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La maladie d'Alzheimer comme syndrome de déconnexion et son impact sur le système du langage

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Résumé

La forme typique de la maladie d'Alzheimer (MA) se caractérise par des troubles progressifs de la mémoire épisodique. Néanmoins, les patients atteints par cette maladie présentent également des symptômes langagiers. Parmi les problèmes langagiers que les patients MA présentent, l'anomie, c'est-à-dire une difficulté à trouver les mots justes, serait le plus prédominant. Ainsi, il s'agit d'un marqueur cognitif intéressant pour la détection de la maladie ainsi que son diagnostic différentiel avec d'autres maladies présentant certains symptômes similaires, telle que la variante sémantique de l'aphasie primaire progressive (vs-APP). Malgré tout, le profil anomique des patients MA reste incomplètement caractérisé sur le plan de la dénomination de certains types d'entités. Par ailleurs, les bases cognitives et cérébrales de l'anomie demeurent sujet de débat dans la MA.

En addition à des dommages structurels ou des altérations fonctionnelles dans des régions cérébrales spécifiques, plusieurs auteurs ont récemment suggéré qu'une déconnexion au sein de réseaux cérébraux pourrait sous-tendre les difficultés cognitives présentées chez les patients MA, incluant les symptômes langagiers. Toutefois, aucune étude n'a validé le fait que la MA était un syndrome de déconnexion à l'aide de la technique des réseaux de covariance structurelle de la matière grise. De surcroît, très peu d'études ont investigué l'impact de la MA sur le réseau cérébral langagier, ce qui pourrait nous apporter un éclairage sur les symptômes langagiers des patients tels que l'anomie.

Le premier volet de la thèse visait à mieux caractériser le profil anomique des patients MA, à le comparer à celui des patients vs-APP et finalement, à clarifier ses bases cognitives et cérébrales (article #1). Les résultats suggéraient d'abord une atteinte diffuse en dénomination pour tous les types d'items (entités non uniques, personnes célèbres, lieux célèbres et logos célèbres) chez les patients MA en comparaison aux sujets contrôles. L'atteinte était néanmoins prédominante pour la dénomination de personnes célèbres, suggérant un profil prosopoanomique dans la MA. Les connaissances sémantiques générales pour ces mêmes entités étaient préservées chez les patients MA, bien qu'une légère altération ait été observée pour les connaissances sémantiques spécifiques. Les résultats comportementaux des patients MA se distinguaient clairement des résultats obtenus chez les patients vs-APP, qui présentaient

une anomie plus sévère et un trouble sémantique net. Le profil d'anomie tel qu'évalué en dénomination de personnes célèbres chez les patients MA corrélait avec l'atrophie de la matière grise dans la jonction temporo-pariétale gauche (une région associée avec l'accès lexical), et ne corrélait pas avec l'atrophie de la matière grise dans le LTA gauche (une région associée à la sémantique). Ainsi, ces résultats soulignent l'apport important du trouble d'accès lexical dans l'anomie chez les patients MA, mais suggère tout de même un trouble de nature mixte en raison des lacunes sémantiques observées chez ces patients pour les connaissances spécifiques.

Le deuxième volet de la thèse visait à démontrer que la MA est un syndrome de déconnexion (article #2), et que cette déconnexion touchait également le réseau cérébral responsable du langage (article #3). D'abord, les résultats ont permis de démontrer des changements de la connectivité structurelle dans les réseaux clés associés à la MA. En effet, une diminution de la connectivité structurelle a été observée dans les sous-composantes du réseau du mode par défaut, apportant ainsi un appui à l'hypothèse de la MA comme syndrome de déconnexion. Ensuite, il a été possible de confirmer que les atteintes de connectivité sont également présentes à l'extérieur du réseau du mode par défaut, soit dans le réseau cérébral langagier. Des diminutions de connectivité fonctionnelle ont principalement été relevées dans le gyrus temporal postérieur moyen gauche et le lobe temporal antérieur gauche, en relation avec d'autres régions du réseau langagier. En lien avec l'anomie chez les patients MA, les altérations de la connectivité fonctionnelle sont compatibles avec la nature mixte de l'anomie chez les patients MA.

Mis ensemble, ces résultats mettent en relief l'importance des marqueurs cognitifs liés à l'anomie et des marqueurs de connectivité cérébrale dans la caractérisation de la MA et son diagnostic différentiel avec d'autres maladies neurodégénératives telles que la vs-APP. Étant donné l'impact au quotidien des troubles langagiers sur les patients MA et leurs proches, nous croyons qu'une meilleure caractérisation des bases cognitives et cérébrales de leurs déficits contribuera au développement d'interventions auprès de ceux-ci.

Mots-clés : maladie d'Alzheimer, langage, anomie, connectivité cérébrale, mémoire sémantique, variante sémantique de l'aphasie primaire progressive

Abstract

The typical form of Alzheimer's disease (AD) is characterized by progressive episodic memory impairments. Nonetheless, patients affected by this disease also present with language symptoms. Among common language deficits in AD, anomia, i.e. a difficulty to recall names, is recognized as the most predominant. Therefore, it represents an interesting cognitive marker for the detection of the disease as well as its differential diagnosis with other neurodegenerative diseases characterized by overlapping symptoms, such as the semantic variant of primary progressive aphasia (sv-PPA). Still, the anomic profile of AD patients remains incompletely characterized in terms of the naming of certain types of entities. Also, the cognitive and cerebral bases of anomia are still a matter of debate in AD.

In addition to structural damage or functional alteration in specific brain regions, many authors have recently suggested that a disconnection across brain networks could sustain cognitive difficulties experienced by AD patients, including language impairments. However, most studies demonstrating that AD is a disconnection syndrome have used functional connectivity techniques, and no study using the gray matter structural covariance networks technique has been conducted to support this hypothesis. In addition, very few studies have investigated the impact of AD on the language brain network, which could significantly extend our understanding of language symptoms such as anomia.

The first section of this thesis aimed to better characterize the anomic profile of AD patients, to compare it with the profile of sv-PPA patients and finally, to clarify its cognitive and cerebral bases (article #1). The results first suggested a diffuse naming impairment affecting every type of items (non-unique entities, famous persons, famous places and famous logos) in AD patients in comparison to control subjects. Famous persons naming was nonetheless predominantly impaired in AD patients in comparison to other types of entities, suggesting a prosopoanomia. General semantic knowledge for these same entities was preserved in AD, although a slight but significant impairment was observed in terms of specific semantic knowledge. Behavioral results in AD patients clearly distinguished them from sv-PPA patients, in which naming, general and specific semantic knowledge were cleary impaired. Famous persons naming in AD patients correlated with gray matter atrophy in the left temporo-parietal

junction (a region functionally associated with lexical access), but not with the left anterior temporal lobe (a region functionally associated with semantics). Overall, these results underline the contribution of a lexical access deficit in anomia in AD patients, but nonetheless argue in favor of a mixed cognitive basis of anomia given that a slight semantic impairment for specific knowledge was also present.

The second section of this thesis aimed at demonstrating that AD is a disconnection syndrome (article #2), and that this disconnection also affects the brain network responsible for language (article #3). Results showed significant changes in the structural connectivity of the key networks in AD. In fact, a reduced structural connectivity was observed in the subcomponents of the default-mode network, giving support to the theory of AD as a disconnection syndrome. Furthermore, our results confirmed that structural connectivity alterations were also present outside of the default-mode network, also affecting the language network. Reduced functional connectivity was mainly observed in the left posterior middle temporal gyrus as well as in the left anterior temporal lobe, in relation to other regions of the language network. These results have implications for our understanding of language symptoms in AD patients, since they are also compatible with a mixed basis (lexical access and semantic impairments) of anomia in AD.

Taken together, these results highlight the importance of anomia as a cognitive marker and structural/functional connectivity as a neuroimaging marker in the characterisation of AD as well as its differential diagnosis with other neurodegenerative diseases such as sv-PPA. Given the negative impact of language difficulties in the daily life of AD patients as well as their caregivers, we believe that a better characterisation of the cognitive and cerebral bases of their language deficits will contribute to the development of interventions.

Keywords : Alzheimer's disease, language, anomia, brain connectivity, semantic memory, semantic variant of primary progressive aphasia

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Article #3 : *Differential language network functional connectivity alterations in Alzheimer's disease and semantic variant of primary progressive aphasia*

Liste des abréviations et des sigles

En français :

Aβ : bêta-amyloïde

ESU : entité sémantiquement unique

GFI : gyrus frontal inférieur

GTPM : gyrus temporal postérieur moyen

IRM : imagerie par résonance magnétique

IRMf : imagerie par résonance magnétique fonctionnelle

IRMf-rs : imagerie par résonance magnétique fonctionnelle en « resting-state »

LCR : liquide céphalo-rachidien

LTA : lobe temporal antérieur

MA : maladie d'Alzheimer

RCSMG : réseaux de covariance structurelle de la matière grise

RMD : réseau du mode par défaut

vs-APP : variante sémantique de l'aphasie primaire progressive

En anglais :

aCompCor : anatomical component-based noise correction

Aβ : amyloid-beta

AD : Alzheimer's disease

ADNI : Alzheimer's Disease Neuroimaging Initiative

ATL: anterior temporal lobe

BOLD : blood oxygen level-dependent

CDR : clinical dementia rating

CSF : cerebrospinal fluid

CTRL : cognitively unimpaired elderly subjects

DARTEL : diffeomorphic anatomical registration using exponentiated lie algebra

DMN : default-mode network

FDR : false discovery rate

fMRI : functional magnetic resonance imaging

FEW : familywise error rate

GDS : Geriatric depression scale

GM : gray matter

IFG : inferior frontal gyrus

MMSE : Mini-Mental State Examination

MNI : Montreal Neurological Institute

MP-RAGE : magnetization prepared rapid gradient echo

MRI : magnetic resonance imaging

NINCDS/ADRDA : National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

pMTG : posterior middle temporal gyrus

PPTT : Pyramids and Palm Trees Test

ROI : region of interest

rs-fMRI/rsfMRI : resting-state functional magnetic resonance imaging

SPM : statistical Parametric Mapping

svPPA : semantic variant of primary progressive aphasia

TPJ : temporo-parietal junction

VBM : voxel-based morphometry

WM : white matter

À tous les patients atteints de maladies neurodégénératives

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Chapitre I : Contexte théorique

1. Introduction générale

Au-delà des troubles de la mémoire caractéristiques de la forme typique de la maladie d'Alzheimer (MA), les patients atteints par cette maladie ont également des déficits langagiers. Ceux-ci peuvent avoir un impact significatif sur leur qualité de vie ainsi que celles de leurs proches. Parmi les problèmes langagiers que les patients MA présentent, l'anomie, c'est-à-dire une difficulté à trouver les mots justes, serait le plus prédominant et apparaitrait dès les premiers stades de la maladie.

Le premier volet de la thèse vise à mieux caractériser l'anomie chez les patients MA, ainsi qu'à clarifier ses bases cognitives et cérébrales (étude #1).

En addition à des dommages structurels ou des altérations fonctionnelles dans des régions cérébrales spécifiques, il est maintenant suggéré qu'une déconnexion au sein de réseaux cérébraux peut sous-tendre les difficultés cognitives présentées chez les patients MA, incluant les difficultés langagières.

Le deuxième volet de la thèse vise à démontrer que la MA est un syndrome de déconnexion (étude #2), et que cette déconnexion touche le réseau cérébral responsable du langage chez les patients MA (étude #3).

Ainsi, en guise d'introduction aux articles composant cette thèse, nous décrirons d'abord le profil clinique des patients, la neuropathologie sous-jacente, les atteintes cérébrales observées et finalement, les troubles langagiers dans la MA. Ensuite, le premier volet, soit les bases cognitives et cérébrales de l'anomie dans la MA, sera abordé. Nous présenterons également la variante sémantique de l'aphasie primaire progressive (vs-APP), qui représente un groupe de comparaison idéal et un modèle pour l'étude de l'anomie sémantique. Le deuxième volet, soit la MA en tant que syndrome de déconnexion, sera par la suite traité. Pour ce faire, nous réviserons la théorie de la dégénérescence des réseaux, les techniques d'imagerie de la connectivité cérébrale et les principaux réseaux impliqués dans la MA, incluant le réseau du langage. Finalement, les objectifs et hypothèses des trois études composant cette thèse seront exposés.

2. La maladie d'Alzheimer (MA)

2.1 Description clinique et critères diagnostiques

La MA est une maladie neurodégénérative causant des symptômes cognitifs et comportementaux ainsi qu'une atteinte fonctionnelle. Il est important de mentionner que le diagnostic définitif de MA ne peut être posé qu'à la suite d'un examen histopathologique *post-mortem*. Ainsi, au point de vue clinique, il est possible de poser un diagnostic de MA probable. Les plus récents critères diagnostiques suggèrent un processus en deux étapes, soit une évaluation des critères généraux de la démence (toutes causes sous-jacentes), puis des critères spécifiques de la MA probable (McKhann et al., 2011).

Tout d'abord, le diagnostic de démence peut être posé lorsqu'un individu présente des symptômes cognitifs ou comportementaux qui 1) interfèrent avec la capacité de fonctionner au travail ou dans les activités habituelles; 2) représentent un déclin en comparaison aux niveaux de fonctionnement et de performance antérieurs; 3) ne sont pas expliqués par un délirium ou une maladie psychiatrique. Par ailleurs, l'atteinte cognitive doit 4) être détectée et diagnostiquée avec une anamnèse auprès du patient et d'un proche informé ainsi qu'une évaluation cognitive objective; 5) impliquer un minimum de deux domaines cognitifs parmi les suivants: mémoire épisodique, raisonnement/habiletés exécutives/jugement, habiletés visuospatiales, langage et personnalité/comportement.

Ensuite, le diagnostic de MA probable peut être posé lorsqu'un individu, en plus de remplir les critères de la démence, présente des symptômes d'apparition insidieuse et progressive. On distingue une présentation amnésique, qui est la plus commune, des présentations non amnésiques. La présentation amnésique est caractérisée par une atteinte de la mémoire épisodique (difficulté à apprendre et à rappeler des informations apprises récemment) et d'une atteinte d'au minimum un autre domaine cognitif parmi ceux énoncés précédemment. Les présentations non-amnésiques incluent la présentation langagière, visuospatiale et exécutive, qui en plus d'une atteinte prédominante de ces domaines cognitifs respectifs, touchent au minimum un autre domaine cognitif. Finalement, le diagnostic de MA est exclu lorsqu'une maladie cérébrovasculaire substantielle, une démence à corps de Lewy, une démence

frontotemporale (variante comportementale), une aphasie primaire progressive (variante sémantique et variante non-fluente) ou une médication qui pourrait expliquer les déficits cognitifs est présente.

Dans le cadre de la présente thèse, le mot MA sera utilisé pour décrire des patients avec la présentation amnésique.

2.2 Neuropathologie

La MA, sur le plan neuropathologique, est caractérisée par des dégénérescences neurofibrillaires intracellulaires (protéine tau) et des dépôts extracellulaires de protéine bêta-amyloïde (Aβ), qui sont associés à des pertes neuronales et synaptiques (Braak & Braak, 1991; Corder et al., 2000). La progression neuropathologique a été caractérisée en termes de stages distincts par Braak et Braak en 1991, et celle-ci a été enrichie par Corder et collègues en 2000. Pour ce qui est des dégénérescences neurofibrillaires, elles progressent du cortex entorhinal (Stades de Braak I et II - Entorhinal), s'étendant via le faisceau perforant vers l'hippocampe et l'amygdale (Stades III et IV - Limbique) et éventuellement vers d'autres régions corticales et sous-corticales (Stades V et VI - Isocortical) (Braak & Braak, 1991). En ce qui concerne le néocortex, la progression semble se dérouler selon la séquence suivante : temporal médian, pariétal, frontal médian, occipital secondaire puis finalement, occipital primaire (Corder et al., 2000). La progression de l'Aβ, quant à elle, se déroule ainsi : portions basales de l'isocortex (Stade A), aires associatives isocorticales (l'hippocampe n'étant que modérément touché) (Stade B) et finalement, toutes les régions de l'isocortex incluant les régions motrices et sensorielles (Stade C) (Braak & Braak, 1991).

Bien que la confirmation de la présence de protéine tau et Aβ ait longtemps nécessité un examen histopathologique *post-mortem*, il est maintenant possible d'inférer leur présence *in vivo* à l'aide de diverses techniques. En plus de l'imagerie tau et l'imagerie Aβ en tomographie par émission de positrons (Jack, Barrio, & Kepe, 2013; Klunk et al., 2004; Saint-Aubert et al., 2017), la ponction lombaire permet l'investigation des biomarqueurs de la MA dans le liquide céphalo-rachidien (LCR). Les patients MA présentent en effet un profil atypique caractérisé par des niveaux anormalement élevés de tau total et de tau phosphorylée, combinés à un niveau anormalement réduit d'Aβ (de Souza et al., 2011; Shaw et al., 2009). Au point de vue

diagnostique, ces investigations permettent d'augmenter la certitude que le syndrome clinique de la MA probable est réellement causé par la neuropathologie Alzheimer (McKhann et al., 2011).

2.3 Atteintes cérébrales

Les études en imagerie par résonance magnétique (IRM) ont permis de révéler que la MA est associée à plusieurs changements cérébraux sur le plan structurel, soit une atrophie de la matière grise et de la matière blanche. Sur le plan de la matière grise, une récente méta-analyse de notre groupe a démontré que l'atrophie est principalement observée dans les hippocampes bilatéraux, les lobes temporaux, le cortex cingulaire postérieur, le lobe pariétal inférieur, le gyrus angulaire, le précunéus, le gyrus occipital moyen, le gyrus frontal inférieur (GFI), l'insula et le thalamus (Chapleau, Aldebert, Montembeault, & Brambati, 2016). Sur le plan de la matière blanche, une méta-analyse récente a mis en relief des altérations très diffuses (Sexton, Kalu, Filippini, Mackay, & Ebmeier, 2011). En effet, une diminution de l'intégrité des fibres de matière blanche a été relevée dans le faisceau unciné, le faisceau longitudinal supérieur, le cingulum postérieur, le splénium du corps calleux ainsi que dans la matière blanche du lobe temporal et du lobe pariétal.

2.4 Les symptômes langagiers dans la MA

La MA est reconnue pour causer des troubles mnésiques importants, comme en témoigne l'appellation de sa forme la plus commune, la présentation amnésique de la MA. Toutefois, tel que mentionné dans les critères diagnostiques (McKhann et al., 2011), le langage est un des domaines cognitifs pouvant être affecté chez les patients atteints. Bien que les symptômes langagiers aient été moins étudiés que les symptômes mnésiques, il est pourtant critique de s'y attarder pour plusieurs raisons. Tout d'abord, ceux-ci sont présents très précocement dans la maladie, voire même jusqu'à 12 ans avant le diagnostic (Amieva et al., 2008). De plus, ces déficits ont un impact fonctionnel important sur les patients et leurs proches. En effet, les atteintes langagières chez les patients MA sont associées à une diminution de la fréquence des activités sociales et une diminution du plaisir de ces activités (Farrell et al., 2014). Elles peuvent ainsi mener à un retrait social, ce qui pourrait mener à une détérioration plus importante du

langage (Farrell et al., 2014). De plus, une étude a montré que les difficultés de langage et de communication sont parmi les conséquences de la maladie qui sont les plus difficiles à surmonter selon les proches aidants de patients MA (Murray, Schneider, Banerjee, & Mann, 1999).

Ainsi, les patients MA présentent, dès les premiers stades de la maladie, des troubles prédominants d'évocation des mots (Macoir, Laforce, Monetta, & Wilson, 2014; Taler & Phillips, 2008; Verma & Howard, 2012). Sur le plan neuropsychologique, ces déficits sont mis en évidence avec des tâches de dénomination d'images et de fluence verbale (Henry, Crawford, & Phillips, 2004; Laws, Adlington, Gale, Moreno-Martinez, & Sartori, 2007). D'autres difficultés langagières sont présentes chez les patients MA, mais celles-ci sont moins prédominantes ou apparaissent dans les stades modérés à avancés de la maladie. Ainsi, des troubles de la lecture (Joyal et al., 2017), de l'écriture (Harnish & Neils-Strunjas, 2008) et de la compréhension (Taler & Phillips, 2008) feraient éventuellement partie du profil clinique de la maladie. La syntaxe, l'articulation et les habiletés phonologiques ne seraient quant à elles que très légèrement touchées, voire relativement préservées chez les patients MA (Taler & Phillips, 2008).

