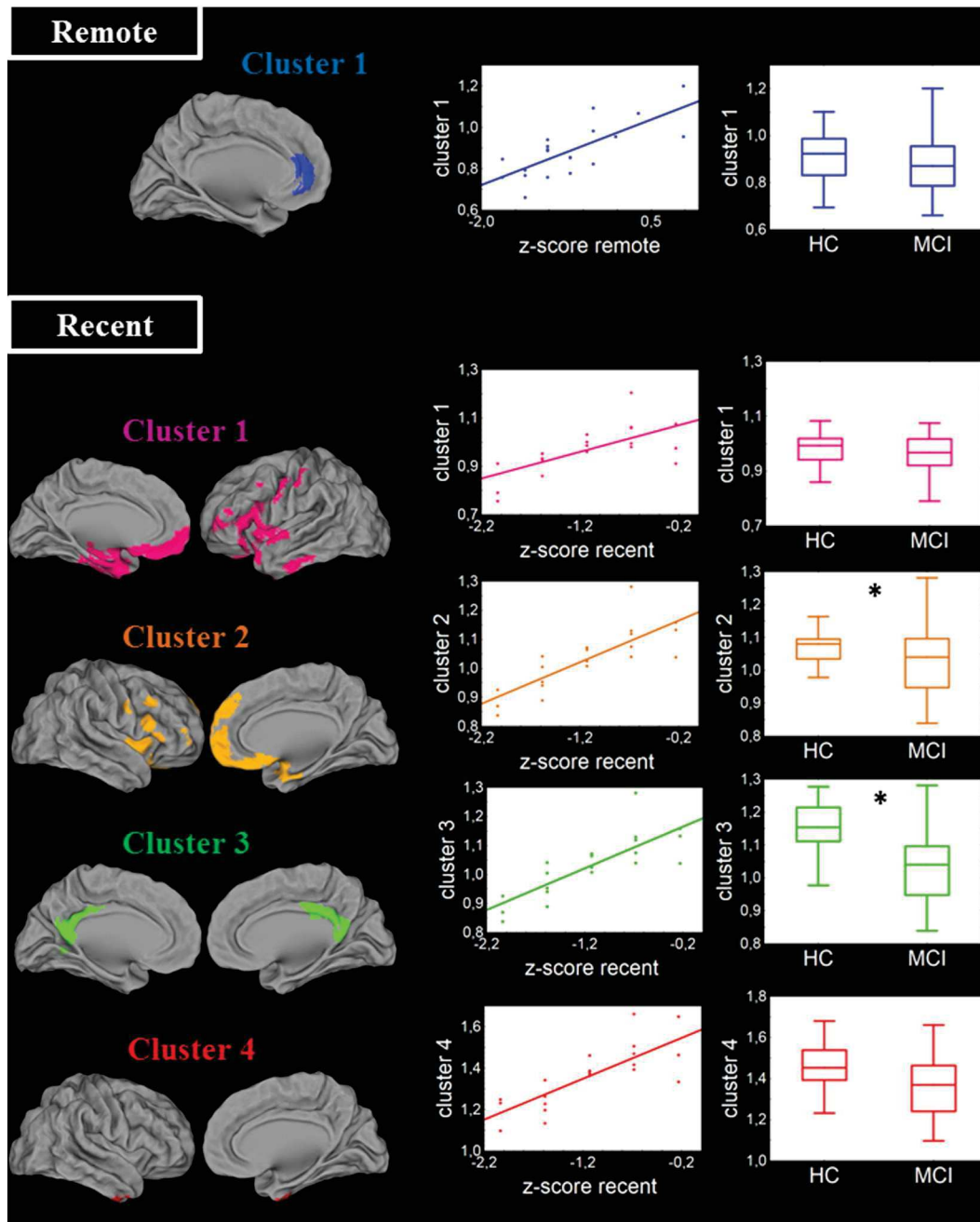


Fig. 3. Positive correlations between episodic autobiographical remote versus recent memory z-scores and brain metabolism, and boxplots of the comparisons of FDG metabolism in each corresponding cluster between healthy controls and aMCI patients.

The DMN is thought to have a role in introspection processes including mind-wandering, prospective thoughts and recollection of autobiographical memories. Our findings as a whole thus reveal the implication of brain areas often co-implicated not only in episodic memory tasks and related processes - especially in autobiographical memory such as introspection, self and emotional processes - but also in semantic processes.

4.2. Remote autobiographical memory correlates

The autobiographical memory score for the remote period was found to correlate not only with anterograde episodic memory, but also with other cognitive functions, i.e. personal semantic memory and, as a trend, global cognitive functions. This is consistent with the view that remote memories tend to be less episodic in nature as they

“semantize” with time (Cermak, 1984; Martinelli et al., 2013; Schmidtke and Vollmer, 1997). Thus, as mentioned in the Introduction section, the retrieval of remote autobiographical memory is expected to depend less on the episodic network structures (medial temporal lobe structures) and more on neocortical structures compared to recent memories (Eustache et al., 2004). Consistent with this interpretation, the neuroimaging analysis did not show a relationship between remote autobiographical memory and the hippocampus (neither to the structure nor to the metabolism). Similarly, Eustache et al. (2004) did not find a link between remote memories and metabolism in the hippocampus but with frontal and posterior regions. Other structural and functional studies in AD however reported a link between remote autobiographical memory performances and the medial temporal volume (Gilboa et al., 2005; Irish et al., 2014; Philippi et al., 2012). The involvement of the hippocampus for both recent and remote memories has also been shown in functional

Table 3
Statistics of the correlations between grey matter volume or metabolism and remote versus recent autobiographical z-scores correcting for age.

	Regions	Coordinates (mm) of the peak voxels within significant clusters			T-value	Cluster size	MCI vs HC		
		x	y	z			t	dl	p
Cluster 1_MRI_remote	L temporal pole L inferior temporal neocortex L fusiform gyrus	−38	−4	−37	4.84	1519	−0.62	43	0.54
Cluster 2_MRI_remote	R temporo-parietal area R angular gyrus R middle occipital gyrus	45	−68	30	5.21	2142	1.44	43	0.16
Cluster 1_MRI_recent	R anterior hippocampus R parahippocampal gyrus R amygdala	13	−5	−23	3.96	1875	2.52	43	0.02
Cluster 2_MRI_recent	L anterior hippocampus L parahippocampal gyrus L amygdala	−12	−7	−23	4.98	3173	2.32	43	0.03
Cluster 1_FDG_remote	L anterior cingulate gyrus	−8	42	2	5.70	316	0.44	43	0.66
Cluster 1_FDG_recent	L medial orbitofrontal L ventro-lateral prefrontal cortex L hippocampal region (i.e. hippocampus, amygdala, parahippocampal and fusiform gyrus extending to the temporal neocortex)	−6	32	−22	6.70	6479	0.27	43	0.79
Cluster 2_FDG_recent	R medial orbitofrontal R ventro-lateral prefrontal cortex R hippocampal region (i.e. hippocampus, amygdala, parahippocampal and fusiform gyrus extending to the temporal neocortex)	6	28	−20	5.88	4279	1.61	43	0.11
Cluster 3_FDG_recent	L posterior cingulate cortex	−6	−56	16	5.70	1001	4.84	43	<0.001
Cluster 4_FDG_recent	R anterior parahippocampal gyrus R fusiform gyrus R inferior temporal gyrus	44	−2	−36	3.54	276	2.40	43	0.02

neuroimaging studies performed in healthy subjects (Addis et al., 2004; Conway et al., 1999; Gilboa, 2004; Maguire, 2001; Maguire and Frith, 2003b; Rekkas and Constable, 2005; Ryan et al., 2001; Steinworth et al., 2006; Viard et al., 2010). Our results may appear as contradictory; however, the hippocampus was also found to be related to remote memories when lowering the statistical threshold ($p < 0.05$ uncorrected) but the relationships were stronger for recent memories. In addition, the involvement of the hippocampus is likely to depend on the task and measures used to assess remote memory. In the present study, despite the fact that only episodic memory events (i.e. recalled with details and situated in time and space) have been counted, it is likely that the events were less episodic in nature for the remote than for the recent period. This probably reflects the ecological situation where individuals rely more on semantic (and other) processes to retrieve remote events than on strictly episodic processes (Cermak, 1984; Martinelli et al., 2013; Schmidtke and Vollmer, 1997) and this is reinforced by the fact that the remote events have been repeated over time since they occurred. It seems yet that, in specific conditions where the subjects are guided and supported to retrieve remote events mostly relying on episodic memory, the hippocampus is significantly involved (Viard et al., 2007; Addis et al., 2004; Conway et al., 1999; Gilboa et al., 2004; Maguire and Frith, 2003a, 2003b; Rekkas and Constable, 2005; Ryan et al., 2001; Steinworth et al., 2006; Viard et al., 2010).