De ce fait, le profil langagier des patients MA peut représenter un marqueur cognitif important de cette maladie. La dénomination d'images présente un intérêt particulier, puisqu'elle permet de mettre en évidence une anomie chez les patients MA, soit une difficulté à trouver les mots justes. Tel que mentionné précédemment, l'anomie représente le trouble langagier le plus précoce et prédominant chez les patients MA, avec les troubles en fluence verbale. Toutefois, les tâches de fluence verbale ne constituent pas un marqueur langagier aussi intéressant puisqu'elles dépendent grandement de processus exécutifs, plus précisément de la génération d'une stratégie de recherche, d'initiation de nouvelles réponses, de monitorage des réponses déjà élicitées et d'inhibition des mauvaises réponses (Henry et al., 2004). Vu ces éléments, l'anomie telle qu'évaluée en situation de dénomination d'images sera étudiée plus spécifiquement dans le volet #1 de la présente thèse.

3. Volet #1: L'anomie et ses bases cognitives et cérébrales dans la MA

3.1 L'anomie dans la MA

Les études relèvent de façon constante une performance plus faible dans les tests de dénomination chez les patients MA en comparaison aux sujets contrôles (Laws et al., 2007). Malgré tout, il semblerait que la performance en dénomination demeure hétérogène chez les patients MA et qu'environ 41% des patients dans les premiers stades de la maladie présentent un déficit net (deux écarts-types sous la moyenne des sujets contrôles) à un test typique comme le *Boston Naming Test* (Domoto-Reilly, Sapolsky, Brickhouse, & Dickerson, 2012). Des études ont décortiqué les erreurs commises par les patients MA lorsqu'ils nomment de façon incorrecte une image. Celles-ci mettent en relief des erreurs de type sémantique (ex. brocoli pour asperge), visuelle (ex. tasse pour masque) ou des omissions, et très peu d'erreurs de type phonologique (ex. stéscope pour stéthoscope) chez les patients MA (Balthazar, Cendes, & Damasceno, 2008; Reilly, Peelle, Antonucci, & Grossman, 2011).

Plusieurs auteurs se sont également intéressés à comprendre si le déficit de dénomination était spécifique à une catégorie d'items, ou en d'autres mots, si les patients MA avaient plus de difficultés à nommer certains types d'items que d'autres. Ces études ont majoritairement porté sur les catégories des items vivants (ex. un animal) et non vivants (ex. un outil). Bien que plusieurs d'entre elles ont suggéré que les patients MA présentaient une performance plus faible pour les items vivants (en comparaison aux non vivants), une méta-analyse a toutefois montré qu'il n'y avait pas de différence significative lorsque toutes les études étaient mises en commun et qu'un contrôle exhaustif des variables psycholinguistiques était effectué (Laws et al., 2007). Une autre catégorisation des items, soit celle entre les entités sémantiquement uniques (ESU) et les entités non uniques, a toutefois été relevée comme pertinente chez les patients MA. Les ESU possèdent une association lexico-conceptuelle unique, c'est-à-dire qu'elle représente le seul exemplaire associé à ce nom (ex. une personne célèbre telle que Elvis Presley). À l'inverse, les entités non uniques ont plusieurs exemplaires pour le même mot (ex. un animal tel qu'un chat). Chez les patients MA, il a été constamment démontré que les déficits de dénomination étaient

plus sévères lorsque les items à nommer étaient des ESU, en comparaison avec des entités non uniques (Delazer, Semenza, Reiner, Hofer, & Benke, 2003; Joubert et al., 2010; Joubert et al., 2008; Semenza, Mondini, Borgo, Pasini, & Sgaramella, 2003; Thompson, Graham, Patterson, Sahakian, & Hodges, 2002). Ainsi, il semblerait que les ESU revêtent d'un intérêt particulier pour la détection de l'anomie chez les patients MA.

3.2 Les bases cognitives de l'anomie

Plusieurs modèles théoriques de la production orale ont décrit les étapes nécessaires à la dénomination d'une image (Caramazza, 1997; Dell, Schwartz, Martin, Saffran, & Gagnon, 1997; Levelt, Roelofs, & Meyer, 1999). Bien que ces modèles diffèrent sur certains détails tels que le nombre et la délinéation des étapes, ainsi que la relation entre celles-ci (sérielle ou bidirectionnelle/interactive), un certain consensus semble malgré tout émerger. Le traitement visuo-perceptif permettrait de percevoir les caractéristiques visuelles afin de reconnaître l'image. Le traitement sémantique permettrait l'accès et le traitement au sein du stock sémantique, soit l'ensemble des connaissances que l'on possède sur un concept (par exemple, ses attributs physiques, ses attributs fonctionnels, le contexte associé à ce concept ou même la catégorie de laquelle il fait partie). Le traitement lexical permettrait de récupérer le mot associé au concept. Le traitement phonologique permettrait de récupérer la forme sonore de ce mot. Le traitement articulatoire permettrait d'énoncer la forme sonore du mot sur le plan moteur. Une atteinte à une ou plusieurs de ces étapes pourrait de ce fait causer un déficit en dénomination d'images.

Chez les patients MA, bien que quelques études aient illustré le fait que des difficultés visuo-perceptives pourraient causer certaines erreurs en dénomination d'images (Balthazar et al., 2008; Rogers & Friedman, 2008), la majorité des auteurs considèrent les deux niveaux suivants comme les causes les plus probables de l'anomie chez les patients MA. Ainsi, les bases cognitives de l'anomie chez les patients MA pourraient être un trouble sémantique ou un trouble d'accès lexical (Gainotti, Silveri, Villa, & Miceli, 1986; Gesierich et al., 2011; Lambon Ralph, Sage, & Roberts, 2000; Nebes, 1989). Malgré tout, la base cognitive de l'anomie dans la MA est encore un sujet de débat, et des études comportementales ont apporté un appui aux deux hypothèses principales.

D'abord, un trouble sémantique signifie qu'il est impossible de produire le mot puisque les connaissances sémantiques sur le concept en soi sont dégradées. En soutien au trouble sémantique chez les patients MA, il a été observé que ceux-ci commettent un grand nombre d'erreurs sémantiques lors des tâches de dénomination (Balthazar et al., 2008; Reilly et al., 2011). De plus, d'autres auteurs ont tenté d'évaluer si les patients MA avaient des connaissances sémantiques préservées ou altérées sur les items qu'ils ne sont pas capables de nommer dans une tâche de dénomination. Ces études ont permis de démontrer qu'il existait une bonne correspondance entre les items non nommés et les items pour lesquels les connaissances sémantiques sont altérées chez les patients MA, supportant également la théorie du trouble sémantique (Chertkow & Bub, 1990; Hodges, Patterson, Graham, & Dawson, 1996; Hodges, Salmon, & Butters, 1992; Joubert et al., 2010). Ensuite, certaines études ont suggéré qu'en plus d'avoir des difficultés à nommer certaines entités, les patients MA avaient aussi de la difficulté à reconnaître les mots non nommés parmi des distracteurs sémantiquement reliés (Huff, Corkin, & Growdon, 1986; Skelton-Robinson & Jones, 1984). Finalement, certaines études ont démontré que les indices phonologiques (premier phonème du mot à nommer) ne permettaient que de minimalement améliorer la performance des patients MA en dénomination (Daum, Riesch, Sartori, & Birbaumer, 1996). Ces auteurs suggèrent que si la base de l'anomie était un déficit d'accès lexical, les indices phonologiques devraient être suffisants pour régulariser la performance des patients avec MA.

Ensuite, un déficit d'accès lexical suggère que les connaissances sémantiques sur le concept à nommer sont préservées, mais qu'il est difficile d'accéder au lexique et d'ainsi récupérer le mot associé à ce concept. En soutien à un trouble d'accès lexical, d'autres études ont à l'inverse montré que les indices phonologiques régularisaient la performance des patients MA en dénomination, ce qui suggèrerait que les troubles de dénomination pourraient être causés en partie par un déficit d'accès lexical (Balthazar et al., 2008). Quant à la correspondance entre les items non nommés et les items pour lesquels les connaissances sémantiques sont altérées, il a également été suggéré que cet effet était fortement lié à la difficulté ou au type de tâches évaluant les connaissances sémantiques, ce qui nuance l'interprétation d'un trouble sémantique net chez les patients avec MA (Bayles, Tomoeda, Kasniak, & Trosset, 1991; Joubert et al., 2010; Rich, Park, Dopkins, & Brandt, 2002). Le nombre élevé de circonlocutions (ex. «ça sert à faire

des cercles en géométrie » pour compas) en dénomination d'images chez les patients MA a par ailleurs été interprété comme une préservation relative des connaissances sémantiques par certains auteurs (Bayles & Tomoeda, 1983). Finalement, des corrélations importantes entre les troubles de dénomination et les fonctions exécutives ont été retrouvées chez les patients MA (Reilly et al., 2011), supportant qu'une atteinte des mécanismes du contrôle exécutif pourrait être reliée à la récupération des mots.

Face à ces résultats contradictoires, une troisième hypothèse a émergé, suggérant que les troubles anomiques chez les patients MA pourraient être de nature mixte, c'est-à-dire en partie expliquée par le trouble sémantique et en partie par le trouble d'accès lexical (Balthazar et al., 2008; Delazer et al., 2003; Reilly et al., 2011; Rich et al., 2002; Salehi, Reisi, & Ghasisin, 2017). Parmi les facteurs confondants, Salehi et collaborateurs ont souligné l'importance du stade de la MA dans la base cognitive de leur anomie, interprétant le profil d'erreurs au *Boston Naming Test* des patients MA dans les premiers stades de la maladie comme un trouble d'accès lexical, bien qu'un trouble sémantique se mettrait en place avec la progression de la maladie (Salehi et al., 2017).

3.3 Les bases cérébrales de l'anomie

En lien avec les deux bases cognitives de l'anomie décrites dans la section précédente et étant les plus probables chez les patients MA, Gesierich et collaborateurs ont mené une étude ayant pour but d'identifier les corrélats fonctionnels de l'accès lexical et des connaissances sémantiques (Gesierich et al., 2011). Dans cette étude en imagerie par résonance magnétique fonctionnelle (IRMf) chez des sujets contrôles, les régions cérébrales activées spécifiquement lors d'associations sémantiques au sujet de personnes célèbres (sémantique) et lors de la dénomination de personnes célèbres (accès lexical) ont été identifiées. Leur étude a permis de démontrer que le lobe temporal antérieur (LTA) gauche était impliqué dans la sémantique, alors que la jonction temporo-pariétale gauche était impliquée dans l'accès lexical. Cette découverte fournit un modèle idéal pour la compréhension des bases cérébrales de l'anomie chez les patients MA.

Au point de vue de la neuroimagerie, plusieurs études ont investigué les corrélats neuronaux des déficits de la dénomination chez les patients MA. Ceux-ci ont été associés à des

dommages structurels (atrophie de la matière grise) ou des altérations fonctionnelles (hypométabolisme ou hypoactivation) dans le GFI gauche (Dos Santos et al., 2011; Melrose et al., 2009; Rodríguez-Aranda et al., 2016; Teipel et al., 2006), la jonction temporo-pariétale gauche incluant le gyrus temporal postérieur moyen (GTPM) gauche (Leyton, Hodges, Piguet, & Ballard, 2017; Nelissen et al., 2007; Vandenbulcke, Peeters, Dupont, Van Hecke, & Vandenberghe, 2007) et le LTA gauche (Apostolova et al., 2008; Brambati et al., 2006; Domoto-Reilly et al., 2012; Grossman et al., 2004; Hirono et al., 2001; Joubert et al., 2010; Lars et al., 2011; Lars, Timo, Michael, & Philipp, 2016; Zahn et al., 2004). Ainsi, les bases cérébrales de l'anomie chez les patients MA semblent recouper les régions définies comme critiques par Gesierich et collaborateurs dans leur modèle de l'anomie et semblent soutenir les deux bases cognitives principales de l'anomie chez les patients MA (trouble sémantique et trouble d'accès lexical) (Gesierich et al., 2011). Malgré tout, les études précédentes en neuroimagerie ont fourni des résultats contradictoires et n'ont ainsi pas complètement permis d'élucider les bases de l'anomie chez les patients MA.

3.4 La variante sémantique de l'aphasie primaire progressive (vs-APP) comme modèle pour l'étude de l'anomie sémantique

La vs-APP est une maladie neurodégénérative touchant de façon prédominante le langage (Gorno-Tempini et al., 2011; Snowden, Goulding, & Neary, 1989). Ces patients présentent en premier plan une anomie (en langage spontané et en dénomination) et un déficit de la compréhension des mots isolés. Sur le plan diagnostique, ces deux symptômes cliniques doivent absolument être présents, en plus de trois des quatre éléments suivants : 1) une perte des connaissances sur les objets, particulièrement les items à basse fréquence et à basse familiarité; 2) une dyslexie ou dysgraphie de surface; 3) une préservation des habiletés de répétition; 4) une préservation de la parole et de la grammaire (Gorno-Tempini et al., 2011). Sur le plan anatomique, les patients vs-APP présente une atrophie marquée des LTA bilatéraux mais prédominante, dans la majorité des cas, dans l'hémisphère gauche (Chapleau et al., 2016). Une revue de la littérature récente de notre groupe (Annexe 1) détaille le profil clinique, anatomique et pathologique des patients vs-APP (Montembeault, Brambati, Gorno Tempini, & Migliaccio, 2018).

Ainsi, puisque la vs-APP est par définition un trouble sémantique, il s'agit d'une population idéale afin de mieux comprendre l'anomie. En plus de la base cognitive de l'anomie qui est bien définie chez les patients vs-APP, il en est tout autant pour la base cérébrale : il a été démontré de façon consensuelle que le LTA gauche était à la source des déficits de dénomination et de mémoire sémantique chez ces patients (Acosta-Cabronero et al., 2011; Brambati et al., 2006; Desgranges et al., 2007; Diehl et al., 2004). Pour ces raisons, les patients vs-APP représentent un groupe de comparaison idéal dans l'objectif de mieux comprendre les bases cognitives et cérébrales de l'anomie chez les patients MA.

3.5 Résumé du volet #1

L'anomie semble être le symptôme langagier prédominant chez les patients MA, et plusieurs études ont jusqu'à maintenant contribué à définir le profil clinique des patients MA aux tâches de dénomination. Toutefois, certaines questions demeurent sans réponses ou débattues.

Tout d'abord, les études actuelles suggèrent que l'anomie touche les entités non uniques, et de façon plus importante, les personnes célèbres chez les patients MA. Toutefois, les études se sont largement restreintes à l'utilisation de personnes célèbres à titre d'ESU, bien qu'il existe plusieurs autres types d'ESU, tels que les lieux célèbres (ex. la Tour Eiffel) et les logos connus (ex. McDonald's, Pictogramme « No Parking »), qui n'ont pas été investigués dans la MA. Il serait intéressant d'évaluer si les troubles de dénomination chez les patients MA s'étendent également à ce type d'entités. L'utilisation de plusieurs types d'ESU pourrait représenter un outil clinique utile afin d'identifier des profils d'anomie (ex. anomie des noms propres ou « prosopoanomie ») et d'améliorer le diagnostic différentiel avec d'autres maladies neurodégénératives dans lesquelles les patients présentent également une anomie, tel que la vs-APP.

De plus, la nature de l'anomie chez les patients avec MA n'est pas encore claire. Sur le plan cognitif, certaines études suggèrent qu'un trouble sémantique est à la base des difficultés de dénomination, d'autres suggèrent qu'il s'agit d'un trouble d'accès lexical et finalement, certains auteurs ont conclu qu'il pourrait s'agir des deux mécanismes simultanément. Au point de vue des corrélats neuronaux, bien que plusieurs régions aient été relevées comme impliquées

dans l'anomie chez les patients MA, aucune étude n'a directement évalué le modèle de Gesierich et collaborateurs (2011) dans cette population, celui-ci définissant le LTA gauche comme région clé dans la sémantique et la jonction temporo-pariétale comme région clé dans l'accès lexical (Gesierich et al., 2011).

4. Volet #2 : La MA comme syndrome de déconnexion

Afin de mieux comprendre les bases cérébrales de différents symptômes cliniques, les chercheurs en neurosciences ont traditionnellement tenté d'identifier les régions cérébrales spécifiques qui étaient à la source de ceux-ci. Dans l'étude du langage, ceci a permis d'identifier les régions cérébrales clés dans lesquelles des dommages structurels ou des altérations fonctionnelles semblaient être associés à l'anomie chez les patients MA (voir section 3.3).

Bien que ces approches s'avèrent essentielles à notre compréhension du cerveau humain, des théories plus récentes suggèrent que celles-ci ne nous fournissent qu'une compréhension partielle des mécanismes cérébraux sous-jacents à certains comportements. Celles-ci s'intéressent de plus en plus à l'interaction entre plusieurs régions cérébrales, soit aux réseaux cérébraux. Dans ce contexte, en addition à des dommages structurels ou des altérations fonctionnelles dans des régions cérébrales spécifiques isolées, une déconnexion au sein de réseaux cérébraux pourrait également sous-tendre des difficultés cognitives. Ceci a clairement été démontré dans la majorité des maladies neurodégénératives, incluant la MA (Seeley, Crawford, Zhou, Miller, & Greicius, 2009). Ainsi, il est possible qu'une déconnexion cérébrale puisse contribuer aux déficits langagiers présentés par les patients MA. Dans ce volet de la présente thèse, les bases théoriques de l'hypothèse de la dégénérescence des réseaux et les techniques d'imagerie de la connectivité cérébrale seront d'abord résumées. Ensuite, nous réviserons les réseaux cérébraux clés qui présentent des altérations chez les patients MA. Finalement, les rares études en connectivité portant sur le réseau cérébral du langage chez les patients MA seront présentées.

4.1 Hypothèse de la dégénérescence des réseaux

Certains auteurs ont proposé un modèle général de la progression de la maladie neurodégénérative nommé l'hypothèse de la dégénérescence des réseaux (« network degeneration hypothesis ») (Reid & Evans, 2013; Seeley et al., 2009). Selon ce modèle, les protéines responsables de la maladie s'agrègeraient dans des populations de neurones sélectives qui résident dans des régions du cerveau spécifiques (Graveland, Williams, & DiFiglia, 1985; Hyman, Van Hoesen, Damasio, & Barnes, 1984; Seeley et al., 2006). Ensuite, ces agents pathologiques seraient transportés à travers les axones et les synapses, puis le dommage se propagerait dans de nouvelles régions, ce qui serait accompagné d'une accentuation des déficits cliniques (Selkoe, 2002). Toutefois, la propagation ne serait pas aléatoire : les nouvelles régions qui seraient affectées plus tard dans la maladie présenteraient des connexions anatomiques connues avec les régions affectées au début de la maladie (Seeley et al., 2008; Seeley et al., 2009). Toujours selon cette théorie, diverses maladies neurodégénératives cibleraient spécifiquement un groupe de régions qui, chez les individus en santé, sont hautement corrélées sur le plan structurel et fonctionnel (Seeley et al., 2009). Dans la MA, ces régions deviendraient ainsi moins associées, ce qui suggère ainsi que la MA est un syndrome de déconnexion, un concept qui a également été abordé par plusieurs autres auteurs (Delbeuck, Van der Linden, & Collette, 2003; Y. He, Chen, Gong, & Evans, 2009; Reid & Evans, 2013; Seeley et al., 2009).