Remote autobiographical memory was found to relate to temporo-parietal and temporal pole volume and anterior cingulate metabolism. The anterior cingulate cortex is known to play a role in attention processes including divided attention (Nebel et al., 2005), and in episodic memory (Martinelli et al., 2013) while the temporal pole is thought to be involved in semantic (naming) tasks and emotional integration of highly processed perceptual inputs (Olson et al., 2007; Semenza, 2011). As for the temporo-parietal junction, this region is included in the DMN and is thought to be involved in episodic and semantic components of autobiographic memories (Renoult et al., 2012). Altogether, our findings suggest that not only multiple processes are involved in the retrieval of remote memories, including semantic and attention but also episodic processes.

4.3. Recent versus remote memories: an interplay between episodic and semantic memory components

Our results suggest that the retrieval of recent memories not only is essentially based on episodic memory abilities but also relies on brain regions involved in semantic processes. This highlights the relevance of semantic processes in the retrieval of autobiographical events. Indeed, even if these recent memories are still very detailed and contextualized, episodic memory requires binding of contextual elements within existing frameworks of conceptual knowledge (Reder et al., 2009). On the other hand, the retrieval of remote memories was found to rely mainly on semantic processes and network. However, behavioural and imaging results also reveal the presence of an episodic component in remote memory retrieval. This is consistent with the fact that remote memories are not expected to be independent from episodic memory structures, but to rely less on these structures, and more on other (neocortical) structures, as compared to recent memories (Moscovitch et al., 2005; Nadel et al., 2007a, 2007b). Moreover, the involvement of the temporal neocortex for both remote and recent memories likely reflects the semantic component associated with autobiographical memories (Svoboda et al., 2006; Holland et al., 2011; Addis et al., 2004; Maguire and Frith, 2003; Gilboa et al., 2005; Renoult et al., 2012). As a whole, our results agree with the idea that autobiographical memories cannot be considered from a binary perspective (i.e. either episodic or semantic in nature) but rather as involving both components to a variable degree. Consistent with this view, several authors have highlighted the existence of an interplay between the episodic and semantic components of memories (Greenberg and Verfaellie, 2010; Irish and Piguet, 2013; Renoult et al., 2012).

4.4. Differential impairment of remote versus recent memory performances and neural substrates in MCI

Consistent with the gradient of Ribot, aMCI patients showed significantly greater impairment for recent than for remote memories in the

present study. This report is consistent with previous studies in AD (Addis and Tippett, 2004; Greene et al., 1995; Irish et al., 2011; Ivanou et al., 2004; Kopelman et al., 1989; Leyhe et al., 2009; Piolino et al., 2003) and aMCI patients (Irish et al., 2010; Leyhe et al., 2009; Murphy et al., 2008).

Moreover, showing that most brain regions involved in recent memories are impaired in aMCI patients compared to controls while those involved in remote memories are relatively preserved, the present study furthers our understanding of the brain mechanisms of the gradient of Ribot, i.e. the fact that recent autobiographical memories are more sensitive while remote ones are more resistant in MCI. Thus, in early AD, atrophy is known to concern firstly the hippocampus before extending to the temporal neocortex and other polymodal association areas (Atiya et al., 2003; Chetelat et al., 2003); the former was related with the events from the recent period while the latter were involved in the retrieval of remote memories. Similarly for metabolism, earliest changes in AD are known to concern the posterior cingulate (involved in the recent period) and temporo-parietal cortex, before extending to medial and lateral prefrontal regions (found for the remote period). In sum, the Ribot gradient is likely to reflect the fact that the neural substrates for remote versus recent memories are distinct, and differentially sensitive to the pathological processes underlying MCI.

4.5. Limitation

A limitation of our autobiographical memory task is that it only assesses a limited number of life periods. It has been shown that a lower number of periods were associated with a greater chance of demonstrating a temporal gradient (Barnabe et al., 2012). It is possible that the assessment of a greater number of epochs (e.g. 5 life periods) would reduce this gradient effect and impacts on our neuroimaging findings. Another limitation relates to the time granted for autobiographical memory recollection. As the participants were asked to give as many events as possible in a limited time (2 min), the performances may have been influenced by initiative search abilities which may be impaired in patients. To ensure that our findings, and more specifically autobiographical memory performances, were not merely the reflect of generative search processes, we used another independent time-limited fluency task as a covariate to control for this factor; the results were essentially unchanged (data not shown). Moreover, the autobiographical fluency task is not as specific as other tasks such as those using specific probing (Autobiographical Interview, Levine et al., 2002; TEMPau, Piolino et al., 2000). Indeed, the richness in episodic details and contextual specificity might influence the results and more specifically the implication of the hippocampus. Future studies using other autobiographical episodic memory tasks would allow further understanding the impact of the task.

4.6. Conclusion

In conclusion, this study contributes to our understanding of the Ribot gradient in aMCI considered as the early (predementia) stage of AD. It would be interesting to further explore this question from a network perspective to highlight the role of connectivity disruption within specific networks. Task-related functional MRI also appears as a complementary approach to grasp a more complete picture of the mechanisms of recent versus remote memory deficits in early AD, allowing to unravel not only regions of impaired activity in aMCI in each condition, but also potential areas of increased activity.

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.nicl.2015.05.010>.

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7.1.3. Perrotin *et al.*, (2016)



Featured Article

Subjective cognitive decline in cognitively normal elders from the community or from a memory clinic: Differential affective and imaging correlates

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Abstract

Introduction: Subjective cognitive decline (SCD) could indicate preclinical Alzheimer's disease, but the existing literature is confounded by heterogeneous approaches to studying SCD. We assessed the differential cognitive, affective, and neuroimaging correlates of two aspects of SCD: reporting high cognitive difficulties on a self-rated questionnaire versus consulting at a memory clinic.

Methods: We compared 28 patients from a memory clinic with isolated SCD, 35 community-recruited elders with similarly high levels of self-reported cognitive difficulties, and 35 community-recruited controls with low self-reported cognitive difficulties.

Results: Increased anxiety and β -amyloid deposition were observed in both groups with high self-reported difficulties, whereas subclinical depression and (hippocampal) atrophy were specifically associated with medical help seeking. Cognitive tests showed no group differences.

Discussion: These results further validate the concept of SCD in both community- and clinic-based groups. Yet, recruitment methods influence associated biomarkers and affective symptomatology, highlighting the heterogeneous nature of SCD depending on study characteristics.

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Keywords:

Alzheimer's disease; Subjective cognitive decline; Cognitive complaint; Preclinical; Beta-amyloid; Florbetapir-PET; MRI; Atrophy; Hippocampus; Anxiety; Depression

1. Introduction

Some elder individuals experience subjective cognitive decline (SCD) while showing normal "objective" cognitive

performances (i.e., scores within the normal range on standardized neuropsychological tests). Although these individuals have been described for decades [1], they have received increasing attention over the past few years, with the growing interest in characterizing preclinical stages of Alzheimer's disease (AD) [2,3]. Indeed, several epidemiologic studies have shown that, in elders without identifiable cognitive deficits, SCD is associated with a higher risk to develop mild cognitive impairment or AD dementia [4–8].

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Recent research has also shown that, at the group level, SCD is associated with neuroimaging biomarkers suggestive of AD (atrophy and/or hypometabolism in temporoparietal regions [9–21] and β -amyloid deposition [18,22–26]), although negative findings have also been reported [27–31] (see Table 1 for review).

This converging evidence suggests that SCD could be among the first clinically observable signs of AD. However, individuals with SCD constitute a heterogeneous population [32]: in a considerable proportion of cases, SCD is likely due to non-AD etiologies including poor general health, sleep disorders, medication, or personality traits [33]. The current challenge is thus to identify the specific characteristics of SCD that are associated with an increased likelihood of AD etiology.

The SCD-Initiative working group recently published a conceptual framework for research on SCD in the context of preclinical AD; this initiative is meant to propose SCD criteria and encourage standardized research to refine our understanding of SCD [34]. Indeed, comparison between existing studies is currently hampered by the wide variability in the definition and criteria used to study SCD (aka “subjective cognitive/memory impairment,” “cognitive/memory complaint,” etc [34]). As recently highlighted [35,36], the recruitment procedure is an important source of variability among studies (see Table 1). SCD has been studied in volunteers from the community [18,22,23,25] or more rarely from population-based samples [14,26]; in these cases, diverse questions or questionnaires were used to quantify SCD [37]. Other studies have used a different approach, specifically assessing patients recruited from a memory clinic [9–11,13,17,24,38–41], that is, patients who sought help because of SCD. In the latter case, it could be hypothesized that the active process of seeking medical help is motivated by more important subjective cognitive difficulties and/or associated concern, which might have clinical relevance [42,43]. Previous studies generally reported AD-like brain alterations in clinical SCD individuals compared with community-recruited controls (see Table 1). However, groups are generally not matched on the level of self-reported cognitive difficulties: when documented, clinical SCD patients report more subjective difficulties than controls [11,24]. Then, it is not clear whether the presence of abnormal AD biomarkers is mainly associated with higher subjective difficulties or with the medical help-seeking behavior per se. Clarifying this point is crucial to determine whether selecting medical help seekers has actual added value to studying SCD and potentially to screen participants in the context of enrichment strategies for clinical trials in clinically normal individuals [3,26,44].