4.2 Techniques d'imagerie de la connectivité cérébrale

Plusieurs techniques peuvent être utilisées pour investiguer la connectivité cérébrale ou en d'autres mots, les relations entre des régions distinctes du cerveau. On distingue deux grandes catégories, soit les approches fonctionnelles, qui utilisent l'activation cérébrale comme paramètre, et les approches structurelles qui utilisent l'intégrité de la matière grise ou de la matière blanche comme paramètre.

4.2.1 Fonctionnelles

L'imagerie par résonance magnétique fonctionnelle à l'état de repos (« resting-state »; IRMf-rs) est devenue dans les dernières années un outil de choix dans l'étude des réseaux cérébraux dans la MA. Cette technique permet d'identifier les régions dans lesquelles le signal

dépendant du niveau d'oxygène sanguin («blood oxygen level-dependent (BOLD) ») sont corrélées dans le temps lorsqu'un individu est dans un état de repos et qu'il n'exécute pas de tâche cognitive (Buckner, Andrews-Hanna, & Schacter, 2008). Cette technique a révélé l'existence d'un réseau fonctionnel principalement associé à l'état de repos, soit le réseau du mode par défaut (« default-mode network »; RMD) (Buckner et al., 2008; Raichle et al., 2001), qui sera décrit en détail dans la section 4.3.1. Puisque toutes les régions cérébrales ont des fluctuations spontanées en termes de signal BOLD, l'IRMf-rs a également permis d'identifier d'autres réseaux de façon très robuste (entres autres, les réseaux de la saillance ou du contrôle exécutif, voir section 4.3.2). L'intérêt de ces réseaux est qu'ils coïncident avec des réseaux fonctionnels bien définis (Seeley et al., 2009). L'IRMf-rs permet ainsi, en une seule séquence de neuroimagerie et sans la nécessité d'administrer des tâches cognitives dans le scanner, d'investiguer l'architecture de plusieurs réseaux cérébraux fonctionnels.

4.2.2 Structurelles

Mis à part les techniques d'imagerie de diffusion, qui représentent les techniques de connectivité structurelle les plus utilisées, l'étude de la covariance structurelle de la matière grise a émergé dans les dernières années (Mechelli, Friston, Frackowiak, & Price, 2005; Zielinski, Gennatas, Zhou, & Seeley, 2010). Cette technique permet d'évaluer la connectivité cérébrale structurelle chez un groupe d'individus en termes de réseaux de covariance structurelle de la matière grise (RCSMG). Celle-ci est basée sur l'observation que la morphologie de certaines régions cérébrales fluctue de façon coordonnée, et ce, à travers la population. Les RCSMG sont de grand intérêt puisque ceux-ci, tout comme les réseaux obtenus en IRMf-rs, reproduiraient les réseaux fonctionnels. À titre de première démonstration de ce phénomène, il a été démontré que le volume de plusieurs composantes du système visuel (le tractus optique, le noyau géniculé latéral et le cortex visuel primaire) covarient à travers la population (Andrews, Halpern, & Purves, 1997). Une étude conduite par Seeley et collègues a également démontré un lien entre les RCSMG et les réseaux fonctionnels intrinsèques, obtenus en IRMf-rs (Seeley et al., 2009), tels que le RMD, le réseau de la saillance, le réseau visuel ou le réseau sensorimoteur. En soutien à la validité des RCSMG, une autre étude a démontré que 30 à 40% des régions qui covariaient en termes d'épaisseur corticale étaient directement reliées par des faisceaux de matière blanche (Gong, He, Chen, & Evans, 2012). Ainsi, bien que complémentaires à d'autres

approches, les RCSMG fournissent un apport unique à notre compréhension de la connectivité cérébrale en raison de leur utilisation d'un paramètre structurel différent, soit les volumes de la matière grise.

Jusqu'à présent, cette technique a été utilisée afin de comprendre la connectivité structurelle chez plusieurs populations, entre autres dans une étude de notre groupe sur les adultes et les personnes âgées (Montembeault et al., 2012), mais également chez les enfants avec et sans trouble de développement (Zielinski et al., 2012; Zielinski et al., 2010) et chez les personnes âgées avec divers troubles cognitifs (Hafkemeijer et al., 2016; Spreng & Turner, 2013). Il semble que ces patrons de covariance pourraient provenir d'influences génétiques (Pezawas et al., 2005; Schmitt et al., 2008; Schmitt et al., 2010), d'influences trophiques mutuelles (Burgoyne, Graham, & Cambray-Deakin, 1993; Ferrer et al., 1995) ou de plasticité reliée à une expérience commune (Dehaene et al., 2010; Draganski et al., 2004; Hyde et al., 2009).

4.3 Réseaux cérébraux clés dans la MA

4.3.1 Réseau du mode par défaut (RMD)

Chez les patients MA, il semblerait qu'une déconnexion survienne au sein du RMD et ce, dès les premiers stades de la maladie, tel que le confirme une méta-analyse récente (Badhwar et al., 2017). Le RMD inclut les régions suivantes : le cortex cingulaire postérieur, le cortex préfrontal antérieur médian, le lobe temporal médian (incluant l'hippocampe), le lobe temporal latéral et le lobule pariétal inférieur (Buckner et al., 2008; Raichle et al., 2001). Ce réseau est actif durant le « repos », c'est-à-dire en l'absence de stimuli externes ou orientés vers un but (Fransson, 2005; Greicius, Krasnow, Reiss, & Menon, 2003; Raichle et al., 2001). Bien que sa fonction précise ne soit pas encore complètement définie, celui-ci agirait comme médiateur des processus internes tels la mémoire épisodique et autobiographique, la théorie de l'esprit, la prise de décisions personnelles et affectives et le fait de réfléchir à son futur (Buckner et al., 2008; Spreng, Mar, & Kim, 2009).

Une des explications possibles à cette diminution de la connectivité chez les patients MA est que son activité continuelle au cours de la vie rendrait ce réseau plus vulnérable (Buckner et

al., 2005) et le prédisposerait aux dépôts Aβ, à une perturbation métabolique et à l'atrophie dans la MA (Buckner et al., 2005). De façon consistante avec cette hypothèse, la topologie des plaques Aβ dans le cerveau des patients MA chevauche de façon évidente la topologie du RMD (Klunk et al., 2004), tout comme leur patron d'atrophie de la matière grise (Lehmann et al., 2013; Seeley et al., 2009).

Bien que la majorité des études chez les patients MA ont considéré le RMD comme un réseau entier, certaines études ont mis en évidence le fait que celui-ci est formé de différentes sous-composantes (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010), dont deux qui semblent particulièrement pertinentes dans l'étude de la MA. Tout d'abord, il y aurait le « midline core », qui inclurait les deux régions principales du RMD, le cortex cingulaire postérieur et le cortex préfrontal antérieur médian, et qui sous-tendrait l'utilisation flexible de l'information pour la prise de décisions personnelles et affectives. Deuxièmement, il y aurait le « medial temporal lobe subsystem », qui serait basé dans l'hippocampe et le cortex entorhinal, en plus du cortex préfrontal ventromédian, du lobule pariétal inférieur postérieur et du cortex rétrosplénial qui serait particulièrement impliqué dans la mémoire épisodique et l'imagerie visuospatiale. Bien que les études précédentes chez les patients MA semblent suggérer une baisse de connectivité fonctionnelle dans des régions associées à ces deux composantes (Badhwar et al., 2017), la majorité de celles-ci ont considéré le RMD comme un réseau unitaire.

4.3.2 Réseau de la saillance et réseau du contrôle exécutif

Les réseaux de la saillance et du contrôle exécutif revêtent d'une importance particulière dans la MA en raison d'études ayant montré une augmentation de la connectivité dans ces réseaux.

Le réseau de la saillance comprend le cortex fronto-insulaire (qui agit comme région principale du réseau), le cortex cingulaire antérieur dorsal, ainsi que plusieurs structures sous-corticales telles que l'amygdale, la substance noire et l'aire tegmentale ventrale (Seeley, Menon, et al., 2007; Zielinski et al., 2012). De façon sommaire, ce réseau est impliqué dans l'habileté à identifier les stimuli nouveaux ou pertinents pour guider le comportement (afin que l'organisme puisse décider de faire ou de ne pas faire une action donnée par la suite) (Craig, 2009; Seeley, Menon, et al., 2007). Il semblerait que ce réseau réponde à un degré de saillance personnelle,

que celle-ci soit cognitive, homéostatique ou émotionnelle, indépendamment de la tâche (Critchley, 2005). Par exemple, il a été démontré que la connectivité de ce réseau soit entre autres associée à ces différentes formes de saillance : les dimensions émotionnelles de la douleur (Peyron, Laurent, & Garcia-Larrea, 2000), l'empathie (Singer et al., 2004), le stress métabolique et la faim (Craig, 2002), les visages des personnes aimées (Bartels & Zeki, 2004), etc.

Plusieurs chercheurs s'intéressent au réseau de la saillance dans la MA, puisque celui-ci montre une corrélation fonctionnelle inverse avec le RMD (Seeley, Allman, et al., 2007). En effet, lorsque le réseau de saillance est activé, le RMD est désactivé, et vice versa, ce qui concorde largement avec le rôle respectif de ces deux réseaux. De façon intéressante, dans la MA, le réseau de la saillance montre une augmentation de connectivité (Agosta et al., 2012; Badhwar et al., 2017; Zhou et al., 2010) accompagnée d'un déclin de la connectivité du RMD. D'autres études ont toutefois montré une baisse de connectivité dans le réseau de la saillance chez les patients MA (Brier et al., 2012; X. He et al., 2014), ce qui confirme l'importance d'approfondir l'étude de la connectivité de ce réseau dans la MA.

Au même titre que le réseau de la saillance, le réseau du contrôle exécutif revêt un intérêt particulier dans la MA en raison de sa connectivité augmentée (Agosta et al., 2012; Filippi et al., 2013; Weiler et al., 2014; Zhang et al., 2009). Le réseau du contrôle exécutif inclut le cortex préfrontal dorsolatéral et le néocortex pariétal (Menon & Uddin, 2010; Seeley, Menon, et al., 2007; Sridharan, Levitin, & Menon, 2008). Ce réseau joue un rôle critique dans les fonctions exécutives, la sélection et l'inhibition de réponses, l'attention soutenue et la mémoire de travail (Seeley, Menon, et al., 2007).

4.4 Le réseau du langage

Les modèles neuroanatomiques classiques du langage, qui sont principalement basés sur l'étude des patients aphasiques suite à un accident vasculaire cérébral, postulent que le langage est sous-tendu par deux centres du langages principaux, soit l'aire de Broca (le pars triangularis et le pars opercularis du GFI gauche) et l'aire de Wernicke (le GTPM gauche dans la jonction temporo-pariétale) (Geschwind, 1970). Même si la fonction et la localisation précises de ces régions ont été un sujet de débat depuis plusieurs années, leur rôle dans le réseau du langage est largement accepté (Dronkers, Ivanova, & Baldo, 2017; Tremblay & Dick, 2016). Toutefois,

l'étude des maladies neurodégénératives, et principalement de la vs-APP, a mis en évidence que cette description du réseau du langage était incomplète. En effet, plusieurs études ont démontré le rôle critique du LTA gauche dans le réseau langagier, principalement au point de vue de la sémantique ou des connaissances conceptuelles (Chedid et al., 2016; Gorno-Tempini et al., 2011; Heilman, 1972; Hodges, Patterson, Oxbury, & Funnell, 1992; Snowden et al., 1989; Wilson et al., 2012). Plusieurs études chez les sujets contrôles utilisant des techniques de connectivité ont par ailleurs appuyé l'inclusion de cette région à titre de centre langagier, avec le GFI gauche et le GTPM gauche (Damasio, Tranel, Grabowski, Adolphs, & Damasio, 2004; Ferstl, Neumann, Bogler, & von Cramon, 2008; Hurley, Bonakdarpour, Wang, & Mesulam, 2015; Mesulam et al., 2013; Schwartz et al., 2009; Ueno, Saito, Rogers, & Lambon Ralph, 2011). De façon intéressante, ces trois régions sont également celles qui ont été rapportées comme les corrélats neuronaux de l'anomie chez les patients avec MA (voir section 3.3).

Néanmoins, chez les patients MA, très peu d'études ont investigué la connectivité du réseau du langage. (Mascali et al., 2018; Weiler et al., 2014; Whitwell et al., 2015). Ces études ont rapporté de façon assez constante une diminution de la connectivité à partir des régions langagières postérieures (telles que le GTPM gauche) (Mascali et al., 2018; Weiler et al., 2014; Whitwell et al., 2015). Les régions langagières antérieures (telles que le GFI gauche) ont quant à elles généré des résultats contradictoires chez les patients MA : une étude a montré une connectivité préservée dans cette région (Weiler et al., 2014), alors qu'une autre étude a montré une connectivité altérée (Mascali et al., 2018). Finalement, aucune étude n'a investigué la connectivité du LTA gauche chez les patients MA.

4.5 Résumé du volet #2

L'ensemble de ces études semble démontrer que la MA est un syndrome de déconnexion. Malgré tout, la majorité des études comportent des limites qu'il serait essentiel d'aborder afin d'améliorer notre compréhension des réseaux cérébraux dans la MA. Tout d'abord, les études de connectivité cérébrale chez les patients MA ont majoritairement utilisé des techniques fonctionnelles et elles portent sur de petits échantillons. Ainsi, il serait essentiel d'utiliser une approche complémentaire de connectivité structurelle, soit les RCSMG, afin d'apporter un soutien plus important à la MA en tant que syndrome de déconnexion. Puisque cette technique

ne nécessite qu'une IRM structurelle, il est beaucoup plus facile d'avoir accès à un échantillon de grande taille, en comparaison aux études en IRMf-rs qui nécessitent une séquence fonctionnelle. Par ailleurs, les études précédentes ont considéré le RMD comme un réseau entier, et aucune étude n'a investigué ses différentes sous-composantes séparément (Andrews-Hanna et al., 2010).

Finalement, les études de connectivité cérébrale dans la MA se sont largement concentrées sur le RMD. Ainsi, bien que quelques études aient montré une augmentation de la connectivité dans les réseaux de la saillance et du contrôle exécutif, ces résultats doivent être répliqués sur d'autres échantillons. De plus, malgré le fait que certaines études aient investigué le réseau du langage chez les patients MA, dans aucune de celles-ci le langage n'était le point focal de l'étude. Ceci fait en sorte que les résultats obtenus dans ce réseau étaient peu, voire nullement interprétés et discutés. Une autre des limitations de ces études concerne le fait qu'aucune de celles-ci n'a investigué la connectivité du LTA gauche chez les patients MA. Considérant le fait qu'un trouble sémantique pourrait être un des mécanismes sous-jacents aux problèmes langagiers chez les patients MA, et que le LTA gauche est une région clé du réseau langagier spécifiquement associée à la mémoire sémantique, l'investigation de sa connectivité pourrait nous éclairer sur les symptômes langagiers des patients MA.

5. Objectifs et hypothèses

De façon générale, le premier volet de la thèse vise à mieux caractériser l'anomie chez les patients MA, ainsi qu'à clarifier ses bases cognitives et cérébrales (étude #1). Le deuxième volet de la thèse vise à démontrer que la MA est un syndrome de déconnexion (étude #2), et que cette déconnexion touche le réseau cérébral responsable du langage (étude #3).

5.1 Volet #1

Le premier objectif de l'article #1 de la présente thèse est de caractériser et de comparer le profil d'anomie des patients MA, des patients vs-APP et des sujets contrôles en utilisant des entités non uniques et des ESU (personnes, lieux et logos célèbres). La première hypothèse est

que les patients MA présenteront une performance significativement plus faible en comparaison aux sujets contrôles, mais significativement plus élevée en comparaison aux patients vs-APP dans toutes les tâches de dénomination. La deuxième hypothèse est que les patients MA et vs-APP seront plus atteints en dénomination d'ESU en comparaison en dénomination d'entités non uniques.

Le deuxième objectif de l'article #1 est de caractériser et de comparer les connaissances sémantiques portant sur ces mêmes entités et auprès des mêmes groupes afin de clarifier les bases cognitives de leur anomie (trouble sémantique vs. trouble d'accès lexical). Le troisième objectif de l'article #1 est d'identifier les corrélats neuronaux des troubles de dénomination des patients MA afin de clarifier les bases cérébrales de leur anomie en termes d'atrophie de la matière grise (dommage au LTA gauche vs. dommage dans la jonction temporo-pariétale gauche). Pour ces deux objectifs, étant donné le nombre substantiel d'études supportant chacune des bases cognitives et cérébrales, nous ne sommes pas en mesure d'élaborer d'hypothèses précises. Il existe trois possibilités : 1) les connaissances sémantiques des entités à nommer sont préservées et l'anomie corrèle avec l'atrophie de la jonction temporo-pariétale chez les patients MA; 2) les connaissances sémantiques des entités à nommer sont atteintes et l'anomie corrèle avec l'atrophie du LTA gauche chez les patients MA; 3) un profil mixte sera observé chez les patients MA.

5.2 Volet #2

L'objectif de l'article #2 est de caractériser et comparer la connectivité cérébrale des RCSMG (« midline core » du RMD, « medial temporal lobe subsystem » du RMD, saillance, contrôle exécutif) d'un grand échantillon de patients MA dans les premiers stades de la maladie, en comparaison aux sujets contrôles. La première hypothèse est qu'une baisse de connectivité structurelle sera observé dans les deux sous-composantes du RMD chez les patients MA, en comparaison aux sujets contrôles. La deuxième hypothèse est qu'une augmentation de la connectivité structurelle sera observé dans les réseaux de la saillance et du contrôle exécutif chez les patients MA, en comparaison aux sujets contrôles.

L'article #3 de cette thèse a pour objectif de caractériser et comparer la connectivité cérébrale fonctionnelle du réseau du langage (investigué avec des régions d'intérêt dans le GFI

gauche, le GTPM gauche et le LTA gauche) chez les patients MA, vs-APP et les sujets contrôles. L'hypothèse est que les patients MA présenteront principalement une diminution de la connectivité fonctionnelle du GTPM gauche, alors que les patients vs-APP présenteront principalement une diminution de la connectivité fonctionnelle du LTA gauche.

Chapitre II: Méthodologie et résultats

Article 1 : Naming unique entities in the semantic variant of primary progressive aphasia and Alzheimer's disease: Towards a better understanding of the semantic impairment

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Abstract

While the semantic variant of primary progressive aphasia (svPPA) is characterized by a predominant semantic memory impairment, episodic memory impairments are the clinical hallmark of Alzheimer's disease (AD). However, AD patients also present with semantic deficits, which are more severe for semantically unique entities (e.g. a famous person) than for common concepts (e.g. a beaver). Previous studies in these patient populations have largely focused on famous-person naming. Therefore, we aimed to evaluate if these impairments also extend to other semantically unique entities such as famous places and famous logos. In this study, 13 AD patients, 9 svPPA patients, and 12 cognitively unimpaired elderly subjects (CTRL) were tested with a picture-naming test of non-unique entities (Boston Naming Test) and three experimental tests of semantically unique entities assessing naming of famous persons, places, and logos. Both clinical groups were overall more impaired at naming semantically unique entities than non-unique entities. Naming impairments in AD and svPPA extended to the other types of semantically unique entities, since a CTRL > AD > svPPA pattern was found on the performance of all naming tests. Naming famous places and famous persons appeared to be most impaired in svPPA, and both specific and general semantic knowledge for these entities were affected in these patients. Although AD patients were most significantly impaired on famous-person naming, only their specific semantic knowledge was impaired, while general knowledge was preserved. Post-hoc neuroimaging analyses also showed that famous-person naming impairments in AD correlated with atrophy in the temporo-parietal junction, a region functionally associated with lexical access. In line with previous studies, svPPA patients' impairment in both naming and semantic knowledge suggest a more profound semantic impairment, while naming impairments in AD may arise to a greater extent from impaired lexical access, even though semantic impairment for specific knowledge is also present. These results highlight the critical importance of developing and using a variety of semantically-unique-entity naming tests in neuropsychological assessments of patients with neurodegenerative diseases, which may unveil different patterns of lexical-semantic deficits.