In addition, most studies have shown that SCD is more associated with subclinical anxiety and depression than to actual cognitive performances [9–16,33,45–47]. Interestingly, evidence also suggests that the psychoaffective symptomatology usually increases in early or preclinical stages of cognitive decline [48,49] and/or that it could even constitute a risk factor for subsequent

cognitive decline [50,51] (for review and discussion, see the articles by Marchant and Howard [52] and Ismail et al [53]). Overall, the relationship between SCD and affective factors needs to be further refined, notably as anxiety and depression seem to parallel self-reported cognitive difficulties and could be associated with (and maybe trigger) medical help-seeking behavior.

Keeping with the aims of the SCD-Initiative and aforementioned caveats in the literature, the objective of the present study was to assess the relevance of recruitment setting in selecting SCD individuals to identify those with preclinical AD. For this purpose, we compared SCD patients recruited from a memory clinic (SCDclinic group) with individuals recruited from a pool of community-recruited volunteers who scored high on a self-rating cognitive difficulty scale (SCDcommunity group). We assessed the relevance of this feature with regard to neuropsychological performances, affective measures, and neuroimaging biomarkers (gray matter atrophy and β -amyloid deposition). We hypothesized that SCD individuals who seek help in a memory clinic would be more likely to have indicators of preclinical AD than those recruited from the general community.

2. Methods

2.1. Participants

A total of 100 cognitively normal individuals were included in the present study. They were all right handed, aged 54 years or older, and included in the multimodal neuroimaging study of early AD (IMAP+) in Caen, France. Participants were recruited from two main sources (see Fig. 1).

Twenty-eight patients were recruited from the local memory clinic (SCDclinic), which they attended because of self-reported cognitive concerns. During the interview, the clinician ensured that the complaint was not related to current medication taking, major psychiatric or neurologic conditions (including major depressive disorder or generalized anxiety disorder), or other medical conditions. Patients underwent standardized neuropsychological testing which did not identify any objective cognitive impairment (scores were in the normal range for each neuropsychological test). Patients were then offered to participate in the IMAP+ study to undergo additional cognitive and neuroimaging examinations.

Seventy-two participants were recruited from the community through public advertising, as they volunteered to participate in the IMAP+ study. They had no history of major medical condition, had never consulted a memory clinic, and performed in the normal range on a standardized neuropsychological examination. This group was further divided into two groups depending on their self-reported cognitive difficulties (see section 2.2.1 below). Using a median split, 35 individuals with low scores were used as a control group and the 35 individuals with the highest scores were considered as the SCDcommunity group; note that two individuals

Table 1
Overview of cross-sectional studies assessing associations between SCD and AD neuroimaging biomarkers in cognitively normal elders

Reference	Cohort	Sample of cognitively normal individuals, n (mean age)	Approach to define/assess SCD	MRI and/or FDG-PET	β-Amyloid PET
Community-recruited volunteers					
Rowe 2010 [61]	AIBL*	n = 177 (71.6)	1 binary question	ns	†
Chetelat 2010 [60]	AIBL*	n = 94 (74.4)	1 binary question	†	ns
Hollands 2012 [29]	AIBL*	n = 273 (~69.5)	1 questionnaire		ns
Zwan 2016 [62]	AIBL*	n = 307 (72.7)	1 binary question		†
Amariglio 2012 [22]	HABS	n = 131 (73.5)	1 composite of 3 questionnaires		‡
Amariglio 2015 [18]	HABS	n = 257 (73.7)	1 composite of 3 questionnaires	‡	‡
Schultz 2015 [12]	*	n = 261 (54.3)	1 binary question	‡	
Perrotin 2012 [23]		n = 48 (73.5)	2 questions assessed separately		†
Snitz 2015a [25]	P-ADRC	n = 92 (81.2)	3 questionnaires assessed separately		†
Gardener 2016 [92]		n = 43 (66)	1 binary question	ns	
SCDclinic vs. community volunteers					
Van der Flier 2004 [9]		28 Cont (75), 20 SCD (72)	Memory clinic consultation	†	
Jessen 2006 [39]	Bonn1	14 Cont (66.5), 12 SCD (66.1)	Memory clinic consultation for <5 y SCD	†	
Tapest 2008 [41]	Bonn1	13 Cont (67.5), 13 SCD (66.4)	Memory clinic consultation for <5 y SCD	†	
Striepens 2010 [13]	Bonn2	48 Cont (65.8), 21 SCD (66.3)	Memory clinic consultation for <10 y SCD, informant confirmed	‡	
Scheef 2012 [10]	Bonn2	56 Cont (66.4), 31 SCD (67.6)	Memory clinic consultation for <10 y SCD with worry, informant confirmed	‡	
Peter 2014 [38]	Bonn2	53 Cont (67.1), 24 SCD (66.0)	Memory clinic consultation for <10 y SCD with worry, informant confirmed	‡	
Erk 2011 [28]	Bonn3	20 Cont (66.8), 19 SCD (68.4)	Memory clinic consultation for <10 y SCD with worry, informant confirmed	ns	
Meibeth 2015 [40]	Bonn2+3	69 Cont (66.1), 41 SCD (68.9)	Memory clinic consultation for <10 y SCD, informant confirmed	†	
Rodda 2010 [64]		14 Cont (63.9), 5 SCD (64.2)	Memory clinic consultation		ns
Hafkemeijer 2013 [17]		29 Cont (71.3), 25 SCD (71.4)	Memory clinic consultation	‡	
Kiuchi 2014 [27]		28 Cont (75.2), 28 SCD (70.5)	Memory clinic consultation	ns	
Ivanou 2015 [63]		31 Cont (70.0), 32 SCD (~70)	Memory clinic consultation	†	ns
Perrotin 2015 [11]	IMAP+	40 Cont (69.4), 17 SCD (67.1)	Memory clinic consultation [§]	‡	
Snitz 2015b [24]	P-ADRC	84 Cont (73.6), 14 SCD (68.1)	Memory clinic consultation [§]		‡
Sun 2016 [31]		61 Cont (65.5), 25 SCD (64.1)	Memory clinic consultation for < 5 y SCD, informant confirmed	ns	
Population-based samples					
Stewart 2008 [14]		n = 1779 (72.5)	2 binary questions (SCD when both positive)	‡	
Mielke 2012 [26]		n = 483 (78)	Composite of 5 questions		‡
Cherbuin 2015 [30]		n = 305 (62.6)	1 binary question	ns	
Other					
Saykin 2006 [15]		n = 80 (72.2); mixed recruitment (community, clinic ...)	Consensus evaluation using a composite index (multiple self and informant-based questionnaires)	‡	
Mosconi 2008 [19]		n = 28 (59); mixed recruitment (community, clinic ...)	Structured informant-corroborated interview	‡	
Van Norden 2008 [16]		n = 500 (65.6); cognitively normal individuals recruited from a neurology clinic (but initial consultation was unrelated to cognition)	Semistructured interview	‡	
Kim 2013 [20]		28 Cont (70.7), 90 SCD (65.8); all recruited in a clinical setting	Reason for seeking help: memory or health promotion?	‡	
Cantero 2016 [21]		n = 95 (68.8); mixed recruitment (community, clinic...)	Questionnaire, structured interview	‡	

Abbreviations: SCD, subjective cognitive decline; AD, Alzheimer's disease; MRI, magnetic resonance imaging; FDG-PET, fludeoxyglucose positron emission tomography; AIBL, Australian Imaging Biomarker and Lifestyle Study; HABS, Harvard Aging Brain Study; IMAP+, Imagerie Multimodale de la maladie d'Alzheimer à un stade Précoce (multimodal imaging of early Alzheimer's disease; same as current article); P-ADRC, Pittsburg Alzheimer's Disease Research Center.

NOTE. The name of the cohort is indicated when several articles were derived from the same cohort and have at least partly overlapping samples. Bonn1, Bonn2, and Bonn3 are three nonoverlapping cohorts recruited in Bonn, Germany. Meiberth 2015 includes data from Bonn2, Bonn3 + additional patients not included in previous articles.

“ns” indicates nonsignificant association on the imaging modality/region of interest assessed.

*Indicates that cohorts are intentionally enriched in individuals at risk for AD (e.g., *APOE*, family history).

†Associations are found but seem more subtle/milder: (1) only significant for one but not all tested biomarkers (e.g., Avanoiu 2015: effect on FDG-PET but not MRI); (2) only significant in a subgroup (e.g., Zwan 2016 and Rowe 2010: relationship between subjective concern and amyloid is only significant in *APOE* $\epsilon 4$ carriers); (3) only significant with one but not all SCD measures when several were used (e.g., Perrotin 2012, Snitz 2015a); (4) in regions not classically suggestive of AD (e.g., Chételat 2010: atrophy restricted to the bilateral superior frontal sulcus); and (5) pattern is suggestive of AD but statistically not significant (e.g., Tepest 2008: subtle deformations are found along the lateral border of the hippocampus).

‡Significant association consistent with SCD as an indicator of preclinical AD (the more the SCD, the more the amyloid/neurodegeneration).