Key words: Naming, Semantically unique entities, Semantic variant primary progressive aphasia, Alzheimer's disease, semantics, lexical access

1. Introduction

The semantic variant of primary progressive aphasia (svPPA), also referred to as semantic dementia, is a neurodegenerative disease characterized by a progressive deterioration of semantic memory (Gorno-Tempini et al., 2011). The core cognitive features of patients with svPPA are impaired confrontation naming and single-word comprehension, most often accompanied with impaired object knowledge as well as surface dyslexia and dysgraphia. While semantic deficits in svPPA patients are relatively isolated, at least in the early stages, Alzheimer's disease (AD) is characterized by a cognitive decline typically beginning with episodic memory impairments but resulting in general debilitating dementia affecting many other cognitive domains (McKhann et al., 2011). Interestingly, language impairments in AD initially affect confrontation naming and verbal fluency (Adlam, Bozeat, Arnold, Watson, & Hodges, 2006; J.R. Hodges & K. Patterson, 1995; Huff, Corkin, & Growdon, 1986; Verma & Howard, 2012).

Therefore, both svPPA and AD patients present with impaired confrontation naming. While it is a core symptom of svPPA (Gorno-Tempini et al., 2011), naming difficulties are much more heterogeneous in AD. Domoto-Reilly and colleagues found that approximately 41% of a large sample of early stages AD patients scored below the normal range when naming common entities (e.g. animals, objects, etc.) on the Boston Naming Test (Domoto-Reilly, Sapolsky, Brickhouse, & Dickerson, 2012). However, deficits in naming semantically unique entities (i.e., entities with a unique semantic and lexical association) such as famous persons have been shown to be more severe than for non-unique entities in AD (Delazer, Semenza, Reiner, Hofer, & Benke, 2003; Joubert et al., 2010; Joubert et al., 2008; Semenza, Mondini, Borgo, Pasini, & Sgaramella, 2003; Thompson, Graham, Patterson, Sahakian, & Hodges, 2002). Considering that both populations present naming impairments, it appears necessary to compare svPPA and AD patients in terms of their ability to name semantically unique entities. Studies which have investigated semantically unique entities in dementia so far have largely focused on famous persons. However, it is necessary to determine if naming deficits in svPPA and AD patients extend to other categories of semantically unique entities such as famous places (e.g. landmarks and buildings) and famous logos (e.g. brands or everyday life pictograms). It is also critical to investigate if some types of items are selectively impaired within each population. The characterization of naming impairments across item types in each clinical population could be

a valuable tool in clinical settings and contribute to identifying specific anomia profiles (e.g. proper name anomia or prosopanomia). It also has the potential to improve differential diagnosis. To our knowledge, famous places have only been investigated in some patient populations such as Mild cognitive impairment patients (Ahmed, Arnold, Thompson, Graham, & Hodges, 2008), post-stroke aphasics (Vitali et al., 2015), traumatic brain injury patients (Milders, 2000), and epileptic patients (Benke, Kuen, Schwarz, & Walser, 2013). Famous logos have never been used with patient populations.

Investigating naming for different types of semantically unique entities is critical for several reasons. First, it is still unclear if famous persons and other entities such as famous places are processed the same way and therefore equally difficult to name for AD and svPPA patients. Previous neuroimaging studies have demonstrated that naming both famous persons and places activate the same brain regions related to semantics (i.e. the left anterior temporal cortex), in addition to brain regions subserving category-specific perceptual processing (i.e. fusiform regions for faces and parahippocampal/lingual regions for places/buildings) (Gorno-Tempini & Price, 2001; Grabowski et al., 2001). This could suggest that both types of entities would be relatively equally impaired in AD and svPPA, as is the case in mild cognitive impairment patients (Ahmed et al., 2008) and traumatic brain injury patients (Milders, 2000). In AD, only famous-landmark identification has been investigated and shown to be as impaired as famous-person identification (Sheardova et al., 2014). Secondly, in comparison to famous persons, famous places might be less time-period sensitive, which might be an advantage for the construction of a validated neuropsychological test that is durable. Finally, logos are different from other types of semantically unique items in the sense that they are characterized by a very stable and invariable perceptual representation. They also have the potential to be a valuable tool for clinicians as an indication of patients' abilities to identify everyday life stimuli.

Comparing svPPA and AD patients on tests of naming and semantic knowledge of semantically unique entities may also provide insight into the nature of the impairment underlying anomia in these patients. Cognitive models of semantic memory suggest that naming impairments may be caused by either 1) a semantic impairment, in which stored information is lost, or 2) impaired lexical access, in which the access to stored information is dysfunctional (Matthew A. Lambon Ralph, 2014). While it is recognized that svPPA naming deficits result from the disease's characteristic progressive degradation of conceptual knowledge (Gorno-

Tempini et al., 2011; Reilly, Peelle, Antonucci, & Grossman, 2011; Rogers & Friedman, 2008), the nature of the impairment underlying anomia in AD is still a matter of debate. Previous studies have compared naming abilities and semantic knowledge in AD, i.e. the ability to name entities versus the ability to answer semantic knowledge questions about the same entities (Chertkow & Bub, 1990; Joubert et al., 2010). A correspondence between naming impairments and impaired semantic knowledge in AD patients was observed, suggesting that word finding difficulties were at least in part due to underlying semantic disruption, which could potentially be combined with additional difficulties in the selection, manipulation, and retrieval of knowledge (Joubert et al., 2010). Other studies observed strong associations between naming abilities and executive functioning in AD patients, suggesting that naming impairments may be associated in part with impaired controlled semantic retrieval (Reilly et al., 2011). In terms of neuroanatomy, these two mechanisms are associated with different brain regions. Semantic processing has principally been associated with anterior temporal lobes (ATL) and lexical access mainly with the temporo-parietal junction (Gesierich et al., 2011; Vitali et al., 2015). While it is widely acknowledged that naming impairments in svPPA are associated with atrophy in the ATLs (Gorno-Tempini et al., 2004; M. Mesulam et al., 2009), previous neuroimaging results in AD patients have provided support for the role of both regions in naming abilities (Domoto-Reilly et al., 2012; Grossman et al., 2004; Lars et al., 2011; N. Nelissen et al., 2011; Natalie Nelissen et al., 2007; Vandenbulcke, Peeters, Dupont, Van Hecke, & Vandenberghe, 2007).

In this study, we aim to characterize and compare naming abilities in 13 AD patients, 9 svPPA patients, and 12 cognitively unimpaired elderly subjects (CTRL). To do so, we used a non-unique-entity naming test (the Boston Naming Test) and experimental semantically-unique-entity naming tests (famous persons, famous places, famous logos). While previous studies suggest that famous-person naming is more impaired than non-unique-entity naming in svPPA and AD, we aimed to evaluate if these impairments also extend to other semantically unique entities such as famous places and famous logos, which have never been studied in this population. In order to provide insight into the nature of the naming impairments observed (i.e. impaired lexical access vs. semantic impairment), semantic knowledge of semantically unique entities (for famous persons and places) was also assessed.

2. Material and methods

2.1 Participants

Thirteen patients with a clinical diagnosis of AD (5 women, 8 men), nine patients with svPPA (2 women, 7 men), and twelve CTRL (4 women, 8 men) took part in this study. Demographics of participants are presented in Table 1. The three groups were matched for age, gender, and education. The svPPA and AD patients were recruited through La Clinique interdisciplinaire de Mémoire du Centre hospitalier universitaire (CHU) de Québec and referred by a behavioral neurologist with expertise in neurodegenerative diseases and cognition (R.J.L.). svPPA patients were diagnosed according to currently accepted criteria (Gorno-Tempini et al., 2011). Diagnosis of AD was made based on the criteria of the National Institute on Aging and the Alzheimer's Association workgroup (McKhann et al., 2011). General exclusion criteria were as follows: native tongue other than French, left-handedness, developmental learning disabilities, past psychiatric disorder, history of traumatic brain injury, and uncorrected hearing and vision problems. The study was approved by the research ethics committee of the CHU de Québec (Project #2015-1909) and written informed consent was obtained from all participants.

2.2 Neuropsychological assessment

All participants completed a battery of standard neuropsychological tests to assess general cognitive status (Mini-Mental State Examination (MMSE); (Folstein, Folstein, & McHugh, 1975)), as well as a number of cognitive domains. These domains include nonverbal and verbal episodic memory (Immediate and delayed recall of the Rey Complex Figure Test (Meyers & Meyers, 1995; Osterrieth, 1944); Rey Auditory Verbal Learning Test (Rey, 1964)); language and semantic memory (Pyramids and Palm Trees Test (PPTT) (Howard & Patterson, 1992); Free fluency, orthographic and semantic fluency (Joanette, Ska, & Côté, 2004)), working memory (Forward and Backward Digit-span (Wechsler, 1997)), visual perception (Benton Line Orientation test (Benton, Hamsher, Varney, & Spreen, 1983; Qualls, Bliwise, & Stringer, 2000); Benton Facial Recognition test (Benton et al., 1983)), visuoconstructional skills (copy of the Rey Complex Figure Test (Meyers & Meyers, 1995; Osterrieth, 1944); Clock-drawing Test (Rouleau, Salmon, Butters, Kennedy, & McGuire, 1992)); and executive functioning (Trail making test A&B (Tombaugh, 2004); Stroop-Victoria Test (Spreen & Strauss, 1998)). Results are presented in Table 1.

2.3 Naming tasks

2.3.1. Non-unique-entity naming task.

The complete version of the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983) was administered to participants. In this task, subjects are asked to name 60 black and white line drawings of single objects. The total score (out of 60) represents spontaneous correct answers (without cues). Scoring was based on a French-speaking Quebec adults validation study (Roberts & Doucet, 2011).

2.3.2. Semantically-unique-entity naming tasks.

Three semantically-unique-entity naming tasks were created. Twenty high quality color pictures were used in each one of the three tasks. For each task, pictures were displayed one at a time in a Powerpoint slideshow and participants were asked to name the item and to respond to some semantic knowledge questions. They had unlimited time to respond and all responses were recorded using a digital recorder. Items for the famous-person and famous-place tests were selected from a previous study (Vitali et al., 2015). The semantically-unique-entity tests were intended to be very easy for cognitively unimpaired French-speaking Quebec older adults in order to reduce the impact of education on the tasks. The tests were specifically designed for this age-group and included items that were culturally and time-period appropriate.

2.3.2.1. Naming and semantic knowledge of famous persons.

First, participants were presented with a series of pictures of famous persons (from politics, show-business, and sports) which they had to name. One point was given if at least the family name was correctly mentioned (out of 20). Second, general and specific semantic knowledge for each famous person was assessed by asking the participant 1) the field that the famous person belongs to (e.g. arts, sports or politics; out of 20; general semantic knowledge); and 2) the reason of their celebrity (e.g. an actor; out of 20; specific semantic knowledge).

2.3.2.2. Naming and semantic knowledge of famous places.

First, participants had to name the famous places (buildings or landmarks) and one point was given if the name was correctly mentioned (out of 20). Second, general and specific semantic knowledge for each item was assessed by asking the participant 1) the location of the place (out of 20; general semantic knowledge); and 2) a specific question about the place (e.g. what is the main function of the White House?; out of 20; specific semantic knowledge).

2.3.2.3. Naming famous logos.

In this task, participants only had to name the famous logos (out of 20). Stimuli included logos of brands (e.g. popular restaurant, sports team or company) and everyday life pictograms (e.g. road signs or pictograms). Semantic knowledge was not evaluated in this task since the overlap between the name and the semantic knowledge of the items was for some items too significant (e.g. a no parking or pedestrian crossing sign).

2.4. Statistical analyses

Previous studies have underlined the necessity of controlling for task difficulty when conducting studies on category-specific differences (Joubert et al., 2010; Lyons, Kay, Hanley, & Haslam, 2006). In order to control for the difficulty of each naming task and to facilitate the interpretation of our results in patient groups, we selected for our analyses 49 items from the Boston Naming Test and 15 items from each of the three semantically-unique-entity naming tests that were matched for naming difficulty in our CTRL group (e.g. equivalent means and standard deviations). The mean for the CTRLs on each modified test was between 93.0 and 93.3%. Percentage of correct responses on these modified tasks will be used in this study.

3. Results

3.1 Naming performance

3.1.1. Naming non-unique entities vs semantically unique entities

There was a significant interaction between Group (CTRL vs AD vs svPPA) and Item uniqueness (non-unique vs unique) on naming scores, $F(2, 31) = 4.599$, $p < .05$, partial $\eta^2 = .229$ (Table 2).

In terms of intergroup analyses, both non-unique and unique entity naming scores were significantly different for all three groups, (Welch's $F(2, 15.362) = 58.959$, $p < .001$ and Welch's $F(2, 15.985) = 196.161$, $p < .001$, respectively). Games-Howell post hoc analysis revealed that svPPA patients had significantly lower performance on both non-unique and unique entity naming, in comparison to CTRL ($p < .001$) and AD patients ($p < .001$). AD patients also showed significantly lower performance on both non-unique-entity naming ($p < .05$) and semantically-unique-entity naming ($p < .01$), in comparison to CTRLs.

Intragroup analyses showed that in AD patients, performance on non-unique-entity naming was significantly superior to performance on semantically-unique-entity naming, $t(12) = 3.235$, $p = < .01$, $d=.90$, while these tests were controlled for task difficulty on the CTRL

group. In svPPA patients, performance on non-unique-entity naming was also significantly superior to performance on semantically-unique-entity naming, $t(8) = 3.016$, $p < .05$, $d=1.00$.

3.1.2. Naming non-unique entities vs. famous persons vs. famous places vs. famous logos

There was a significant interaction between Group (CTRL vs AD vs svPPA) and Item type (non-unique vs famous persons vs famous places vs famous logos) on naming scores, $F(6, 93) = 4.045$, $p < .001$, partial $\eta^2 = .207$ (Table 2, Figure 1).

Intergroup analyses showed that famous-person naming scores were significantly different for all three groups, Welch's $F(2, 18.123) = 264.727$, $p < .001$. Games-Howell post hoc analysis revealed that both AD and svPPA patients had significantly lower performance on famous-person naming than CTRL ($p < .001$), and that svPPA patients had significantly lower performance than AD patients ($p < .001$). A similar pattern was observed on famous-place and famous-logo naming, in which the scores were significantly different for all three groups (Welch's $F(2, 18.593) = 126.922$, $p < .001$; Welch's $F(2, 14{,}602) = 51.843$, $p < .001$). Games-Howell post hoc analysis revealed that svPPA and AD patients presented lower performance on famous-place naming than CTRLs ($p < .001$ and $p < .05$, respectively) and that svPPA patients had lower performance than AD patients ($p < .001$). On famous-logo naming, svPPA and AD patients also presented lower performance than CTRL ($p < .001$ and $p < .05$, respectively) and svPPA patients also showed lower performance than AD patients ($p < .001$).

For the intragroup analyses, naming scores were significantly different between all item types in the AD group, $F(3,36) = 7.108$, $p < .001$, partial $\eta^2 = .37$. Post hoc analyses revealed that AD patients had significantly lower performance on famous persons, in comparison to non-unique entities ($p < .01$), famous places ($p < .05$) and famous logos ($p < .05$). In svPPA patients, naming scores were also significantly different between all item types, $F(3,24) = 6.084$, $p < .01$, partial $\eta^2 = .43$. Post hoc analyses revealed that svPPA patients had significantly lower performance on famous places, in comparison to non-unique entities ($p < .01$) and famous logos ($p < .05$). They also presented significantly lower performance on famous persons in comparison to non-unique entities ($p < .05$). The other comparisons were non-significant.

3.2 Naming vs. semantic knowledge

3.2.1. Naming vs. general vs. specific semantic knowledge (Famous persons)

There was a significant interaction between Group (CTRL vs AD vs svPPA) and Condition (naming vs. general semantic knowledge vs. specific semantic knowledge), $F(2.5, 38.7) = 34.115$, $p < .001$, partial $\eta 2 = .688$ (Table 2, Figure 2).

Intergroup analyses showed that both general and specific semantic knowledge of famous persons was significantly different for all three groups ($F(2, 31) = 23.542$, $p < .001$; Welch's $F(2, 15.814) = 54.088$, $p < .001$, respectively). For general and specific semantic knowledge, svPPA patients presented significantly lower performance than both AD patients ($p < .01$ and $p < .001$, respectively) and CTRLs ($p < .01$ and $p < .001$, respectively). However, while AD patients had lower performance than CTRLs for specific semantic knowledge ($p < .05$), their performance was equivalent to CTRLs on general semantic knowledge ($p = .376$).

For the intragroup analyses, scores for the famous persons were significantly different between all conditions in CTRLs, $F(2, 22) = 8.407$, $p < .01$, partial $\eta^2 = .433$. Post hoc analyses revealed that in the CTRL group, general and specific semantic knowledge for famous persons was equivalent ($p = .287$) but superior to naming ($p < .05$). In AD and svPPA scores were also significantly different between all conditions ($F(1.1, 13.3) = 34.996$, $p < .001$, partial $\eta^2 = .745$; $F(2, 16) = 130.339$, $p < .001$, partial $\eta^2 = .942$, respectively). Post hoc analyses revealed that AD and svPPA patients presented a similar pattern with better performance for general semantic knowledge ($p < .001$) than for specific semantic knowledge, and with both types of knowledge superior to naming ($p < .001$; $p < .05$, respectively).

3.2.1. Naming vs. general vs. specific semantic knowledge (Famous places)

There was a significant interaction between Group (CTRL vs AD vs svPPA) and Condition (naming vs. general semantic knowledge vs. specific semantic knowledge), $F(4, 62) = 10.263$, $p < .001$, partial $\eta 2 = .398$ (Table 2, Figure 2).

Intergroup analyses for semantic knowledge of famous places yielded similar results to semantic knowledge of famous persons. Both general and specific semantic knowledge of famous places was significantly different for all three groups (Welch's $F(2, 14.878) = 19.717$, $p < .001$; Welch's $F(2, 18.021) = 48.423$, $p < .001$, respectively). For general and specific semantic knowledge, svPPA patients presented significantly lower performance than AD patients ($p < .01$ and $p < .001$, respectively) and CTRLs ($p < .001$). However, while AD patients had lower performance than CTRLs for specific semantic knowledge ($p < .05$), their performance was equivalent to CTRLs on general semantic knowledge ($p = .268$).

Intragroup analyses showed that CTRLs and AD patients had a similar pattern of results. In both groups, scores were significantly different between all conditions ($F(2, 22) = 27.107$, $p < .001$, partial $\eta^2 = .711$; $F(2, 24) = 22.723$, $p < .001$, partial $\eta^2 = .654$, respectively). Furthermore, post hoc analyses showed that in these two groups, naming and general knowledge for famous places was equivalent ($p = .815$ for CTRL and $p = .186$ for AD), but superior to specific semantic knowledge ($p < .001$). svPPA patients' scores were also significantly different between all conditions ($F(1.2, 9.5) = 25.612$, $p < .001$, partial $\eta^2 = .762$). However, they showed lower scores on naming in comparison to both specific and general semantic knowledge ($p < .05$ and $p < .01$, respectively). Specific semantic knowledge scores were also significantly lower than general semantic knowledge scores in svPPA patients ($p < .01$).

3.3. Rates of impairments on naming tests

Impaired performance was defined as 2 SDs below the CTRLs mean. On the non-unique-entity naming test, 100% of svPPA patients and 46.2% of AD patients showed impaired performance. On the famous-person test, 100% of svPPA patients and 69.2% of AD patients had impaired performance. On the famous-place test, 100% of svPPA patients and 38.5% of AD patients showed impaired performance. On the famous-logo test, 100% of svPPA patients and 61.5% of AD patients had impaired performance.

Looking at the overlap of impairment across the unique-entity naming tests, the performance of 100% of svPPA patients was impaired on all 3 tests. Of the AD patients, 15.4% showed unimpaired performance on any of the tests, 38.5% had impaired performance on one test only, 7.6% on two tests and 38.5% on all three tests.