§For these studies, SCD was solely defined as seeking help at a memory clinic. Additional questionnaires were used to quantify/illustrate the higher self-reported cognitive difficulties in the participants but were not part of the SCD/non-SCD classification procedure.

with median values were not included in any group but were still included in the complementary analyses.

All participants were independent in daily life, did not use any psychoactive medication, and gave informed consent to the study. Importantly, none of the participants knew their *APOE* genotype or florbetapir status when enrolling in the present study.

2.2. Behavioral testing

2.2.1. Self-reported cognitive difficulties

SCD was assessed with the Cognitive Difficulties Scale [54], a 39-item questionnaire that requires participants to rate how often they experience particular cognitive difficulties in everyday life on a 5-point scale (from “never” = 0 to “very often” = 4). In the present study, we used the sum of the self-ratings from 26 items as a measure

of self-reported cognitive difficulties, higher scores indicating more subjective difficulties. These 26 items were identified in a previous independent study conducted in 1648 cognitively normal elder French individuals [55] using a principal component analysis. The rationale for choosing this reduced score, rather than the total 39 item-based score (although they are strongly correlated, $r = 0.99$ [55]), was that it excluded some items that were very rarely endorsed by our participants, not relevant to our main focus, and/or highly gender biased (e.g., “I need to check or double check whether I locked the door, turned off the stove”; “I misplace my clothing”; “I forget steps in recipes I know well and have to look them up”).

2.2.2. Affective measures

Depressive symptomatology and trait anxiety were assessed using the Montgomery-Asberg Depression Rating Scale and Spielberger State-Trait Anxiety Inventory (STAI), respectively.

2.2.3. Cognitive measures

Participants underwent a comprehensive neuropsychological test battery designed to screen the main cognitive functions including verbal, visual, and autobiographical episodic memory; language abilities; working memory; executive functioning; processing speed; praxis; and visuospatial functioning [56]. To obtain robust proxies of cognitive abilities and minimize the issue of multiple statistical testing when comparing groups, composite scores were created for processing speed, executive functions, language, episodic memory (free recall), and autobiographical memory, considering both people and events (see [Supplementary Material](#) for further detail). For all composite scores, higher values indicate better performances.

2.3. Brain imaging acquisition and processing

Gray matter volume and β -amyloid deposition were measured in all participants using structural magnetic resonance imaging (MRI) and florbetapir positron emission tomography (PET), which were performed on the same 3T

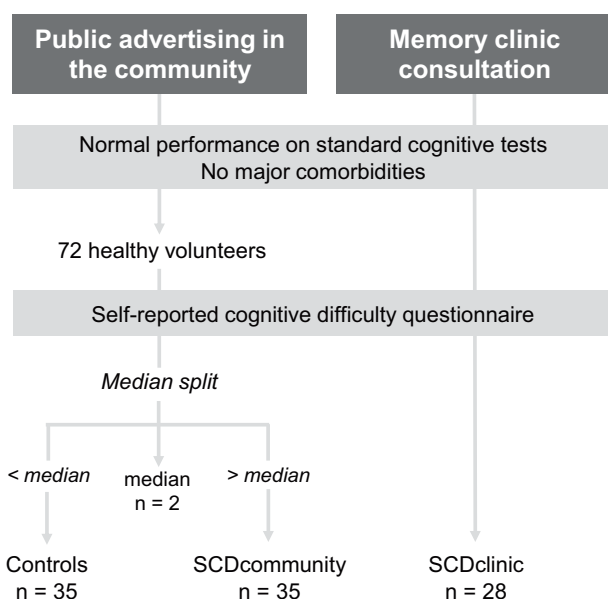


Fig. 1. Flow chart of participant selection and categorization.

MRI and computed tomography–PET scanners at the Cyceron Centre (Caen, France). For florbetapir-PET, six individuals (four SCDclinic and two SCDcommunity) underwent a 10-minute acquisition, whereas the 94 others had a 20-minute scan. The data presented in this article include all 100 participants, but results remained highly similar without these 6 individuals (see [Supplementary Material](#)).

The procedures for imaging data handling and transformation are similar to those used in our previous publications [56] and are detailed in the [Supplementary Material](#). Briefly, MRI data were processed using the voxel-based morphometry (VBM5) toolbox, and neocortical standardized uptake value ratio (SUVR) values were derived from PET images (using cerebellar gray matter as a reference) and used either as a continuous variable or to classify subjects as florbetapir positive or negative, using a threshold derived from an independent group of young individuals [56].

2.4. Statistical analyses

Group differences on demographic, cognitive, and affective measures were assessed using analysis of variance (ANOVA) for continuous variables with one three-level (group) factor and using the Fisher exact test for categorical variables. When the main effect of group was significant ($P < .05$), post hoc analyses were performed using the Fisher least significant difference test using the STATISTICA software (v10.0, StatSoft Inc., Tulsa, OK).

Group differences in gray matter volume were assessed voxelwise using SPM5; between-group differences were considered significant when fulfilling both a $P_{\text{uncorrected}} < .005$ threshold at the voxel level and $P < .05$ threshold at the cluster level. Mean cortical florbetapir-PET SUVR and β -amyloid status were compared between groups with one-way ANOVA and the Fisher exact test, respectively. All comparisons were repeated covarying for demographic variables, and results remained unchanged (see [Supplementary Material](#)).

Complementary analyses were conducted using the measure of self-reported cognitive difficulties as a continuous

variable and assessing potential demographical, cognitive, affective, and neuroimaging correlates. These correlations were run separately in participants recruited from the community ($n = 72$, altogether) and from the memory clinic ($n = 28$). This approach was particularly relevant for the community-recruited sample, as dichotomization of continuous variable (as used in the main analyses to split the community-recruited sample into controls and SCDcommunity) can lead to loss of information and inflation of both false-positive and false-negative findings [57].

3. Results

3.1. Group characteristics

Subjects in the SCDcommunity were significantly older than those of the control group (Table 2). The three groups did not differ in terms of sex ratio, education, and *APOE* $\epsilon 4$ status. Subjects in both SCDclinic and SCDcommunity groups reported more cognitive difficulties than the control group, although they did not significantly differ from each other.

3.2. Behavioral measures

Of the 8 measures (Fig. 2), only the two affective variables showed significant between-group differences. Both ANOVAs were still significant after applying stringent Bonferroni correction ($\alpha = 0.05/8 = 0.00625$) and when controlling for demographic variables (see [Supplementary Material](#)). Post hoc comparisons showed distinct patterns of group differences for anxiety and depression. On the one hand, anxiety was associated with higher levels of self-reported cognitive difficulties but not with medical help seeking: both SCD groups had higher STAI scores than the controls but did not differ from one another. On the other hand, increased depressive symptomatology was specifically associated with medical help seeking: only the SCDclinic group differed from the other two. Note that even in the SCDclinic group, values remained subclinical,

Table 2
Demographics and cognitive scores across groups

	Controls (n = 35)	SCDcommunity (n = 35)	SCDclinic (n = 28)	Tests	Pairwise comparison
Age	65.6 \pm 8.6	70.8 \pm 7.5	67.6 \pm 7.7	$F(2, 95) = 3.75$	$P = .03$ Controls < SCDcommunity**
Female, n (%)	18 (51)	21 (60)	11 (46)	Fisher exact test	$P = .29$
Education	11.9 \pm 3.4	12.6 \pm 4.2	13.3 \pm 3.4	$F(2, 95) = 1.05$	$P = .35$
<i>APOE</i> $\epsilon 4$ carrier, n (% available)	7 (20)	8 (23)	4 (17)	Fisher exact test	$P = .95$
CDS (sum of 26 items)	16.1 \pm 4.9	33.6 \pm 9.5	39.0 \pm 13.6	$F(2, 95) = 57.51$	$P < .001$ Controls < SCDcommunity*** Controls < SCDclinic***
MMSE	28.9 \pm 1.1	28.9 \pm 1.0	28.8 \pm 1.2	$F(2, 95) = 0.11$	$P = .90$
Mattis	142.0 \pm 2.2	141.9 \pm 2.8	141.7 \pm 2.5	$F(2, 95) = 0.2$	$P = .86$

Abbreviations: SCD, subjective cognitive decline; CDS, Cognitive Difficulty Scale; MMSE, Mini-Mental State Examination; SD, standard deviation; ANOVA, analysis of variance; LSD, least significant difference.

NOTE. Values indicate mean \pm SD or number (percentage). When the ANOVA reached significance, Fisher's LSD tests were used. * $P < .05$, ** $P < .01$, *** $P < .001$.

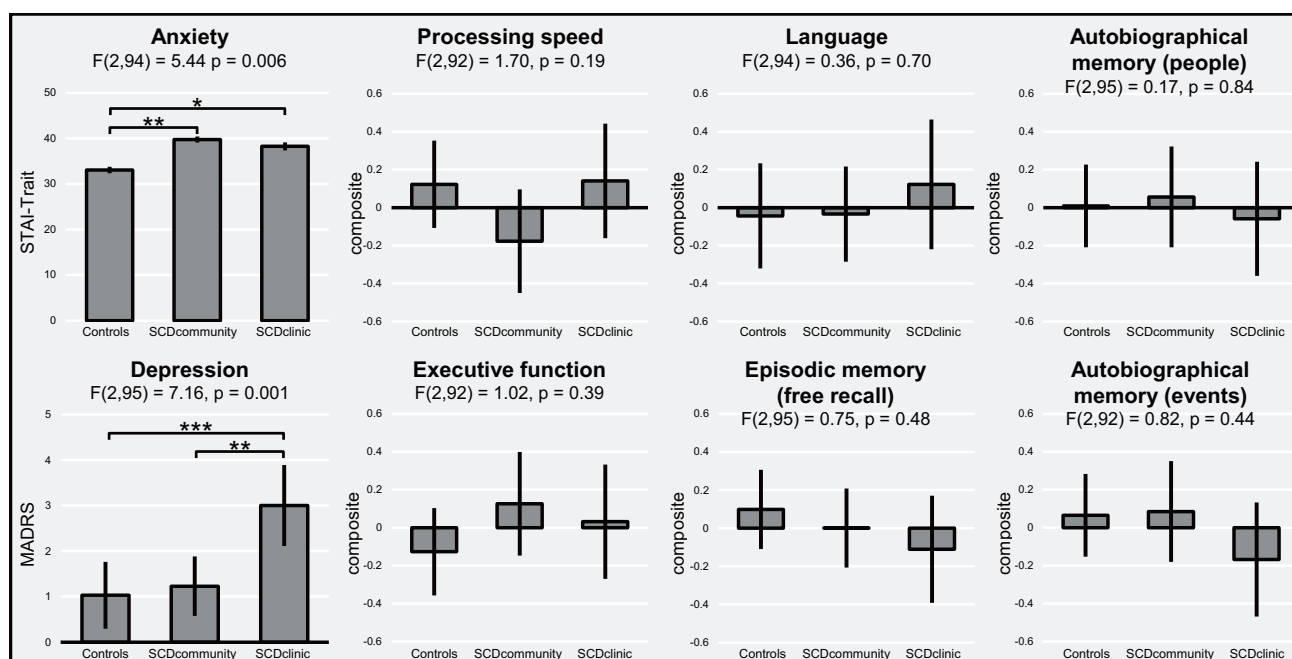


Fig. 2. Group comparison on affective and cognitive scores. Graphs indicate mean value and 95% confidence intervals. F and p values correspond to one-way ANOVA's; post hoc analyses were performed with the Fisher least significant difference test * $p < .05$, ** $p < .01$, *** $p < .001$. Abbreviations: STAI, Spielberger State-Trait Anxiety Inventory; SCD, subjective cognitive decline; MADRS, Montgomery-Asberg Depression Rating Scale.

that is, in the range of values classically reported in nondepressed healthy individuals [58,59].

Contrastingly, none of the cognitive scores showed significant group difference, whether demographic variables were controlled for or not (Supplementary Material).

3.3. Brain imaging

β -Amyloid imaging differed between groups. The proportion of florbetapir-positive individuals was elevated in both SCD groups compared with controls (Fig. 3A). A similar pattern was observed when florbetapir-SUVr was treated as a continuous variable (Fig. 3B), and results remained unchanged when controlling for demographics (Supplementary Material).

When comparing the SCDcommunity with the controls, no significant anatomic difference was found. Contrastingly, significantly lower gray matter values were found in the SCDclinic group when compared with the SCDcommunity group, predominantly in the left hippocampus and parahippocampus, bilateral lateral and anterior temporal lobes, bilateral insula, and the left parietal cortex (Fig. 3D). There were no differences in the reverse contrasts.

3.4. Complementary analyses

Within the SCDclinic group, self-reported cognitive difficulties were not correlated to any demographic, cognitive, affective, or neuroimaging measure (all P 's $> .05$ uncorrected).

In the community-recruited group ($n = 72$), subjective cognitive difficulties were related to age ($r_{(70)} = 0.34$; $P = .003$) and anxiety ($r_{(69)} = 0.49$; $P < .001$) but no other

demographic or cognitive variable (all P 's $> .05$ uncorrected). Voxelwise analyses did not identify significant relationships between subjective cognitive difficulties and gray matter volume, whereas they were related to florbetapir-SUVr ($r_{(70)} = 0.36$; $P = .002$, Fig. 3C). When including all previously identified predictors in a confirmatory multiple regression model, age, trait anxiety, and florbetapir-SUVr independently contributed to subjective cognitive difficulties (see Supplementary Material for further information).

4. Discussion

The present study aimed at further characterizing cognitively normal elders who experience SCD, in line with the idea that SCD could be an early indicator of AD. More specifically, we investigated the differential characteristics associated with two features or potential definitions of SCD to better understand their meaning and relation to pre-clinical AD: the presence of high self-reported cognitive difficulties and the memory clinic help-seeking behavior. Our results suggest that these two aspects have differential affective and neuroimaging correlates: high self-reported cognitive difficulties, independent of recruitment setting, are related to β -amyloid deposition and anxiety, whereas seeking help at a memory clinic is associated with additional subclinical depressive symptomatology and atrophy.

4.1. SCD and amyloid imaging

Previous studies suggested that SCD was associated with the presence of β -amyloid deposition in elders recruited

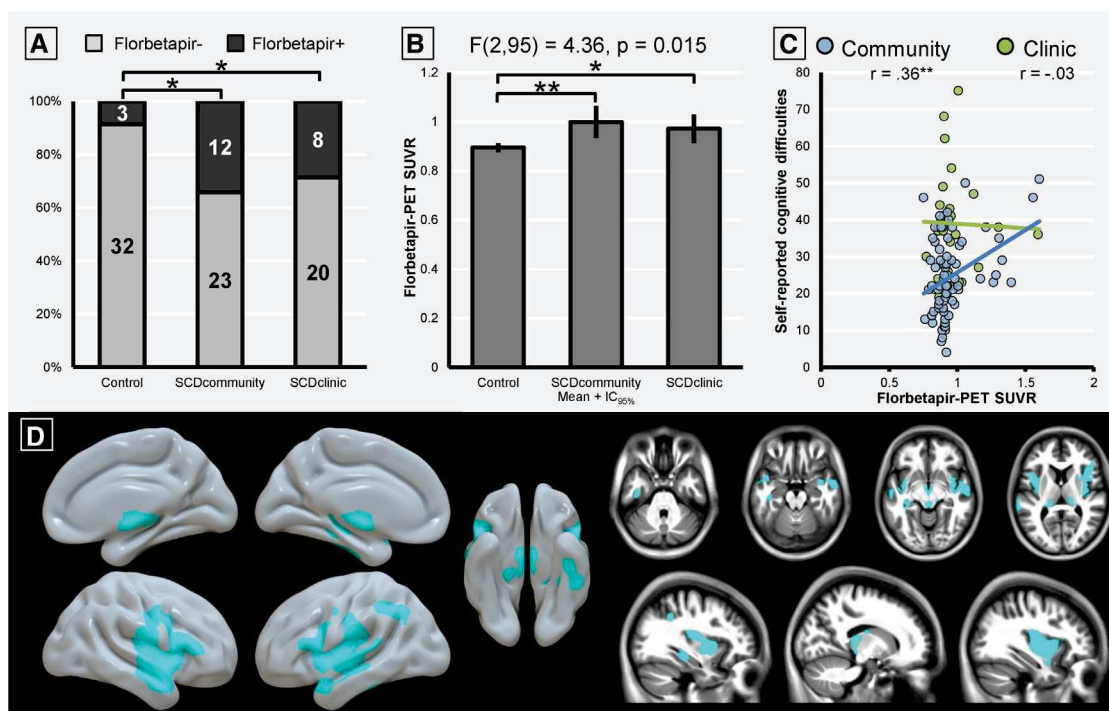


Fig. 3. Neuroimaging results. Florbetapir-PET was compared between groups using global neocortical SUVR as a binary (A) or continuous (B) variable ($*P < .05$, $**P < .01$). Confirmatory analyses (C) showed a significant correlation between florbetapir SUVR and self-reported cognitive difficulties in the whole community-recruited sample but not in the group of patients recruited in the memory clinic. Structural magnetic resonance imaging was analyzed voxelwise and identified regions of significantly lower volume in SCDclinic as compared with SCDcommunity (D, $P < .005$ at the voxel level, $P < .05$ at the cluster level). Abbreviations: SCD, subjective cognitive decline; PET, positron emission tomography.

from the community [18,22,23,25]. However, this effect seems subtle as it was found with some, but not all, measures of subjective complaint [23,25]. Moreover, other publications (from the Australian Imaging Biomarkers and Lifestyle cohort) have reported negative results [29,45,60] or found associations only in *APOE* $\epsilon 4$ carriers [61,62]. Lastly, data from the population-based Mayo Clinic study of aging indicated that subjective memory concerns predicted β -amyloid PET positivity, especially in young (<80 years old) elders. The present findings reinforce these previous results, showing that, in a community-recruited sample of cognitively normal individuals in their mid-50s to mid-70s, higher self-reported cognitive difficulties were associated with florbetapir-SUVR.