3.4. Post-hoc voxel-based morphometry analysis

The behavioral results of the intragroup analyses revealed a selective vulnerability for famous-person naming in AD patients (in comparison to other types of entities). In order to provide further insight into the nature of the famous-person naming impairments observed (i.e. impaired lexical access vs. semantic impairment), a voxel-based morphometry analysis was conducted. Based on previous studies, we hypothesized a significant correlation between the famous-person naming scores and the temporo-parietal junction gray matter (GM) volume if the naming impairments were related to impaired lexical access, and a correlation with the ATL GM volume if they were related to a semantic impairment (Gesierich et al., 2011; Vitali et al., 2015). Therefore, we correlated the GM volume in two regions of interest (left ATL (-39, 15, -

33) and left temporo-parietal junction (-42, -60, 48)) with the famous-person naming scores in the AD group. The regions of interest were 10 mm spheres based on coordinates obtained in a previous fMRI study investigating famous-person naming and semantics (Gesierich et al., 2011).

3.4.1. Image acquisition.

Out of our 13 AD patients, 12 underwent a Magnetic Resonance Imaging protocol including a high-definition T1 brain image. The brain structural MRI scans were obtained with a 3T Philips Achieva TX scanner at IRM Québec-Mailloux in Quebec City. A volumetric magnetization prepared rapid gradient echo (MP-RAGE) sequence was used to acquire a high-resolution T1 3D structural image (TR = 8.2 ms, TE = 3.7 ms, FoV= 250 mm, flip angle = 8◦, 256×256 matrix, 180 slices/volume, slice thickness = 1mm, no gap).

3.4.2. Image preprocessing.

The structural images were preprocessed using voxel-based morphometry (VBM) implemented in SPM12 using MATLAB 7.14.0.739 (Mathworks, Natick, MA). The images were segmented into gray (GM) and white (WM) matter. Affine registered tissue segments were used to create a custom template using the DARTEL (diffeomorphic anatomical registration using exponentiated lie algebra) approach (Ashburner, 2007). For each participant, the flow fields were calculated during a template creation, which described the transformation from each native GM image to the template. These were then applied to each participant's GM image. The VBM analysis was based on modulated GM images, where the GM value for each voxel was multiplied by the Jacobian determinant derived from spatial normalization to preserve the total amount of GM from the original images (Ashburner & Friston, 2000). The resulting modulated and normalized images were then smoothed with a Gaussian kernel of 8 mm FWHM.

3.4.3. Statistical analysis.

The VBM analysis was performed on smoothed GM images. First, the famous-person naming scores were entered as covariate of interest in a multiple regression statistical model, with age and gender as nuisance covariates. A contrast was set to identify voxels that correlated with famous-person naming scores in each of our regions of interest.

The correlation was tested using a [1] t-contrast, assuming that decreased naming scores would be associated with decreased GM volumes. The significance of each effect of interest

was determined using the theory of Gaussian fields (Friston et al., 1995). Statistical threshold of $p<0.05$ corrected for multiple comparisons was used.

3.4.4. Voxel-based morphometry results

In AD patients, famous-person naming scores correlated with the ROI in the left temporo-parietal junction (x=-42, y=-51, z=51, T=5.45, number of voxels=6, p<.05 FWE corrected within our ROI), but not with the ROI in the left ATL (figure 3).

In order to demonstrate that this result in the left TPJ was specific to the naming performance, and not an effect of semantic processing or dementia severity, we re-ran the analyses including the famous-person specific semantic knowledge and the MMSE scores as nuisance covariates in the model. The correlation between famous-person naming and GM atrophy in the left TPJ remained significant. Finally, to further demonstrate that the correlation observed in the left TPJ was not an effect of a general semantic impairment, we ran a correlation analysis using the PPTT score as the covariate of interest with age and gender as nuisance covariates. No significant correlation was observed in the left TPJ as a result of this analysis.

4. Discussion

In the present study, we aimed to characterize and compare the ability to name non-unique and unique entities (famous persons, famous places, famous logos) in CTRL, AD and svPPA participants. Our behavioral results showed that both AD and svPPA patients were overall more impaired at naming semantically unique entities than non-unique entities on tests that were controlled for difficulty in the CTRL group. We also showed that naming impairments in AD and svPPA extend to different types of semantically unique entities, since a CTRL > AD > svPPA pattern was found on the performance of all naming tests (famous persons, famous places, famous logos). However, all types of entities were not equally impaired within each group. Analyses comparing item types in each group showed that famous-person naming was particularly impaired in AD, revealing a profile similar to what has been previously described as prosopanomia (Carney & Temple, 1993; Geva, Moscovitch, & Leach, 1997; Semenza, Sartori, & D'Andrea, 2003). In svPPA patients, our results showed that famous-place naming was particularly impaired, as well as famous-person naming. In terms of the comparison between naming and semantic knowledge, svPPA patients were impaired on all conditions (naming, specific and general semantic knowledge) on both famous-person and famous-place

tests. However, although AD patients were most significantly impaired on famous-person naming, they showed preserved general semantic knowledge for these items, suggesting that their naming difficulties might be related, at least in part, to impaired lexical access. Our post-hoc analysis was in line this idea, since the severity of deficits for naming famous persons in AD correlated with GM volume in the left temporoparietal junction, a region that is functionally associated to lexical access (and not with the left ATL, which has been found to be correlated with semantic knowledge, i.e. see Joubert et al. 2010).

The findings reported here replicate earlier studies documenting more severe naming impairments for semantically unique entities in neurodegenerative diseases (Delazer et al., 2003; Joubert et al., 2010; Joubert et al., 2008; Semenza, Mondini, et al., 2003; Thompson et al., 2002). Several studies have investigated what makes semantically unique items special and therefore harder to name in certain diseases. In terms of neuroimaging, it has been suggested that processing semantically unique entities and linking them with their names requires a greater amount of metabolic resources (Gorno-Tempini & Price, 2001; Ross & Olson, 2012; Carlo Semenza, 2009). More precisely, the uniqueness of semantic associations and the presence of a proper name associated with the semantically unique item modulates brain activity in the left ATL, overall involving a wider left-hemispheric cortical network (Ross & Olson, 2012). Other authors have also suggested that semantic breakdown may be more important for unique entities than for non-unique entities due to the idiosyncratic features of the former (Joubert et al., 2010; Joubert et al., 2008). In our study, all famous persons and places and some famous logos (e.g. brands of well-known restaurants or companies) were associated with a proper name. This could, in part, account for our results. Retrieval of proper names is thought to be more difficult than retrieval of common nouns (even in cognitively unimpaired elderly subjects), which could be due to the less frequent association between a proper name and what it refers to (Bredart, 1993; Bredart, Brennen, & Valentine, 2002; Semenza, Nichelli, & Gamboz, 1996)). In the context of neurodegenerative diseases in which cerebral resources are limited, this discrepancy between unique and non-unique-entity naming might be amplified.

Since all previous studies in AD and svPPA have focused on famous-person naming, the novelty of this study consisted in evaluating if semantically-unique-entity naming impairments in these populations extend to other types of items such as famous places and logos and to investigate if some types of items are selectively impaired within each population. The

characterization of naming impairments across item types in each clinical population could be an invaluable tool in clinical settings and contribute to identifying specific anomia profiles (e.g. proper name anomia or prosopanomia). Indeed, both AD and svPPA patients exhibited impairments, to different degrees (CTRL>AD>svPPA), on all types of semantically unique entities. However, all types of entities were not equally impaired within each group.

Famous-person naming appears to be a very sensitive measure to detect naming impairments in neurodegenerative patients. AD patients presented a significantly greater vulnerability for famous-person naming in comparison to all other types of items, while in svPPA patients, famous persons were some of the most difficult items to name along with famous places. We hypothesize that this selective vulnerability for famous persons might be due to the fact that out of all the semantically unique entities evaluated in this study, famous-person names appear to present the less frequent association with their referent. Conversely, a lot of famous-place names include (and begin with, in French) a common noun describing what the place is (e.g. Tower in Eiffel Tower, Falls in Niagara Falls) which might also serve as a cue to retrieve the appropriate name. Similarly, some of the items on our famous-logo naming test also include a common noun in their name (e.g. Pedestrian crossing, No smoking). Another hypothesis to explain the selective impairments for naming famous persons in AD is the fact that face perception has recently been shown to be affected to some extent in this disease (Lavallee et al., 2016). In our sample, AD patients did not present a significant impairment on the Benton facial recognition test, even though a trend towards lower scores was observed. However, this hypothesis remains unlikely in our sample, since AD patients were successful in responding to our general semantic knowledge question (and 89.7% for the specific semantic knowledge question), which confirms that AD patients were able to recognize the famous persons presented to them. Our results for the AD group correspond to prosopanomia, a category-specific anomia for faces (Carney & Temple, 1993; Geva et al., 1997; Semenza, Sartori, et al., 2003). It is described as a condition in which naming persons based on their faces is impaired, but in which face perception and access to semantic knowledge or autobiographical information from faces is preserved.

In addition to their impairment in famous-person naming, famous-place naming was also significantly impaired in svPPA patients in comparison to the other types of entities. These results suggest that naming deficits in svPPA are more severe and less selective, which is in line

with svPPA's characteristic progressive degradation of conceptual knowledge (Gorno-Tempini et al., 2011; Reilly et al., 2011; Rogers & Friedman, 2008). AD patients were not specifically impaired on famous-place naming in comparison to other types of items, which is not in line with findings suggesting that famous buildings/places are a similarly vulnerable category to famous persons in mild cognitive impairment individuals (Ahmed et al., 2008), and traumatic brain injury patients (Milders, 2000). However, the naming tests in these studies were not controlled for difficulty in CTRL, which makes the interpretation of their results and the comparison with our results more complex. While previous neuroimaging studies have demonstrated that processing famous persons and places activates the same brain regions related to semantics (i.e. the left anterior temporal cortex) (Gorno-Tempini & Price, 2001; Grabowski et al., 2001), it remains unclear if naming both types of items activates similar brain regions. While our study does not provide a clear explanation for this discrepancy between famous-person and famous-place naming in AD, the differences between these two types of entities might provide hypotheses to explore in future studies. While all famous persons are natural entities, famous places can be either natural (e.g. Niagara Falls) or man-made artefacts (e.g. the Eiffel Tower) (Tranel, Enekwechi, & Manzel, 2005). Also, famous persons, in comparison to famous places, might more importantly involve processes related to social and affective associations (Ross & Olson, 2012; Simmons, Reddish, Bellgowan, & Martin, 2010). These differences between famous persons and places underline the relevance of combining the use of these two types of items in clinical settings. Finally, famous logos yielded mixed results. Even though they proved to be helpful in detecting naming impairments in svPPA and AD in comparison to CTRL, they only provided limited additional information beyond commonly used naming tests such as the Boston Naming Test. These results obtained for famous-logo naming are not in line with the specific impairment for semantically-unique-item naming. Even though the naming tests used were matched for difficulty in the CTRL group, we hypothesize that famous logos might be more familiar than famous places or persons and possibly as familiar as non-unique entities. It has previously been shown that svPPA and AD patients are more impaired at naming less familiar entities (Hirsh & Funnell, 1995; Kremin et al., 2001; Taylor, 1998). Stimuli in this task represented logos that are encountered quite often in daily life (e.g. road signs, popular restaurants, etc.), which might account for the fact that neither AD nor svPPA patients were specifically impaired on this semantically unique entity type in comparison

to non-unique entities. Furthermore, tests were not specifically matched on the psycholinguistic characteristics of their stimuli. Even though they were matched for difficulty in the CTRL group, which potentially limits the influence of these variables, this remains a limitation of this study. Future studies investigating semantically-unique-item naming should use items that are specifically matched on familiarity, name agreement, word frequency, visual similarity, and semantic relatedness. These variables have been shown to be important predictors of naming accuracy and speed in individuals with neurodegenerative diseases (Astell & Harley, 1998; Hirsh & Funnell, 1995; Kremin et al., 2001; Montanes, Goldblum, & Boller, 1996; Taylor, 1998; Tippett, Meier, Blackwood, & Diaz-Asper, 2007). Future neuroimaging studies investigating famous-logo processing and naming could also help us determine if these processes require greater cognitive resources in a similar way to famous persons and places (Gorno-Tempini & Price, 2001; Ross & Olson, 2012; Semenza, 2009).

Although both clinical groups present with naming impairments, one of the remaining debates in the literature relates to the mechanisms underlying them (i.e. semantic impairment vs. impaired lexical access), especially in AD. While previous behavioral studies support both the semantic impairment hypothesis (Chertkow & Bub, 1990; Giffard et al., 2002; Laisney et al., 2011; Predovan et al., 2013) and the inefficient retrieval hypothesis (Nebes, Martin, & Horn, 1984; Ober & Shenaut, 1995; Rich, Park, Dopkins, & Brandt, 2002), some authors have actually suggested that naming impairments might reflect both mechanisms (Joubert et al., 2010; Rogers & Friedman, 2008). Unfortunately, traditional explicit naming tasks present the limitation of not providing information on the underlying nature of naming impairments. However, we conducted two additional analyses suggesting that famous-person naming impairments in AD might at least in part arise from impaired lexical access. First, at the behavioral level, we added a second part to our famous-person and famous-place naming tasks, in which both general and specific semantic knowledge were assessed. In comparison to both CTRL and AD patients, svPPA patients were affected in naming, as well as for general and specific semantic knowledge for both famous persons and famous places. Overall, these results on semantic knowledge also demonstrate that the two patient groups, in addition to performing differently on naming tasks, also perform differently on both specific and general semantic knowledge (with svPPA patients being unequivocally more impaired than AD patients). These results are in line with a semantic impairment in svPPA. On the opposite, AD patients were significantly impaired on famous-

person and famous-place naming in comparison to CTRL, while presenting preserved general semantic knowledge. Furthermore, on the famous-person test, specific semantic knowledge in AD was significantly inferior to CTRL, but still relatively preserved for the misnamed items (89.7% in comparison to 59% in naming). In contrast to what is observed on the famous-person test, in which naming is more impaired than general semantic knowledge for both svPPA and AD patients, this effect is only observed in svPPA patients for the famous-place test. Second, neuroimaging analyses showed that famous-person naming impairments in AD correlated with atrophy in the temporo-parietal junction, a region functionally associated with lexical access, and not with the ATL. Interestingly, there is a perfect overlap with the coordinates found in our study and a previous neuroimaging study investigating famous-person processing (Gorno-Tempini and Price 2001). Thus, our results suggest that in AD patients, impaired lexical access significantly contributes to the naming impairments observed for famous persons and that their profile is similar to that of prosopanomia.

In conclusion, the results presented here have significant clinical implications in the assessment of language and semantic memory in neurodegenerative diseases. First, we characterized for the first time the naming abilities in two neurodegenerative populations across many types of semantically unique and non-unique entities. The pattern of naming performance in each group might be very helpful for differential diagnosis purposes. Our results also provide insight into the nature of the naming impairments observed (i.e. impaired lexical access vs. semantic impairment), with the help of additional questions assessing general and specific semantic knowledge as well as neuroimaging. These results suggest that naming difficulties for famous persons in AD might be related at least in part to impaired lexical access, while svPPA patients' naming impairments are associated with a semantic impairment. Finally, our results highlight the critical importance of adding a variety of semantically-unique-entity naming tests in neuropsychological assessments of patients with neurodegenerative diseases, since these tests can inform clinicians on the nature of the naming impairments observed which differ depending on the type of neurodegenerative disease.

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Tables

Table 1. Demographic and neuropsychological characteristics

	CTRL (*n* = 12)	AD (*n* = 13)	svPPA (*n* = 9)	*p* value	Intergroup differences
Demographics					
Gender (F/M)	4/8	5/8	2/7	NA	NA
Age (in years)	66.8 (8.7)	70.6 (8.0)	65.2 (11.2)	= .36	CTRL = AD = svPPA
Education (in years)	16.9 (3.4)	15.5 (4.1)	16.1 (4.1)	= .65	CTRL = AD = svPPA
Neuropsychological assessment					
Global cognitive status					
MMSE	29.0 (0.7)	25.0 (2.7)	25.2 (2.1)	< .001	CTRL > AD = svPPA
Episodic memory					
RCFT (Immediate recall)	19.5 (4.1)	6.0 (3.7)	9.6 (5.7)	< .001	CTRL > AD = svPPA
RCFT (Delayed recall)	20.5 (4.5)	5.5 (4.7)	8.4 (5.2)	< .001	CTRL > AD = svPPA
RAVLT (Trials 1-5)	52.9 (7.1)	27.8 (5.9)	29.5 (7.8)	< .001	CTRL > AD = svPPA
RAVLT (Immediate recall)	10.9 (2.6)	3.2 (2.6)	4.8 (2.3)	< .001	CTRL > AD = svPPA
RAVLT (Delayed recall)	10.8 (2.6)	1.9 (2.8)	4.7 (2.7)	< .001	CTRL > AD = svPPA
RAVLT (Recognition)	46.8 (2.1)	32.3 (7.8)	41.0 (5.7)	< .001	CTRL = svPPA > AD
Language and semantic memory					
Pyramids and Palm Trees Test	50.3 (1.4)	48.1 (2.4)	31.7 (12.5)	< .001	CTRL = AD > svPPA
Free Fluency	66.5 (17.0)	39.0 (14.8)	30.7 (12.0)	< .001	CTRL > AD = svPPA

Letter Fluency - P	27.3 (8.4)	19.7 (8.1)	13.2 (5.7)	< .001	CTRL = AD CTRL > svPPA; AD = svPPA
Semantic Fluency - Clothing	25.7 (4.7)	14.2 (6.8)	9.1 (7.8)	< .001	CTRL > AD = svPPA
Similarities subtest - WAIS-III	18.9 (4.3)	15.3 (4.9)	6.1 (2.9)	< .001	CTRL = AD > svPPA
Visual perception					
Benton Line Orientation test	27.7 (2.2)	24.5 (6.6)	26.6 (2.4)	= .23	CTRL = AD = svPPA
Benton facial recognition test	47.8 (2.9)	45.3 (3.1)	44.4 (3.4)	< .05	CTRL = AD = svPPA
Visuoconstruction					
RCFT (copy)	32.4 (2.6)	27.5 (7.7)	29.7 (4.5)	= .10	CTRL = AD = svPPA
Clock-drawing test	9.3 (1.0)	7.5 (2.3)	7.8 (1.9)	< .05	CTRL = svPPA > AD
Clock-copy test	9.7 (0.5)	9.3 (0.8)	9.7 (0.4)	= .20	CTRL = AD = svPPA
Executive functions / working memory					
Trail making test A (s)	30.0 (5.7)	76.3 (88.1)	47.9 (13.0)	= .12	CTRL = AD = svPPA
Trail making test B (s)	61.5 (20.0)	238.8 (141.8)	113.4 (66.8)	< .001	CTRL = svPPA > AD
SVT Word-color interference task	127.2 (31.1)	221.0 (108.7)	135.1 (35.8)	< .01	CTRL = svPPA > AD
Digit span	18.7 (4.4)	15.8 (2.5)	14.6 (3.7)	< .05	CTRL = AD CTRL > svPPA; AD = svPPA

(Abbreviations: MMSE = Mini-Mental State Examination; RCFT: Rey Complex Figure Test; RAVLT: Rey Auditory Verbal Learning Test; SVT = Stroop-Victoria Test)

Table 2. Summary of intergroup and intragroup differences for all naming tests

	CTRL (*n* = 12)	**AD (*n* = 13)**	**svPPA (*n* = 9)**	***p* value**	**Intergroup differences**
Naming non-unique entities vs semantically unique entities					
Non-unique entities	93.0 (6.4)	79.3 (16.4)	25.3 (17.6)	< .001	CTRL > AD > svPPA
Unique entities	93.3 (5.4)	69.9 (19.5)	14.7 (10.7)	< .001	CTRL > AD > svPPA
***p* value**	≥ .05	< .01	< .05		
Intragroup differences	Non-unique = Unique	Non-unique > Unique	Non-unique > Unique		
Naming non-unique entities vs. famous persons vs. famous places vs. famous logos					
Non-unique entities	93.0 (6.4)	79.3 (16.4)	25.3 (17.6)	< .001	CTRL > AD > svPPA
Famous persons	93.3 (7.0)	59.0 (25.1)	10.0 (8.8)	< .001	CTRL > AD > svPPA
Famous places	93.3 (10.3)	74.9 (23.4)	8.9 (12.9)	< .001	CTRL > AD > svPPA
Famous logos	93.3 (5.7)	75.9 (18.0)	25.2 (19.7)	< .001	CTRL > AD > svPPA
***p* value**	≥ .05	< .001	< .01		
Intragroup differences	Non-unique = Persons = Places = Logos	Persons < Non-unique = Places = Logos	Places < Non-unique = Logos; Persons < Non-unique		
Naming vs. general vs. specific semantic knowledge (Famous persons)					
Naming	93.3 (7.0)	59.0 (25.1)	10.0 (8.8)	< .001	CTRL > AD > svPPA
General SK	100.0 (0.0)	98.5 (4.0)	77.5 (15.3)	< .001	CTRL = AD > svPPA
Specific SK	97.3 (5.3)	89.7 (8.9)	28.3 (19.1)	< .001	CTRL > AD > svPPA
***p* value**	< .01	< .001	< .001		
Intragroup differences	Naming < Specific SK = General SK	Naming < Specific SK < General SK	Naming < Specific SK < General SK		
Naming vs. general vs. specific semantic knowledge (Famous places)					
Naming	93.3 (10.3)	74.9 (23.4)	8.9 (12.9)	< .001	CTRL > AD > svPPA
General SK	95.0 (8.1)	83.6 (24.0)	39.3 (25.5)	< .001	CTRL = AD > svPPA
Specific SK	80.0 (11.4)	59.0 (24.3)	16.3 (16.3)	< .001	CTRL > AD > svPPA

***p* value**	< .001	< .001	< .001
Intragroup differences	Naming = General SK > Specific SK	Naming = General SK > Specific SK	Naming < Specific SK < General SK

(Abbreviations: SK = Semantic Knowledge)

Figures

Figure 1. Performance of CTRL, AD and svPPA groups at naming non-unique entities, famous persons, famous places and famous logos.