Contrastingly, only a few studies have assessed β -amyloid imaging in SCDclinic patients; they reported contradicting results showing increased [24] or similar [63,64] PET uptake values compared with community-recruited healthy elders. However, groups were not matched on their level of self-reported cognitive difficulties [24] (or this was not documented [63,64]), so the group differences were potentially driven by this confound factor rather than the help-seeking behavior per se. The design of our study enabled us to distinguish the respective influence of these two factors and showed that seeking help at a memory clinic was not associated with higher β -amyloid burden: SCDclinic and SCDcommunity groups had very similar β -amyloid deposition (see Fig. 3).

These results have important implications for future clinical trials, especially as the field progressively moves toward interventions in preclinical AD [65] and notably in cognitively normal individuals with evidence for β -amyloid deposition [3,66]. Indeed, to optimize cost-effectiveness, screening procedures should help identify individuals with a high likelihood to harbor amyloidosis, therefore minimizing the rate of β -amyloid negative findings and subsequent exclusions. The present study adds to previous data [18,22,23,25,26], indicating that (1) selecting individuals with high self-reported cognitive difficulties could help identify β -amyloid-enriched groups and that (2) selecting patients from a memory clinic does not improve the likelihood of a positive florbetapir-PET scan compared with their community-recruited counterparts.

4.2. SCDclinic versus SCDcommunity: Why do patients seek medical help?

Our study also sheds light on why some individuals seek help at a memory clinic as we assessed the idiosyncrasies of these patients compared with community-recruited individuals with similar reports of cognitive difficulties. A few studies [67–71] have assessed factors associated with help-seeking behavior, but most were not restricted to elders with formally assessed normal cognitive performances and, to our knowledge, none of them included neuroimaging biomarkers. Existing literature indicates that medical help seeking can be triggered or facilitated by multiple factors including worry

associated with family history of dementia [67,70], low quality of life [67], poor physical health [68], and socioeconomic barriers (high cost/low access to health care [71]). Help seeking might also be influenced by individuals' knowledge, causal beliefs, and attitudes regarding memory function, aging, and dementia [69–71]. The role of affective factors has been debated as some [68] but not others [67,70] have found higher depression/anxiety symptomatology in SCDclinic compared with SCDcommunity individuals. Similarly, the impact of personality traits such as extraversion or neuroticism is unclear [67,68].

Our finding of lower brain volume and especially in some regions suggestive of AD (medial, anterior, and lateral temporal lobe and parietal cortex [56,72,73]) reveals that the medical help-seeking behavior may also have anatomic substrates and could be interpreted as an indicator of participants' awareness of ongoing pathologic processes. Interestingly, this preserved awareness might be characteristic of the earliest stages of AD as it strongly contrasts with the anosognosia that can be observed in early dementia [74] and even seems to develop 2 to 3 years before dementia onset [75]. However, the cross-sectional design of the present study does not allow clarifying whether these structural brain differences represent life-long features or ongoing neurodegenerative process. Yet, and given the well-known relationships between atrophy in these regions and increased subsequent cognitive decline or AD risk [76–84], our findings support the view that the memory clinic setting is a relevant feature to select SCD individuals with an increased likelihood of developing AD.

Similarly, the slight but significant increased depressive symptomatology observed in the SCDclinic group compared with SCDcommunity could be consistent with the fact that increased depressive affect is frequently associated with early cognitive deficits [85] or subsequent dementia [49] and could be a prodromal sign of AD [48]. Interestingly, the SCDclinic group showed increases in both anxiety and depression compared with controls. The co-occurrence of these affective symptoms is not uncommon, notably in older individuals [86], and although the relationships between subthreshold anxiety and depression are controversial [87,88], the tripartite model of affective disorders stipulates that they are both manifestations of a more general distress factor characterized by high negative affect [89]. Within this theoretical framework, it is interesting to consider that the between-group increase in neuroimaging biomarker abnormalities (control < SCDcommunity < SCDclinic) is paralleled by an increment in this general affective burden, reinforcing the idea that psychological distress could be an early sign of AD.

4.3. Conclusions, limitations, and future directions

As a whole, our results contribute to identifying the characteristics of SCD individuals who might be at higher risk of AD and bring new evidence that, at the group level, elders

with SCD but normal neuropsychological examination should not be considered as “worried well.” Investigating the recruitment setting, our study suggests that medical help seeking is an important feature that is specifically associated with increased likelihood of atrophy in AD-sensitive regions and higher intensity of depressive symptomatology. This overall increased burden of affective and biomarker abnormalities suggests that SCDclinic, at least at the group level, is probably further along the AD trajectory than SCDcommunity. If so, upcoming longitudinal data should indicate steeper cognitive decline and brain changes in SCDclinic compared with SCDcommunity.

The strength of this study relies on the comparison of detailed neuropsychology and multimodal neuroimaging data between two groups of individuals with two different aspects of SCD, all assessed on the same MRI and PET scanners. However, it should be noted that patients included in the present study were meticulously selected for having neither major comorbidities nor cognitive deficits and were recruited from an academic memory clinic, which prevents generalization of our results to all help-seeking individuals with SCD. Although group definition was based on a global score derived from a self-rated questionnaire, complementary approaches could be used to better characterize resulting groups, such as investigating informant reports or performing a qualitative analysis of SCD (e.g., distinguishing self-reports for distinct cognitive domains). In addition, the sample sizes are relatively small: larger studies will be needed to confirm these results. Larger samples would also enable further analysis at the individual level, classifying each individual according to biomarkers of both β -amyloid and neurodegeneration [18,56], as these biomarker-defined stages are associated with differential rates of cognitive decline [90,91]. Lastly, longitudinal studies (including the upcoming follow-up data from the IMAP+ study) will be very important to assess whether the rate of “objectively measured” cognitive decline and neuroimaging biomarker abnormalities differ among the SCDclinic, SCDcommunity, and control groups.

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Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jalz.2016.08.011>.

RESEARCH IN CONTEXT

1. Systematic review: The authors performed a thorough review of the literature on SCD and AD neuroimaging biomarkers using PubMed and by going through articles both cited in and citing the PubMed-identified publications using Google Scholar. The review, presented in Table 1, showed major between-study discrepancies in recruitment settings, definition of SCD, and results in the existing literature.
2. Interpretation: Our findings added to the growing evidence that, in groups of cognitively normal elders, SCD is related to both neuroimaging biomarkers of AD and affective symptoms. In addition, the study identified a major influence of sampling methods and recruitment setting on biomarker results in individuals with SCD.
3. Future directions: These results have major impact on future studies in preclinical AD, notably in terms of enrichment for clinical trials. Future studies are needed to assess the cognitive and clinical changes associated with the different aspects of SCD.

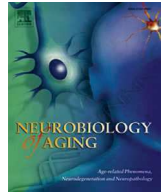
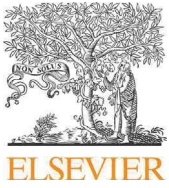
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7.1.4. Branger *et al.*, (2016)



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 (A β) 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 [¹⁸F]florbetapir and [¹⁸F]fluorodeoxyglucose and an magnetic resonance imaging scan to measure A β burden, hypometabolism, and atrophy, respectively. Longer sleep latency was associated with greater A β 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 A β 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.

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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 (A β) 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 A β levels in brain interstitial fluid. In addition, chronic sleep restriction (4 hours of sleep per night) for 21 days significantly increased A β deposition in multiple brain areas. Both animal and human studies have reported diurnal physiological fluctuations in A β 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 A β are disrupted in mouse models of AD (Roh et al., 2012) and in individuals with A β 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 β _{1–42} than in those with normal CSF A β _{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 [¹¹C] 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 A β 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 A β burden in healthy adults. Using a questionnaire developed in our laboratory, we assessed sleep quality over the previous 5 years, a period during which A β deposition might occur covertly, to determine whether long lasting sleeping difficulties have an impact on A β load. Sleep variables were first correlated with florbetapir-PET data reflecting in vivo A β 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 fluoro-deoxyglucose (FDG)-PET and GM volume measured with structural T1 magnetic resonance imaging (MRI). We hypothesized that sleep quality would be related to A β 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, visuo-spatial 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 A β 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 Sydeman, 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 mm², in-plane resolution = 1 × 1 mm²).

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 HhaI 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.

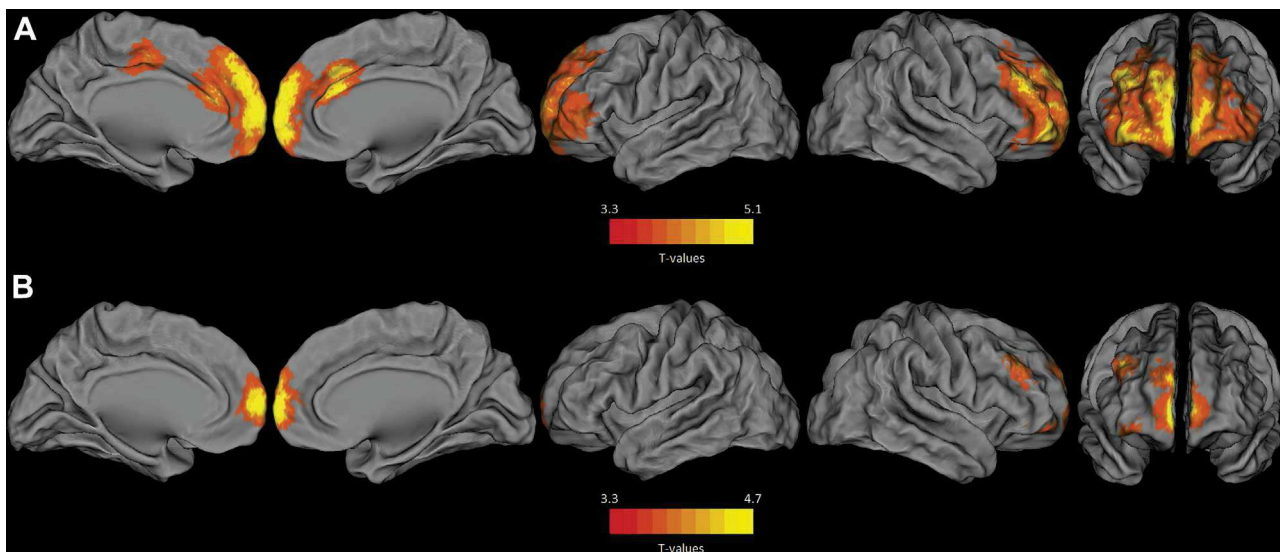


Fig. 1. Regression analysis between sleep latency and A β deposition (measured by florbetapir-PET) in healthy individuals with no covariate (A) and when age, anxiety and depression scores, BMI, and ApoE ϵ 4 status were entered as covariates (B). Results are displayed at $p < 0.001$ with a minimum cluster 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: A β , 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 A β 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 ϵ 4 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 ϵ 4 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.

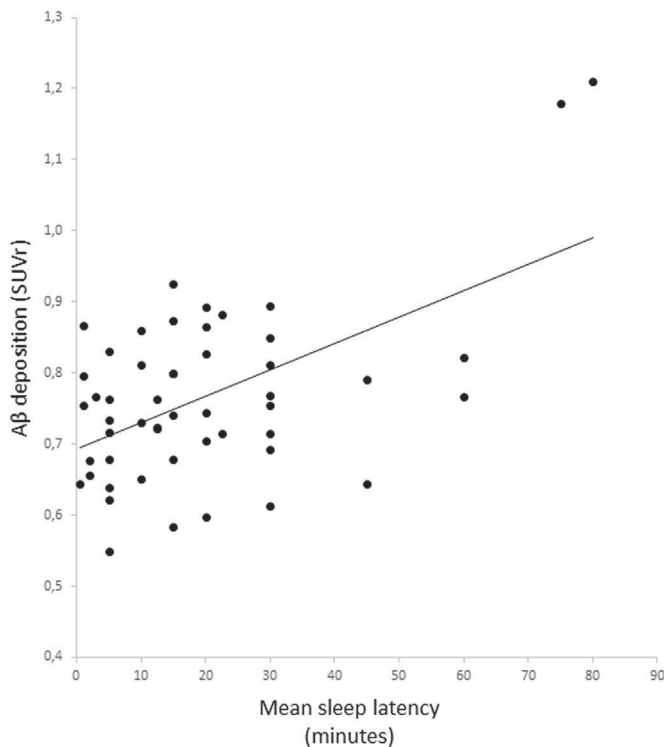


Fig. 2. Plot illustrating the correlation between A β deposition and sleep latency, controlling for the effects of age, BMI, anxiety and depression scores, and ApoE ϵ 4 status. Abbreviations: A β , amyloid-beta; ApoE, apolipoprotein E; BMI, body mass index; SUVR, standardized uptake value ratio.

4. Discussion

Using multimodal neuroimaging (florbetapir-PET, FDG-PET, and structural MRI), we examined the associations between self-reported sleep variables and AD biomarkers (A β 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 A β burden and lower volume in frontal areas.

Our results are consistent with two PET studies that found associations between self-reported sleep quality and A β burden (Spira et al., 2013; Sprecher et al., 2015). They are also in line with another study based on actigraphic recordings and CSF A β measurements, which revealed differences in sleep efficiency between participants with abnormal CSF A β 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 A β burden.

Voxel-wise regression analyses revealed an association between sleep disturbances and A β deposition in prefrontal areas, in line with Sprecher et al. (2015). Spira et al. (2013), however, reported associations between sleep duration and mean A β 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 A β deposition at an early stage in AD (Thal et al., 2002). The specific location of A β 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 frontoinsula 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 frontoinsula 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, A β burden, and brain atrophy. Previous research has highlighted bidirectional relationships between sleep and A β 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 A β 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 A β 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 A β deposition (measured with florbetapir-PET) than on glucose metabolism (estimated by FDG-PET). The results we observed were independent of ApoE ϵ 4 status. However, there is evidence that ApoE ϵ 4 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 ϵ 4 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 ϵ 4 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 A β deposition (Landau et al., 2012; Liang et al., 2010) and increased brain volume (Arenaza-Urquijo et al., 2013; Valenzuela et al., 2008), our study

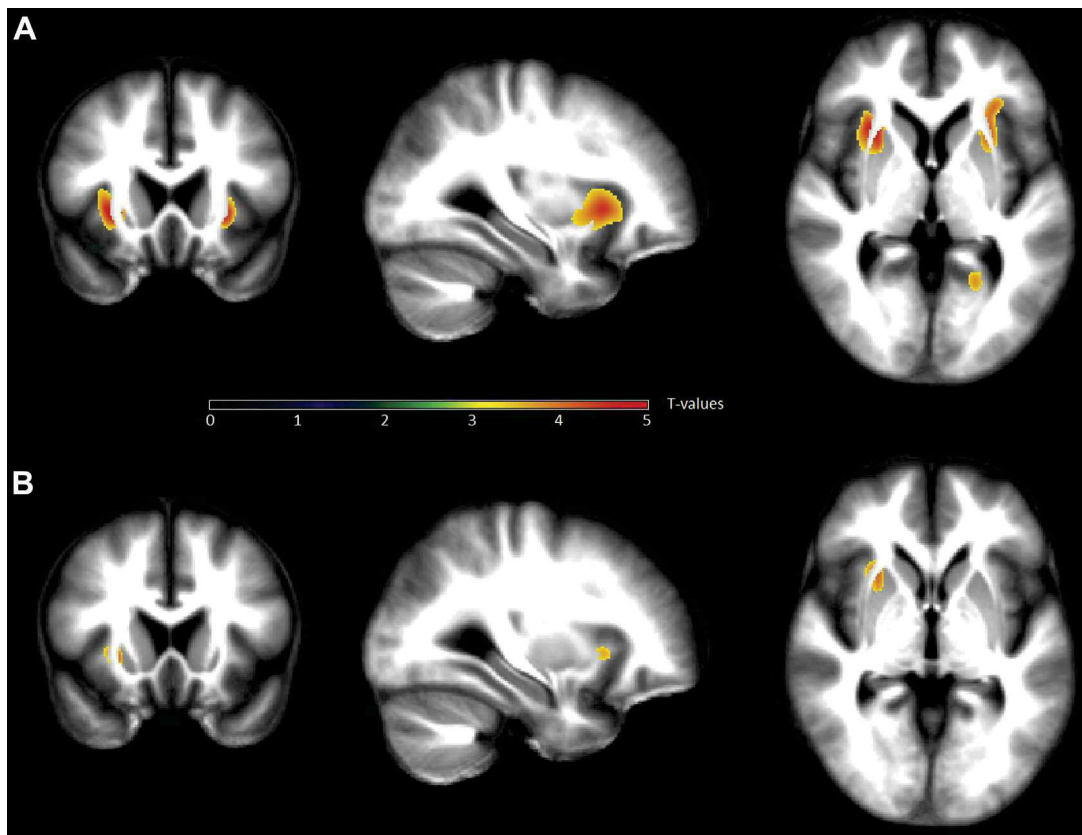


Fig. 3. Regression analysis between the number of nocturnal awakenings and lower gray-matter volume in healthy individuals with no covariate (A), and when age, anxiety and depression scores, BMI and ApoE ϵ 4 status were entered as covariates (B). Results are displayed at $p < 0.001$ with a minimum cluster 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 A β 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 A β

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	3104	26	16	-2	5.00
R olfactory and rectus gyri					
L insula, putamen, superior and inferior frontal gyri	2012	-26	13	-4	4.53
L olfactory gyrus					
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.