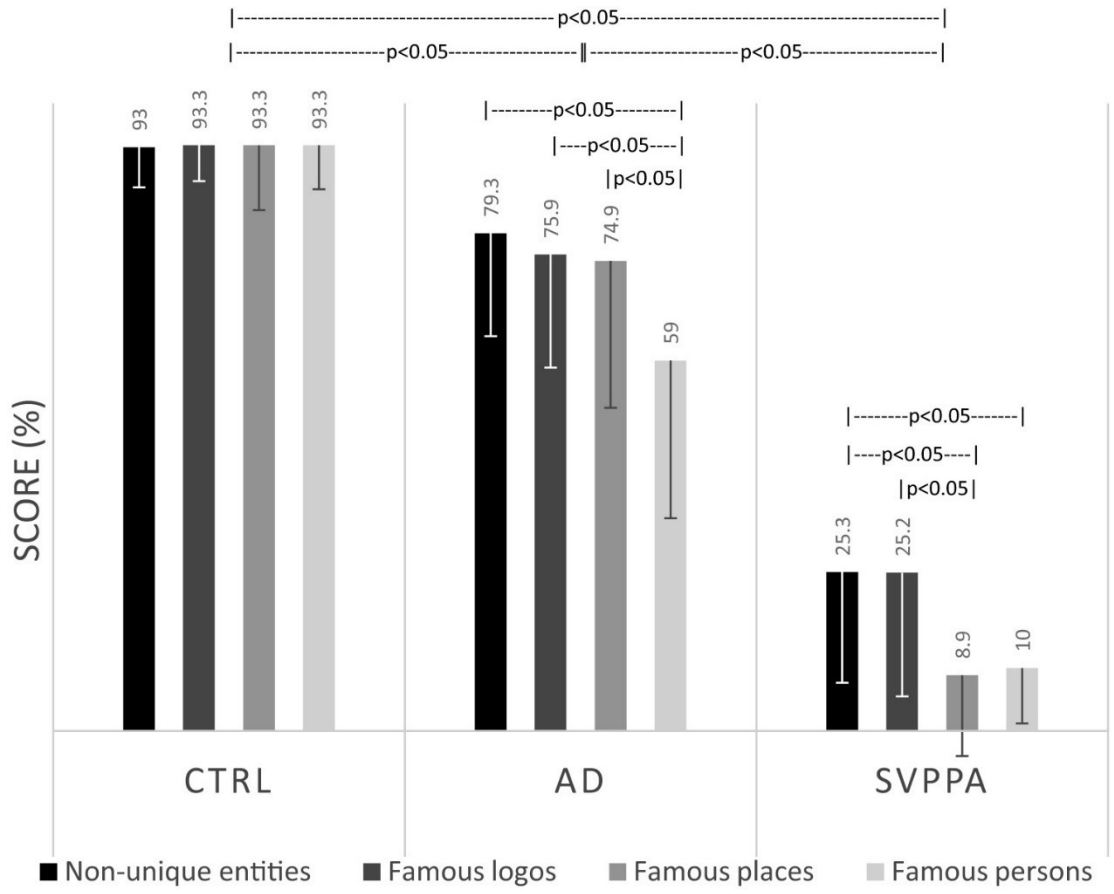


Figure 2. Performance of CTRL, AD and svPPA groups at naming vs. general semantic knowledge vs. specific semantic knowledge for A) famous persons B) famous places.

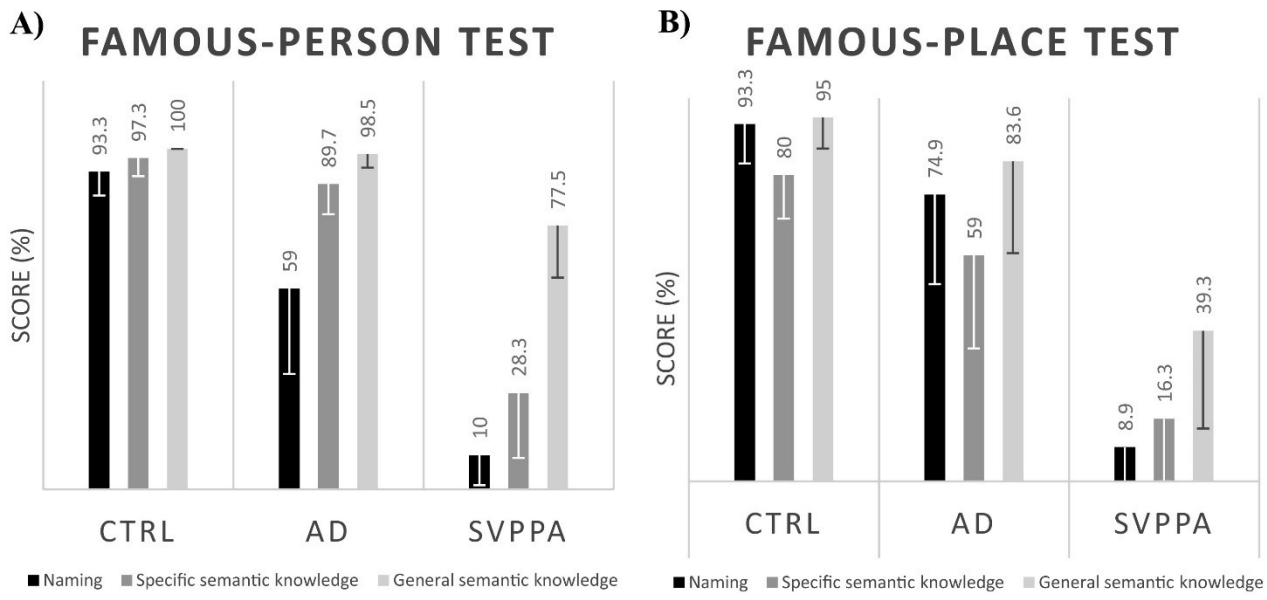
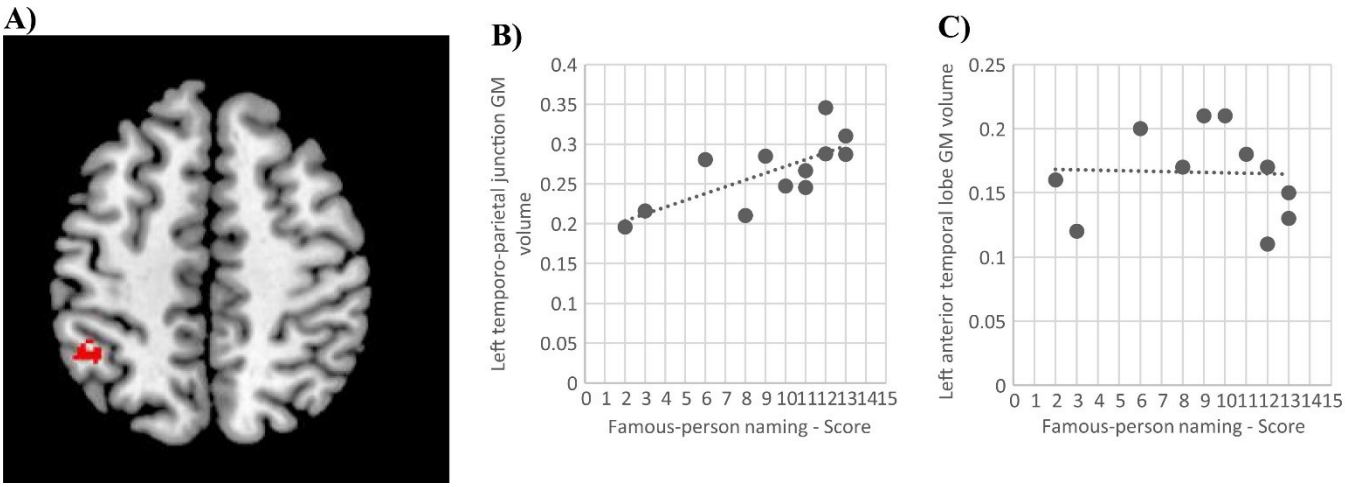


Figure 3. A) Voxels in which the gray matter (GM) volume positively correlate with the performance on the famous-person naming task in AD patients; B) Significant relationship between GM volume in the left temporo-parietal junction significant cluster and famous-person naming scores in AD patients; C) Absence of relationship between GM volumes of the left anterior temporal lobe ROI and famous-person naming scores in AD patients.



A) for display $p < 0.01$ uncorrected; the results is significant at $p < 0.05$ corrected within our ROI

Article 2 : Altered Gray Matter Structural Covariance Networks in Early Stages of Alzheimer's Disease

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Abstract

Clinical symptoms observed in Alzheimer's disease (AD) patients may reflect variations within specific large-scale brain networks, modeling AD as a disconnection syndrome. The present magnetic resonance imaging study aims to compare the organization of gray matter structural covariance networks between 109 cognitively unimpaired controls (CTRL) and 109 AD patients positive to Beta-amyloid at the early stages of the disease, using voxel-based morphometry. The default-mode network (medial temporal lobe subsystem) was less extended in AD patients in comparison to CTRL, with a significant decrease in the structural association between the entorhinal cortex and the medial prefrontal cortex and the dorsolateral prefrontal cortex. The default-mode network (midline core subsystem) was also less extended in AD patients. Trends toward increased structural association were observed in the salience and executive control networks. The observed changes suggest that early disruptions in structural association between heteromodal association cortices and the entorhinal cortex could contribute to an isolation of the hippocampal formation, potentially giving rise to the clinical hallmark of AD, progressive memory impairment. It also provides critical support to the hypothesis that the reduced connectivity within the default-mode network in early AD is accompanied by an enhancement of connectivity in the salience and executive control networks.

Key words: Anatomical Structural Covariance; Dementia; Default-mode network; Magnetic Resonance Imaging; Salience network

1. Introduction

Alzheimer's disease is the most common form of dementia, characterized by a cognitive decline beginning with memory impairments and resulting with general debilitating dementia. Alzheimer's disease is characterized by intracellular tau-associated neurofibrillary tangles and extracellular amyloid-β (Aβ) associated plaques in the brain. Over the time course of the disease, pathology propagates stepwise following a specific topological pattern targeting specific large-scale distributed brain networks (Braak & Braak, 1991; Corder et al., 2000). The mechanisms determining this defined anatomical propagation of the disease are still poorly understood. Although the precise timing and mechanism of synaptic degeneration is not known, a growing body of evidence suggests that the presence of Aß exerts its toxic effect by disrupting synaptic signaling (reviewed in (Knobloch & Mansuy, 2008), whether it is its sole cause or not. More specifically, the presence of soluble, oligomeric form of Aß, rather than Aß plaques themselves, would have a key role in dendritic spine loss and synaptic alterations, ultimately resulting in cognitive dysfunctions. In this framework, some clinical symptoms observed in Alzheimer's disease patients may reflect variations or dysfunctions within specific large-scale brain networks, rather than neural loss in a focal brain region, modeling Alzheimer disease as a disconnection syndrome (Delbeuck et al., 2003; Palop, Chin, & Mucke, 2006; Reid & Evans, 2013).

The relatively recent development of resting state or intrinsic connectivity network functional magnetic resonance imaging has become a valuable tool for mapping large-scale network connectivity alterations in Alzheimer's disease. The resting state fMRI (rsfMRI) technique allows us to detect brain regions in which the blood oxygen level-dependent (BOLD) signal fluctuations correlate across time when an individual is left in wakeful rest (Buckner, Andrews-Hanna, & Schacter, 2008). This technique, when applied to healthy subjects, has revealed the existence of a functional network associated with task-free states, and is referred to as the default mode network (DMN) (Buckner et al., 2008; Raichle et al., 2001). It consists of an anatomically defined set of regions including the posterior cingulate cortex, the anterior medial prefrontal cortex, the medial temporal lobe, the lateral temporal cortex, and the inferior parietal lobule. Converging pieces of evidence indicate that connectivity reduction in the DMN occurs in Alzheimer's disease (Gili et al., 2011; M. D. Greicius et al., 2004; Seeley et al., 2009; Zhou et al., 2010). One possible explanation is that DMN's continuous activity would determine

an activity-dependent or metabolism-dependent cascade of events, contributing to the formation and diffusion of the pathology of Alzheimer's disease (Buckner et al., 2005). Consistent with this hypothesis, maps of Aß plaques taken in Alzheimer's disease living patients (Klunk et al., 2004) show a brain distribution remarkably overlapping the anatomy of the DMN. It should be noted that the great majority of these studies have mainly focused on either one single DMN (using an independent component analysis approach) or on connectivity from a seed region in the posterior cingulate cortex (in a cross-correlation approach). However, the DMN is not as homogeneous as previously described. It rather appears to be organized in multiple interacting subsystems, providing differential contribution to specialized brain functions (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Uddin, Kelly, Biswal, Castellanos, & Milham, 2009). Recent evidence (Andrews-Hanna et al., 2010) indicates that the DMN includes at least two components that would be worth investigating separately, so as to better understand the pattern of reduced DMN connectivity in Alzheimer's disease: 1) the midline core, which includes the posterior cingulate and anterior medial prefrontal cortex, reflects the core set of "hubs" within the DMN and sustains the flexible use of information for self-relevant, affective decision making; 2) the medial temporal lobe subsystem, which is anchored by the hippocampus and the entorhinal cortex and includes the ventral medio-prefrontal cortex, posterior inferior parietal lobule and retrosplenial cortex, participates in episodic memory and visuo-spatial imagery, i.e., functions that are usually impaired in Alzheimer's disease.

Although the majority of these studies report decreased connectivity, some evidence of enhanced resting state functional connectivity has been reported in Alzheimer's disease patients compared to controls. Firstly, increased connectivity has been observed in the anterior portion of the salience network (Supekar, Menon, Rubin, Musen, & Greicius, 2008; Zhou et al., 2010), a network that presents anti-correlated intrinsic connectivity with the DMN (Seeley, Allman, et al., 2007). This network is anchored by dorsal anterior cingulate cortex and orbital frontoinsular cortices, with robust connectivity to subcortical and limbic structures (Seeley, Menon, et al., 2007). This network is thought to support the processing of diverse homeostatically relevant internal and external stimuli. According to some authors, the increased connectivity observed in Alzheimer's disease could suggest that these patients rely on the anterior prefrontal networks as a way to compensate the weakened connectivity in the posterior DMN (Zhou et al., 2010). Secondly, increased connectivity has also been observed in the executive control network

(Agosta et al., 2012; Filippi et al., 2013; Weiler et al., 2014), a compensatory network associated with better performance in many cognitive tasks when recruited in AD patients (Grady et al., 2003). This network is anchored by the dorsolateral prefrontal cortex and parietal neocortices (Menon & Uddin, 2010; Seeley, Menon, et al., 2007; Sridharan et al., 2008) and plays a critical role in executive functions such as sustained attention, working memory, response selection, and response suppression (Seeley, Menon, et al., 2007).

Recent research and neuroimaging methodological developments seem to suggest that the study of anatomical structural covariance could represent a valuable tool to investigate the topological organization of the brain (for a review see (Alexander-Bloch et al., 2013), providing complementary information to other functional and structural connectivity approaches. This approach is based on the observation that related regions co-vary in morphometry characteristics. The first evidence comes from a post-mortem study showing that anatomically-related components of the visual system (i.e., the optic nerve, the lateral geniculate nucleus and the primary visual cortex) co-vary in volume across individuals (Andrews et al., 1997). Further evidence demonstrates that individuals with greater cortical thickness of Broca's area of the inferior frontal cortex also generally present greater cortical thickness of Wernicke's area of the superior temporal cortex (Lerch et al., 2006). It has been hypothesized that the pattern of structural covariance would be associated with the pattern of functional and/or structural connectivity, as revealed by previous rsfMRI (Seeley et al., 2009) and diffusion imaging (He et al., 2007) studies. According to recent evidence, the pattern of structural covariance should be better explained by the pattern of functional connectivity rather than the architecture of white matter fiber bundles (Gong et al., 2012), suggesting that areas that co-vary in morphological characteristics could belong to the same functional networks. However, it must be noted that there is neither a direct correspondence nor a complete overlap between functional connectivity and structural covariance networks. The mechanisms underlying structural covariance and its relationship with functional connectivity are very complex and are not yet completely understood. Some factors modulating the development of anatomical structures and the inter-regional covariance such as developmental, genetic and environmental factors could partly explain this inconsistency (Alexander-Bloch et al., 2013). In addition, some methodological limitations related to each technique (such as noise processing in resting state data, misregistration in brain-damaged or atrophic patient populations in anatomical imaging) could

also contribute to this result. With these limitations in mind, many authors agree that the study of structural correlative networks (SCN) represents an informative tool to investigate the topological organization of the brain (Alexander-Bloch et al., 2013; Reid & Evans, 2013) and could provide complementary information with respect to other connectivity approaches, such as resting state fMRI and/or diffusion brain imaging.

In the present study, we compared the pattern of structural covariance of gray matter (GM) volume in 109 Alzheimer's disease patients at early stages of the disease and 109 cognitively unimpaired controls (CTRL) subjects. Based on previous reported literature (Montembeault et al., 2012; Zielinski et al., 2012; Zielinski, Gennatas, Zhou, & Seeley, 2010), the SCNs with seed regions anchoring the DMN (medial temporal lobe subsystem), the DMN (midline core subsystem), the salience network and the executive control network were selected for between-group analysis. The study was conducted using voxel-based morphometry (VBM) (Ashburner & Friston, 2000), a neuroimaging technique that allows us to map the pattern of covariance between the GM volume of an a priori selected "seed" brain region (i.e. a critical region of the network itself) and the GM volume throughout the entire brain (Mechelli et al., 2005). This technique has already been successfully used in healthy aging, neurodegenerative disease and psychiatric disorders (Montembeault et al., 2012; Seeley et al., 2009; Spreng & Turner, 2013; Zielinski et al., 2012). All structural MRI images were obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI), an open access database of serial MRI, biological markers, clinical, and neuropsychological assessments of Alzheimer's disease patients and CTRL. Since it has been hypothesized that connectivity changes in Alzheimer's disease are associated with the presence of Aβ (Knobloch & Mansuy, 2008), only Alzheimer's disease patients with high Aβ1-42 concentration in the CSF and CTRL with low Aβ1-42 concentration according to current accepted cut-off (Shaw et al., 2009) were included in the study.