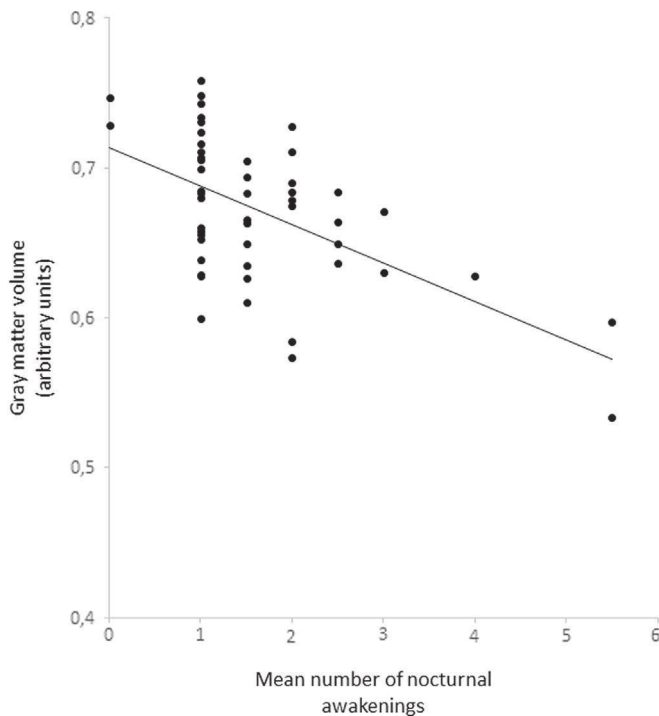


Fig. 4. Plot illustrating the correlation between gray matter volume and the mean number of awakenings, controlling for the effects of age, BMI, anxiety and depression scores, and ApoE $\epsilon 4$ status. Abbreviations: ApoE, apolipoprotein E; BMI, body mass index.

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 A β 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 A β 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 A β 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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7.2. Contrôle qualité des données acquises en IRMf au repos

Dans le cadre de cette thèse, la qualité des données IRMf au repos a été minutieusement vérifiée pour chaque participant. Dans un premier temps, un contrôle visuel a été effectué pour s'assurer de l'absence de lésion ou d'anomalie du signal (la plus classique étant un hypersignal dû à des couronnes dentaires), de problème de positionnement de la tête du sujet par rapport à la boîte (pour que tout le cerveau soit bien enregistré), de volumes coupés, de pertes de signal trop importantes en frontal et / ou temporal et de stries du signal qui seraient dues à trop de mouvements du participant. Ces paramètres de mouvements, ont fait l'objet d'un contrôle cette fois-ci quantitatif à l'aide de la toolbox TSDiffana qui calcule la variance entre les volumes ou entre les coupes au cours du temps.

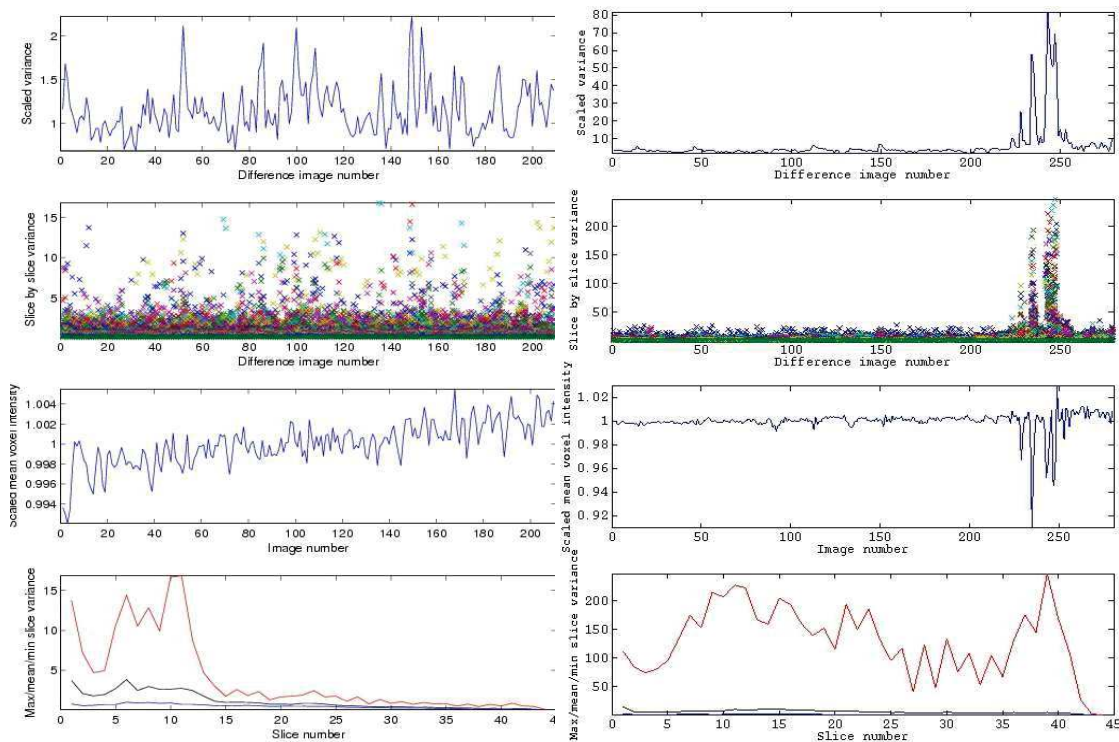


Figure 20 : Exemple du contrôle TSDiffana de 2 examens en IRMf au repos, le premier à gauche ayant des graphes aux profils et amplitudes jugés satisfaisants pour que les données soient exploitables contrairement au deuxième situé à droite.

Enfin, une fois que les données ont été prétraitées, une vérification des paramètres de recalage spatial a été effectuée de sorte que seuls les examens pour lesquels la translation est inférieure à 3mm (car elle ne doit pas excéder la taille du voxel fonctionnel qui est de 2.8mm) et la rotation est inférieure à 1.5 degrés sont acceptés.

Titre : Connectivité fonctionnelle au repos : relation avec la topographie et la propagation des atteintes structurales, fonctionnelles et moléculaires dans la maladie d'Alzheimer

Résumé : L'amélioration des techniques d'imagerie cérébrale a permis de grandes avancées dans la compréhension et la prédiction des mécanismes physiopathologiques de la Maladie d'Alzheimer (MA). Récemment, des travaux ont émis l'hypothèse d'une neurodégénérescence transneuronale selon laquelle les maladies neurodégénératives cibleraient des réseaux fonctionnels spécifiques où elles apparaîtraient et se propageraient. Cette thèse visait à tester cette hypothèse dans le cadre de la MA en étudiant les liens entre la connectivité fonctionnelle au repos et les atteintes structurales, métaboliques et moléculaires. Un premier volet a été consacré à la caractérisation des atteintes fonctionnelles, structurales et métaboliques au sein des réseaux ventral et dorsal du cortex cingulaire postérieur (CCP) dans le *Mild Cognitive Impairment* (MCI) et la MA. Cette étude transversale a suggéré une vulnérabilité plus précoce (dès le stade de MCI) du réseau ventral en atrophie et en connectivité fonctionnelle au repos tandis que l'hypométabolisme était présent dans les deux réseaux chez les MCI et les MA. Le second volet a permis d'évaluer l'influence de la connectivité spécifique (de la région la plus atteinte) versus de la connectivité globale (d'une région avec le reste du cerveau, particulièrement élevée dans les régions hubs) sur la topographie et la propagation de l'atrophie, de l'hypométabolisme et des dépôts amyloïdes sur 18 mois dans la MA. Cette étude longitudinale a révélé que l'atrophie apparaîtrait et se propagerait via la connectivité spécifique en évitant les régions hubs qui sont davantage vulnérables à l'hypométabolisme et aux dépôts amyloïdes.

Title: Resting-state functional connectivity: relationships with topography and propagation of structural, functional and molecular disruptions in Alzheimer's disease

Abstract: Advances in neuroimaging techniques have allowed considerable improvement of the understanding and the prediction of the pathophysiological processes of Alzheimer's disease (AD). Recent findings suggested a transneuronal spread hypothesis of neurodegeneration according to which neurodegenerative disease would target specific functional networks among which it would appear and spread. This thesis aimed at assessing this hypothesis in AD by studying the relationships between resting-state functional connectivity and structural, metabolic and molecular alterations. Firstly, we identified the functional, structural and metabolic alterations within the ventral and the dorsal posterior cingulate cortex (PCC) networks in Mild Cognitive Impairment (MCI) and AD. This transversal study suggested an early vulnerability (since the MCI stage) of the ventral network regarding atrophy and resting-state functional connectivity disruptions while hypometabolism concerned both ventral and dorsal networks in MCI and AD patients. Secondly, we assessed the relative influence of the specific connectivity (of the region the most disrupted) versus the global connectivity (of one region with the rest of the brain, especially high in hub regions) on the topography and the propagation of atrophy, hypometabolism and amyloid deposition over 18 months in AD. This longitudinal study revealed that atrophy would appear and propagate through the specific connectivity by avoiding hub regions which would be more vulnerable to the hypometabolism and amyloid deposition.

Mots-clés : Maladie d'Alzheimer, Imagerie par résonance magnétique, Tomographie par émission de positons, Connectivité fonctionnelle, Réseaux cérébraux, Propagation

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