2. Materials and methods

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu) (see supplementary material for more information). For up-to-date information, see www.adni-info.org.

2.1 Subjects

T1 MRI brain scans were obtained from the ADNI database from the screening visit. One hundred and nine Alzheimer's disease patients in the early stages of the disease (age range 56-88 years, mean age=74.3±7.8 years, females/males=50/59) and 109 CTRL subjects (age range 56-90 years, mean age=74.2±6.3 years, females/males=50/59) were included in the study. These two groups of participants were matched by age, years of education, total number of subjects, gender and magnetic field strength of the scanner used for their scans (1.5T / 3T = 62/47 in both groups). Also, only participants who were right-handed, who had English as their first language and who had available CSF biomarkers were considered for this study. All participants had no additional diseases expected to interfere with the study and showed a negative history of neurological disease and/or psychiatric disorder.

The criteria for classification of the subjects were as follows. To be included in the CTRL group, participants had to: 1) present no memory complaints; 2) show normal memory function documented by scoring at specific cutoffs on the Logical Memory II subscale (delayed Paragraph Recall) from the Weschler Memory Scale – Revised (≥9 for 16 years and more of education; ≥5 for 8-15 years of education; ≥3 for 0-7 years of education); 3) present a Mini-Mental State Exam (MMSE) score between 24 and 30 (inclusive); 4) present a CDR (Clinical Dementia Rating) score of 0; 5) be cognitively normal, based on an absence of significant impairment in cognitive functions or activities of daily living.

To be included in the Alzheimer's disease group, participants had to: 1) present memory complaints verified by study partner; 2) show abnormal memory function documented by scoring at specific cutoffs on the Logical Memory II subscale (delayed Paragraph Recall) from the Weschler Memory Scaled – Revised (≤8 for 16 years and more of education; ≤4 for 8-15 years of education; ≤2 for 0-7 years of education); 3) present an MMSE score between 20 and 26 (inclusive); 4) present a CDR score of 0.5 or 1.0; 5) present National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable Alzheimer's disease.

At the screening visit, all subjects were required to provide informed consent as compatible with the local sites (Institutional Review Board regulations).

2.2 Biomarkers collection

In order to take into consideration NINCDS/ADRDA criteria for probable Alzheimer's disease dementia with intermediate evidence of the Alzheimer's disease pathophysiological

process, we added an exclusion criterion related to CSF Aβ in our study (McKhann et al., 2011). Therefore, only Alzheimer's disease with high Aβ1-42 concentration in the CSF and CTRL with low Aβ1-42 concentration according to current accepted cut-off (Shaw et al., 2009) were included in the study.

CSF was collected in the morning after an overnight fast using a 20- or 24-gauge spinal needle, frozen within one hour of collection, and transported on dry ice to the ADNI Biomarker Core laboratory at the University of Pennsylvania Medical Center. The complete descriptions of the collection and transportation protocols are provided in the ADNI procedural manual at www.adni-info.org.

2.3 Clinical assessment

In addition, all subjects provided demographics, family history, and medical history. All subjects were given physical and neurological examinations, and vital signs were recorded. As mentioned, all subjects had been administered the MMSE (Folstein et al., 1975), CDR (Berg, 1988), Geriatric Depression Scale (GDS) (Yesavage & Sheikh, 1986) and the ADNI administration of Logical Memory II (Weschler, 1987). At baseline, standard neuropsychological tests were administered to all subjects, assessing classical cognitive domains: (a) Long-term memory: Rey Auditory Verbal Learning Test (Rey, 1964), (b) Attention: Trail making test A (Reitan, 1958), (c) Executive functions: Trail Making Test B (Reitan, 1958), (d) Language: Category Fluency Test (Butters, Granholm, Salmon, Grant, & Wolfe, 1987); (e) Boston Naming Test (30 items version) (Kaplan et al., 1983), and (f) Praxia/Spatio-temporal orientation: Clock Drawing Test (Goodglass & Kaplan, 1983).

All of the participants' scores are summarized by diagnostic group (mean and standard deviation for quantitative measures, proportion or percent for categorical variables) in Table 1. Group characteristics at screening and baseline were analyzed using a series of two-independent-samples T-tests for comparing means.

The mean scores for the screening measures (MMSE, CDR, GDS, and Logical Memory II) revealed better performance in the CTRL compared to the Alzheimer's disease group, at a threshold of $p<0.001$. The neuropsychological battery indicated that, generally, subjects with Alzheimer's disease were impaired in all of the cognitive areas tested, compared to CTRL.

2.4 Image acquisition

Images were acquired during the screening visit. In both group, 62 subjects were from ADNI1 (1.5T scanners) and 47 subjects were from ADNI2 (3T scanners). At each site, the subjects underwent the standardized MRI protocol of ADNI as described at http://www.loni.ucla.edu/ADNI/Research/Cores/index.shtml. Briefly, the ADNI protocol includes T1-weighted acquisition based on a sagittal volumetric magnetization prepared rapid gradient echo (MP-RAGE) sequence collected from a variety of MR-systems with protocols optimized for each type of scanner. Representative imaging parameters were as follows: repetition time = 2,300 milliseconds; inversion time = 1,000 milliseconds; echo time = 3.5 milliseconds; flip angle = 8°; field of view = 240x240 mm; and 160 sagittal 1.2-mm-thick slices and a 192x192 matrix yielding a voxel resolution of 1.25x1.25x1.2 mm, or 180 sagittal 1.2-mm-thick slices with a 256x256 matrix yielding a voxel resolution of 0.94x0.94x1.2 mm. The full details of the ADNI MRI protocol have been previously described (Jack, Bernstein, et al., 2008).

2.5 Data analysis

Both image preprocessing and statistical analysis were performed using SMP8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) running on MATLAB 7.14.0.739 (Mathworks, Natick, MA).

2.5.1 Image preprocessing.

The structural images were preprocessed using the VBM8 (http://dbm.neuro.uni-jena.de/vbm/) toolbox. First, the T1-weighted volumetric images were manually re-oriented to be approximately aligned with the ICBM152-space (i.e., MNI-space) average template distributed with SPM8. This was performed to ensure reasonable starting estimates for the segmentation routine. The re-oriented T1 scans were then segmented into gray and white matter. Affine registered tissue segments were used to create a custom template using the diffeomorphic anatomical registration using exponentiated lie algebra (DARTEL) approach (Ashburner, 2007). For each participant, the flow fields were calculated during a template creation, which described the transformation from each native GM image to the template. These were then applied to each participant's GM image. DARTEL toolbox represents one of the highest-ranking registration methods and provides higher sensitivity for voxel-based morphometry (Bergouignan et al., 2009; Klein et al., 2009), as it has been proven in both healthy subjects and Alzheimer's disease patients (Cuingnet et al., 2011).

The VBM analysis was based on the modulation of the GM segments by the nonlinear normalization parameters to account for brain size differences. Image process quality was verified by visual inspection of pre-processed images and sample homogeneity check using covariance (VBM8 toolbox). The modulated and warped images were then smoothed with a Gaussian kernel of 8 mm FWHM.

2.5.2 Statistical analysis.

A statistical analysis was performed on modulated GM images using the (general linear model (GLM) as implemented in SPM8 (Friston et al., 1994). To investigate the network structural covariance, regional GM volumes of four ROIs were extracted from the 218 preprocessed images. The ROIs were selected within the right entorhinal cortex (MNI coordinates: 25, -9, -28), left posterior cingulate cortex (MNI coordinates: -2, -36, 35), right frontoinsular cortex (MNI coordinates: 38, 26,−10), and right dorsolateral prefrontal cortex (MNI coordinates: 44, 36, 20). These regions anchor the DMN (medial temporal lobe subsystem), DMN (midline core subsystem), salience and executive control networks, respectively. The right entorhinal cortex coordinates were retrieved from the Anatomy toolbox (Eickhoff et al., 2005) and the entorhinal cortex was chosen as the seed region, as it is the link between the neocortex and the hippocampal formation (Bernhardt et al., 2008). Left posterior cingulate cortex (Spreng & Turner, 2013; Zielinski et al., 2012), right frontoinsular cortex, and right dorsolateral prefrontal cortex (Montembeault et al., 2012; Zielinski et al., 2010) coordinates were included in previous studies investigating GM structural covariance. Analyses using contralateral ROIs (obtained by changing the sign the x-coordinate for each seed) were performed (Mechelli et al., 2005; Montembeault et al., 2012; Zielinski et al., 2010).

The GM volume was then calculated and extracted from a 4 mm radius sphere around those coordinates from the modified GM images. Four separate correlation analyses were performed by entering the extracted GM volumes from each ROI as a covariate of interest. The statistical model included binary covariates indicating each subject's magnetic strength of the scanner (1.5T or 3T) and gender, as well as covariates indicating the age and years of education of each subject. Subject groups (CTRL and Alzheimer’s disease) were modeled separately in all of the analyses.

First, specific contrasts were set in order to identify, for each ROI, voxels that expressed a positive correlation within each group (CTRL and Alzheimer’s disease). Resulting correlation

maps for each group were thresholded at $p \leq 0.05$, corrected for familywise error rate (FWE), and displayed on a standard brain template to allow qualitative comparisons between the two groups, and voxel counts for each network in each group.

Furthermore, statistical contrasts were set to identify, for each ROI, voxels that expressed differences in the regression slopes between Alzheimer's disease and CTRL. For this study, we will refer to these differences in slopes as the differences in 'structural association.' Specific T contrasts were established to map the voxels that expressed a stronger structural association in CTRL compared to Alzheimer's disease, and vice versa. The threshold for the resulting statistical parametric maps was established at a voxel-wise at $p \leq .001$ (uncorrected) and then FWE corrected for multiple comparisons at $p \leq 0.05$. A correction for non-stationary smoothness was then applied (Hayasaka, Phan, Liberzon, Worsley, & Nichols, 2004) using the implementation of this method in the VBM5 toolbox: this is necessary to avoid false positives with VBM (Ashburner & Friston, 2000).

3. Results

3.1 Patterns of structural association in CTRL and Alzheimer's disease (Figure 1, Supplementary tables 1 to 16)

In order to qualitatively compare the patterns of positive correlations in both groups, statistical brain maps are presented in Figure 1. In both DMN networks, the CTRL group presents a greater amount of voxels (medial temporal lobe subsystem: 24902 voxels; midline core subsystem: 12879 voxels) than the Alzheimer's disease group (medial temporal lobe subsystem: 10807 voxels; midline core subsystem: 9129 voxels). However, in both the salience network and the executive control network, the Alzheimer's disease group presents a greater amount of voxels (salience: 5172 voxels; executive control: 22068 voxels) than the CTRL group (salience: 2428 voxels; executive control: 12025 voxels).

Regions presenting a structural association with the seed regions of each network of CTRL and Alzheimer's disease subjects are listed in supplementary tables 1 to 16. Our results are generally consistent with network descriptions in the literature (Andrews-Hanna et al., 2010; Raichle et al., 2001; Seeley, Menon, et al., 2007).

3.2 Decreased structural association in Alzheimer's disease compared to CTRL (Tables 2 & 3, Figure 2)

Within the SCN anchored to the right enthorinal cortex, decreased structural association in Alzheimer's disease was observed between the right entorhinal cortex and left medial prefrontal cortex (x=-12, y=24, z=29, cluster p<.001) and right dorsolateral prefrontal cortex (x=27, y=55, z=11, p<.05) clusters (Table 2, Figure 3).

Within the SCN anchored to the left posterior cingulate cortex, decreased structural association in Alzheimer's disease was observed between the left posterior cingulate cortex and the left inferior orbito-frontal cortex (x=-45, y=39, z=-9, cluster p<.05) cluster (Table 2, Figure 3).

No decreased association was observed in Alzheimer's disease compared to CTRL in the SCN anchored to right frontoinsular cortex (salience), nor in the SCN anchored to right dorsolateral prefrontal cortex (executive control).

Analyses using contralateral regions of interest (ROIs) (obtained by changing the sign on the x-coordinate for each seed) showed a decreased structural association in Alzheimer's disease in the SCN anchored to the left entorhinal cortex. Decreased structural association was observed between the left entorhinal cortex and the left paracentral lobule (x=-1, y=-2, z=57, cluster p<.001) and the right superior/middle frontal gyrus (x=28, y=1, z=54, cluster p<.05; x=27, y=48, z=18, cluster p<.05) clusters. No other significant differences were observed in SCN anchoring the contralateral seeds (anchored to the right posterior cingulate cortex, the left frontoinsular cortex and the left dorsolateral prefrontal cortex) (Table 3).

3.3 Increased structural association in Alzheimer's disease compared to CTRL

Although the comparison between Alzheimer's disease and CTRL did not reach the pre-established statistical threshold, a qualitative analysis seems to indicate a more extended pattern of structural association in the salience network (Figure 1, Figure 3, Supplementary tables 3 and 11) and in the executive control network (Figure 1, Figure 4, Supplementary tables 4 and 12) in Alzheimer's disease than in CTRL.

4. Discussion

The present study aimed to characterize Alzheimer's disease-related changes in the GM of the SCNs in the early stages of the disease. The patterns of SCN observed in the CTRL group are generally consistent with the same networks derived from previous resting state and structural covariance studies (Supplementary tables 1 to 8) (Andrews-Hanna et al., 2010;

Raichle et al., 2001; Seeley, Menon, et al., 2007). Compared to CTRL, Alzheimer's disease subjects with abnormal Aβ1-42 levels showed a decreased structural association mainly in the medial temporal lobe subsystem of the DMN, and to a lesser degree, in the midline core subsystem of the DMN. Although no significant differences were observed at the pre-established threshold of significance, a qualitative comparison between the two groups revealed that the salience and the executive control SCNs were more extended in the Alzheimer's disease group than in the CTRL group. No increased structural association was observed in the Alzheimer's disease group compared to the CTRL group. Altogether, these results provide critical support to the hypothesis that Alzheimer's disease is a disconnection syndrome targeting specific large-scale brain networks, in accordance with the network degeneration hypothesis.

Alzheimer's disease is a neurodegenerative disease that progressively disrupts the patient's cognitive capacities. Usually, the first function to be affected is episodic memory (Crowell, Luis, Cox, & Mullan, 2007; Greene, Baddeley, & Hodges, 1996), followed by attentional (Perry & Hodges, 1999), semantic memory (Blackwell et al., 2004; J. R. Hodges & K. Patterson, 1995), and linguistic or visuospatial deficits (M. A. Lambon Ralph, Patterson, Graham, Dawson, & Hodges, 2003; Perry & Hodges, 2000). Modern neurosciences clearly indicate that neural networks represent the scaffolding architecture of the organization of cognitive functions within the brain (M. Mesulam, 2009). In this framework, according to the network degeneration hypothesis, Alzheimer's disease selectively targets large-scale functional networks that are formed in healthy humans during development (Seeley et al., 2009), and would in turn determine the development and deterioration of cognitive symptoms over time (Palop et al., 2006; Selkoe, 2002). The potential mechanisms of network-based disease pattern are still matter of debate. However, a recent study by Zhou and colleagues (Zhou, Gennatas, Kramer, Miller, & Seeley, 2012) strongly supports the hypothesis of the transneuronal spread, according to which some toxic agents propagate along interconnected neurons.

Many researchers speculate that Aβ accumulation may be an initiating event that leads to neuronal dysfunction, neurodegeneration, and cognitive loss (Jack, Lowe, et al., 2008; Morris et al., 2009; Walsh & Selkoe, 2007). Interestingly, Alzheimer's disease patients show a pattern of Aβ plaque deposition remarkably overlapping the set of regions implicated in the DMN (Buckner et al., 2005), which suggests a possible link between amyloid-β and the intrinsic connectivity. Indeed, findings in both healthy adults and Alzheimer's disease patients provide

critical support to this hypothesis, revealing that the DMN functional connectivity is altered by the presence of Aβ (Mormino et al., 2011; Myers et al., 2014). In this framework, our results are consistent with this hypothesis and expand these previous findings. Firstly, our results indicate that Alzheimer's disease patients with Aβ positive are characterized by a selective and reduced structural association among different regions forming the DMN. Although structural covariance data cannot be considered as a direct measure of connectivity, a convergence between intrinsic connectivity and structural covariance has been reported in healthy subjects, thus demonstrating that these two patterns mirror each other (Seeley et al., 2009). This effect can be ascribed to the fact that synchronous neuronal firing promotes network-based synaptogenesis, as demonstrated by previous physiological studies (Bi & Poo, 1999; Katz & Shatz, 1996). Consistently, the patterns of structural covariance observed in our CTRL group (Figure 1, Supplementary tables 1 to 8) was overlapping with patterns obtained using fMRI-based intrinsic connectivity (Andrews-Hanna et al., 2010; Raichle et al., 2001; Seeley, Menon, et al., 2007). However, it must be noted that there is neither a direct correspondence nor a complete overlap between functional connectivity and structural covariance networks. While initial evidence for distinct subsystems within the DMN was provided by Andrews-Hanna and colleagues, these subsystems are distinct yet interactive: during certain experimentally-directed and spontaneous acts of future-oriented thought, these dissociated components are simultaneously engaged, presumably to facilitate construction of mental models of personally significant events (Andrews-Hanna et al., 2010; Andrews-Hanna, Smallwood, & Spreng, 2014). In particular, it is reported that the midline core is highly correlated with a dorsal medial subsystem as well as with the medial temporal subsystem, which is investigated in the present study. Even though findings by Andrews-Hanna and colleagues have been replicated (Choi, Yeo, & Buckner, 2012), providing strong evidence of the subdivision of the DMN in three subsystems, differences between analyses have emerged and demonstrate the heterogeneity within the DMN. Nonetheless, our results seem to suggest that, through the use of a different methodological approach, our results provide critical support to the hypothesis that Alzheimer's disease patients with a proven presence of Aβ manifest selective altered connectivity within the DMN network at early stages of the disease.

Secondly, these results show that, at early stages of the disease, decreased structural association in the medial temporal lobe subsystem of the DMN would present the most

prominent impact of the disease. In fact, major differences between Alzheimer's disease and CTRL subjects were observed when we explored the SCN anchored to the entorhinal cortex. Reduced structural association between the entorhinal cortex and the medial prefrontal cortex was observed. A functional disconnection between the prefrontal cortex and the hippocampus in Alzheimer's disease has previously been observed (L. Wang et al., 2006). The medial prefrontal cortex is thought to play a critical role in learning associations between context, events, locations, and corresponding adaptive responses (Euston, Gruber, & McNaughton, 2012). Furthermore, the medial prefrontal cortex likely relies on its strong connections to the hippocampus to support rapid learning and memory consolidation (Euston et al., 2012). It was also suggested that the memory breakdown in early Alzheimer's disease is related to a reduction in the integrated activity between these two areas (Grady et al., 2001). A decrease in the structural association between the entorhinal cortex and the precuneus was also observed. A previous rsfMRI study showed a clear disconnection between the hippocampus and precuneus and suggested that the hippocampus-precuneus functional connectivity should be considered as an early sign of Alzheimer's disease (Kim et al., 2013), which is consistent with our results. The precuneus is thought to play a critical role in visuo-spatial imagery (Cavanna & Trimble, 2006). Overall, our results are generally concordant with studies showing compromised white matter projections to the hippocampus - particularly in the perforant path - in the early stages of Alzheimer's disease and also in patients with mild cognitive impairment (Stoub et al., 2006; C. Wang et al., 2012). Early disruptions in structural association between the heteromodal association cortices and the entorhinal cortex could contribute to an isolation of the hippocampal formation, giving rise to the clinical hallmark of Alzheimer's disease, i.e. progressive memory impairment, as well as visuospatial deficits.

Decreased structural association was also observed in the midline core subsystem of the DMN, which is anchored in the left posterior cingulate cortex. More specifically, decreased structural association was detected between the seed region and the inferior orbitofrontal gyrus. It has been recently proposed that the DMN often extends to the lateral frontal cortex, despite the fact that this region is not reported as part of the network (Spreng, Mar, & Kim, 2009). Nonetheless, it has been recently demonstrated that the combined activity of these two regions underlies the cognitive function of long-term memory, which is usually impaired in Alzheimer's disease patients (Liu, Dong, Chen, & Xue, 2013).

Although disconnection seems to be the signature of Alzheimer's disease pathology, it has been recently proposed that the reduced connectivity within the DMN is accompanied by a robust enhancement of connectivity in the salience network (Hu et al., 2010; Zhou et al., 2010). Even though we did not observe any significant increase in structural association in the salience network anchored to the frontoinsular cortex, which is a key region of the salience network in the early stages of Alzheimer's disease, our results presented a trend towards a more extended SCN in Alzheimer's disease compared to CTRL. In fact, the qualitative analysis of voxel counts in the salience SCN presented a more extended salience network in Alzheimer's disease patients than in CTRL. The neurobiology underlying the salience network/DMN relationship is unclear, but past studies suggest that this increase in resting state connectivity of the salience network occurs in the context of decreased DMN connectivity, and may thus represent a compensatory mechanism (Machulda et al., 2011). Therefore, we hypothesize that significant increases in structural association between regions of the salience network (as observed with our technique) might occur in later stages of Alzheimer's disease as a result of a stronger DMN disconnection. Furthermore, our results also presented a trend towards a more extended executive control SCN (anchored in the dorsolateral prefrontal cortex) in Alzheimer's disease compared to CTRL. Interestingly, our data suggest that in patients with Alzheimer's disease, the dorsolateral prefrontal cortex presents a trend towards an increased structural association with posterior regions (such as the posterior cingulate cortex and the precuneus). These regions present a significant decreased structural association with the entorhinal cortex. Consistent with previous reports (Agosta et al., 2012; Filippi et al., 2013; Weiler et al., 2014; Zhou et al., 2010), our findings support the fact that Alzheimer's disease is associated with opposing connectivity effects in the DMN and frontal networks, such as the salience and executive control networks.

In summary, this work demonstrates that the study of SCNs using VBM is an effective method to comprehensively investigate different networks that are of interest in Alzheimer's disease. We suggest that the study of structural covariance represents a valuable complementary tool to better characterize the network-level anatomical changes that come with Alzheimer's disease. As the first study to simultaneously investigate four key networks on a large sample of Alzheimer's disease patients, our results provide support for the hypothesis that Alzheimer's disease is a disconnection syndrome that targets specific brain networks, beginning with a disconnection of the medial temporal lobe from associative and visual areas. Future studies

investigating the progression of SCNs in Alzheimer's disease may help clarify the mirror role of the DMN and the salience network as well as the potentially compensatory role of the executive control network in Alzheimer's disease patients. Furthermore, the study of gray matter structural covariance in AD should extend to other brain networks of interest.

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Tables

Table 1. Demographic and neuropsychological characteristics of Alzheimer's disease and CTRL

	Alzheimer's disease	CTRL	$T_{(216)}$
Number of participants	109	109	
Age, years	74.3 (±7.8)	74.1 (±6.0)	-0.27
Age (range)	56-88	56-90	
Gender			
Male (%)	59 (54.1)	59 (54.1)	
Female (%)	50 (45.9)	50 (45.9)	
Education, years	15.7 (±2.8)	16.1 (±2.8)	1.08
Education (range)	6-20	8-20	
Scanner strength			
1.5T (%)	62 (56.9)	62 (56.9)	
3T (%)	47 (43.1)	47 (43.1)	
Aβ level	132.8 (±23.2)	242.54 (±27.4)	24.97*
Aβ level (range)	81.8-187.2	192.5-394.1	
Clinical Dementia Rating	0.8 (±0.3)	0.0 (±0.0)	-28.49*
Geriatric Depression Scale	1.5 (±1.3)	0.8 (±1.2)	-4.44*
Global cognition			
MMSE	23.2 (±1.9)	29.2 (±1.2)	26.72*
Memory			
Logical memory, immediate recall	4.1 (±2.8)	13.8 (±3.1)	24.43*
Logical memory, delayed recall	1.3 (±1.7)	12.9 (±3.3)	32.43*
AVLT, immediate recall	24.8 (±8.4)	52.52 (±11.9)	19.80*
AVLT, delayed recall	0.9 (±1.8)	7.5 (±3.9)	14.21*
Attention			
TMT A (sec.)	66.4 (±37.1)	34.0 (±10.2)	-8.77*
Executive functions			

TMT B (sec.)	188.8 (±83.2)	79.3 (±30.5)	-12.79*
Language			
Category fluency	12.3 (±4.8)	19.9 (±5.9)	10.51*
Boston naming test	22.6 (±6.4)	27.8 (±2.3)	8.05*
Praxia/Spatio-temporal orientation			
Clock drawing – score	3.2 (±1.4)	4.7 (±0.7)	9.85*
Clock copy – score	4.3 (±0.97)	4.8 (±0.7)	5.57*

T = independent-samples T-test values; * $p<0.001$. Values are presented a mean ± SD, number (%), or median (range). (Abbreviations: AVLT = Auditory verbal learning test; TMT = Trail making test)

Table 2. The group differences in the SCN topology based on the comparison CTRL>Alzheimer's disease for the main seed regions.

Network	**Cluster** / peak regions		MNI coordinates			Extent	Max T	P (corr.) - cluster
		Side	x	y	z			
Default-Mode (medial temporal lobe subsystem) (R EC)	**Medial prefrontal cortex (32)**	**L**	**-12**	**24**	**29**	**3275**	**4.66**	**.000**
	Paracentral lobule	R	6	6	54	s.c.	4.38	
	Middle cingulate cortex	R	8	-8	51	s.c.	4.29	
		L	-8	9	41	s.c.	3.94	
		L	-3	-5	48	s.c.	3.69	
	Precuneus	R	5	-36	53	s.c.	3.81	
	Posterior / middle cingulate cortex	R	11	-20	51	s.c.	3.49	
	Anterior cingulate cortex	L	-2	36	14	s.c.	3.35	
	Dorsolateral prefrontal cortex (46)	**R**	**27**	**55**	**11**	**681**	**4.11**	**.032**
	Middle prefrontal cortex	R	26	42	24	s.c.	3.85	
Default-Mode (midline core subsystem) (L PCC)	**Inferior orbito-frontal cortex (12)**	**L**	**-45**	**39**	**-9**	**560**	**4.10**	**.048**
	Pars orbitalis	L	-48	28	-15	s.c.	3.38	

Max T is the maximum T statistic of each local maximum. P≤0.05 based on non-stationary cluster-extent correction. (Abbreviations: R = Right; L = Left; EC = Entorhinal cortex; PCC = Posterior cingulate cortex)

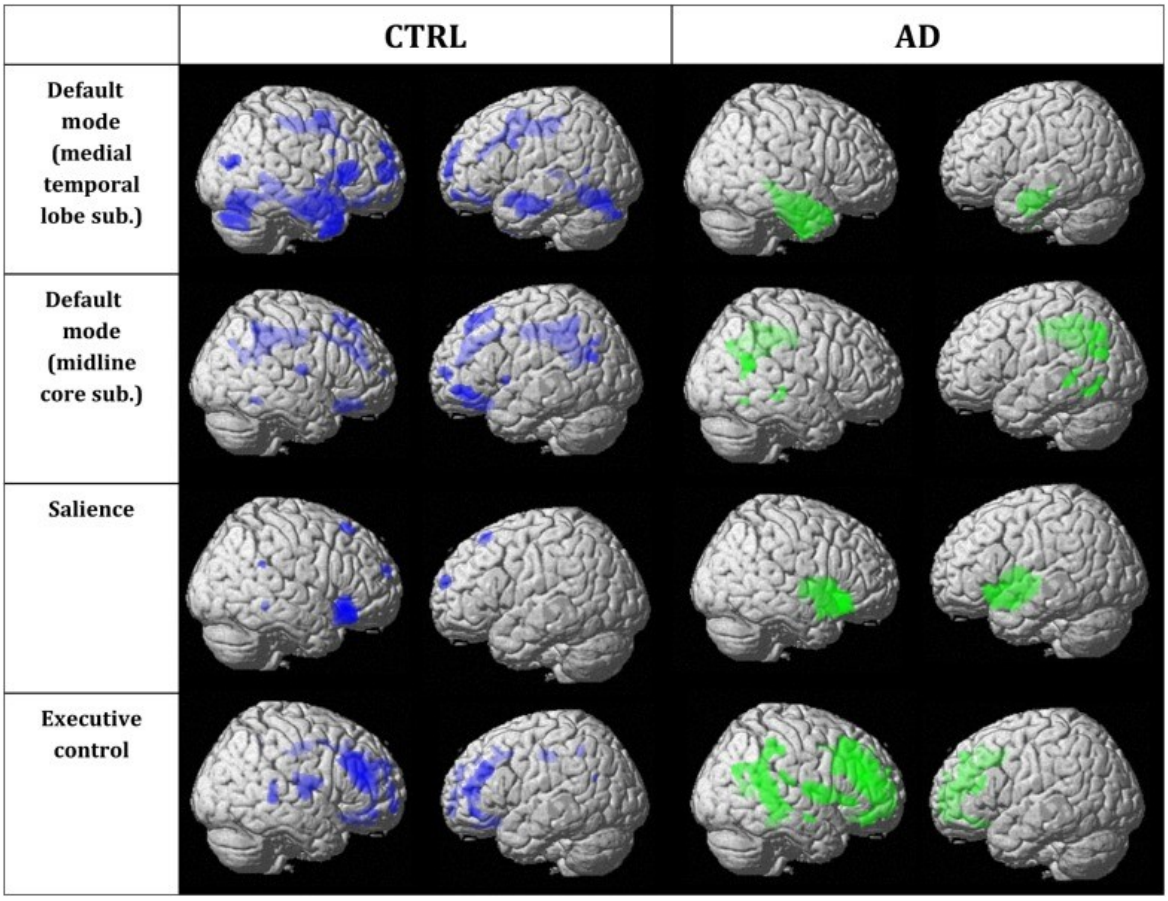
Table 3. The group differences in the SCN topology based on the comparison CTRL>Alzheimer's disease for contralateral seeds.

Network	**Cluster** / peak regions	MNI coordinates				Extent	Max T	P (corr.) - cluster
		Side	X	y	Z			
Default-Mode (medial temporal lobe subsystem) (L EC)	**Paracentral Lobule (6)**	**L**	**-1**	**-2**	**57**	**7174**	**4.89**	**.000**
	Posterior cingulate cortex	R	2	-33	51	s.c.	4.74	
	Paracingulate cortex	R	3	-8	68	s.c.	4.46	
	Precuneus	L	-8	-57	59	s.c.	4.41	
		L	-2	-71	35	s.c.	4.39	
		L	-6	-45	65	s.c.	4.35	
		R	9	-50	56	s.c.	3.82	
		R	9	-45	69	s.c.	3.51	
		R	12	-71	51	s.c.	3.36	
	Posterior/middle cingulate cortex	R	9	-21	54	s.c.	4.14	
	Middle cingulate cortex	R	1	16	41	s.c.	3.83	
	Calcarine fissure	R	3	-80	15	s.c.	3.81	
		R	1	-66	15	s.c.	3.80	
	Medial prefrontal cortex	R	6	25	60	s.c.	3.62	
	Superior/middle frontal gyrus (6/8)	**R**	**28**	**1**	**54**	**999**	**4.69**	**.012**
	Superior/middle frontal gyrus (6/8)	**R**	**27**	**48**	**18**	**583**	**4.01**	**.045**

Max T is the maximum T statistic of each local maximum. $p \leq 0.05$ based on non-stationary cluster-extent correction. (Abbreviations: R = Right; L = Left; EC = Entorhinal cortex)

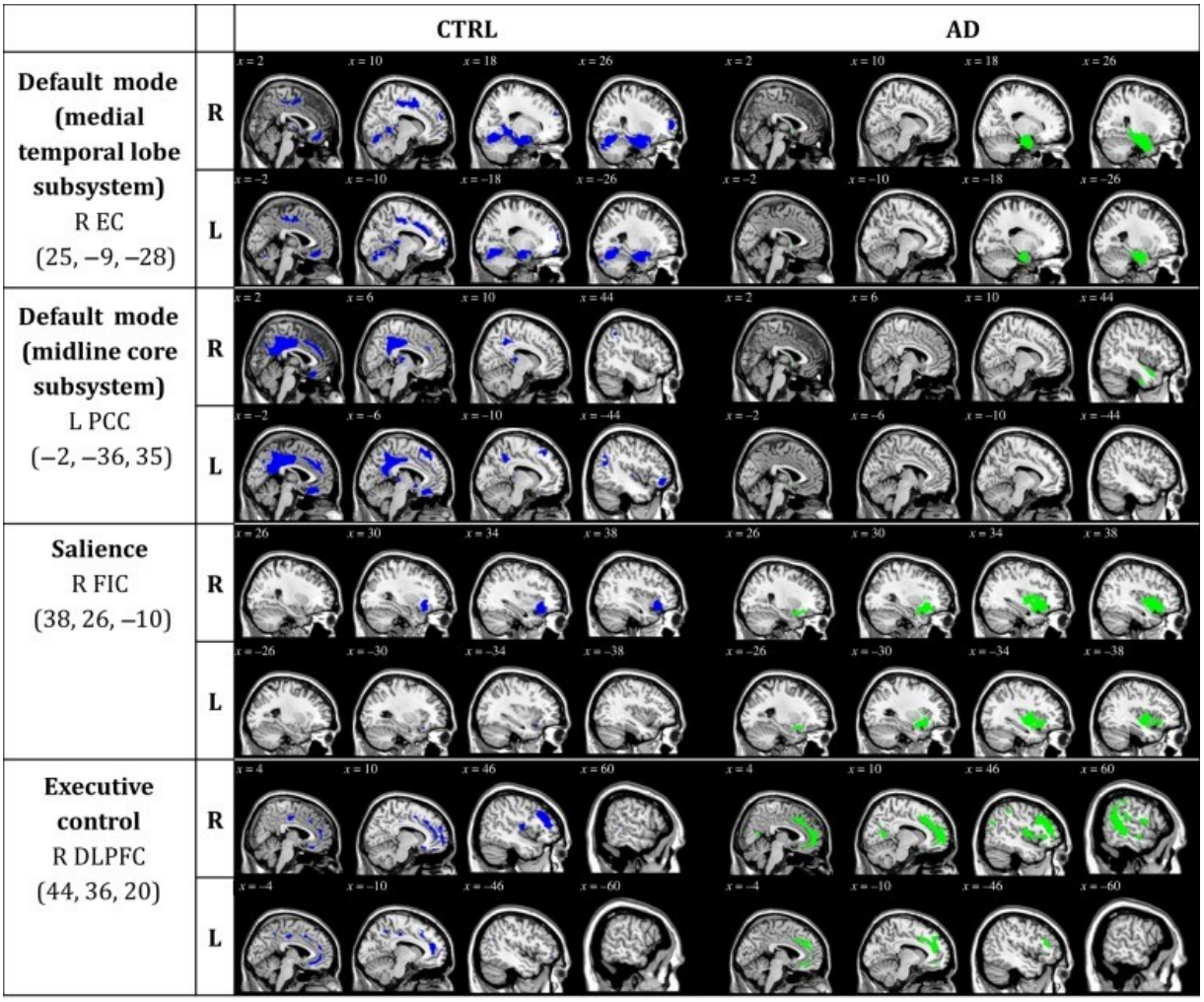
Figures

Figure 1. Statistical maps depict brain regions in which gray matter intensity covaried with that of the seed region of interest for each network in each group. z-statistic maps (P ≤.05, FWE-corrected) displayed on a standard brain render.



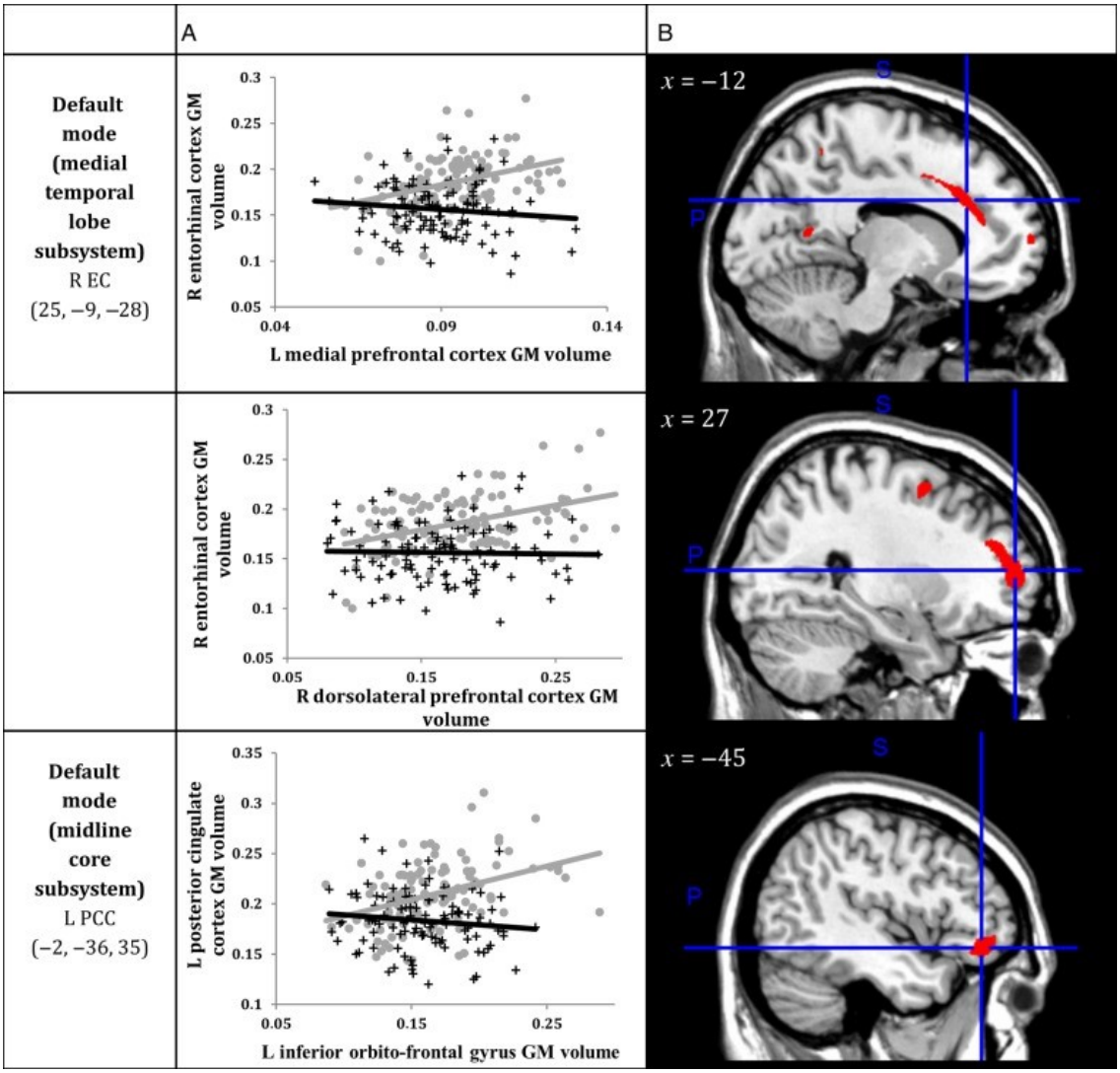
(Abbreviations: sub. = subsystem; CTRL = cognitively unimpaired controls; AD = Alzheimer's disease patients)

Figure 2. Statistical maps depict brain regions in which gray matter intensity covaried with that of the seed region of interest (ROI; listed at left) in each group. z-statistic maps (P ≤.05, FWE-corrected) displayed on different slices of a standard brain template.



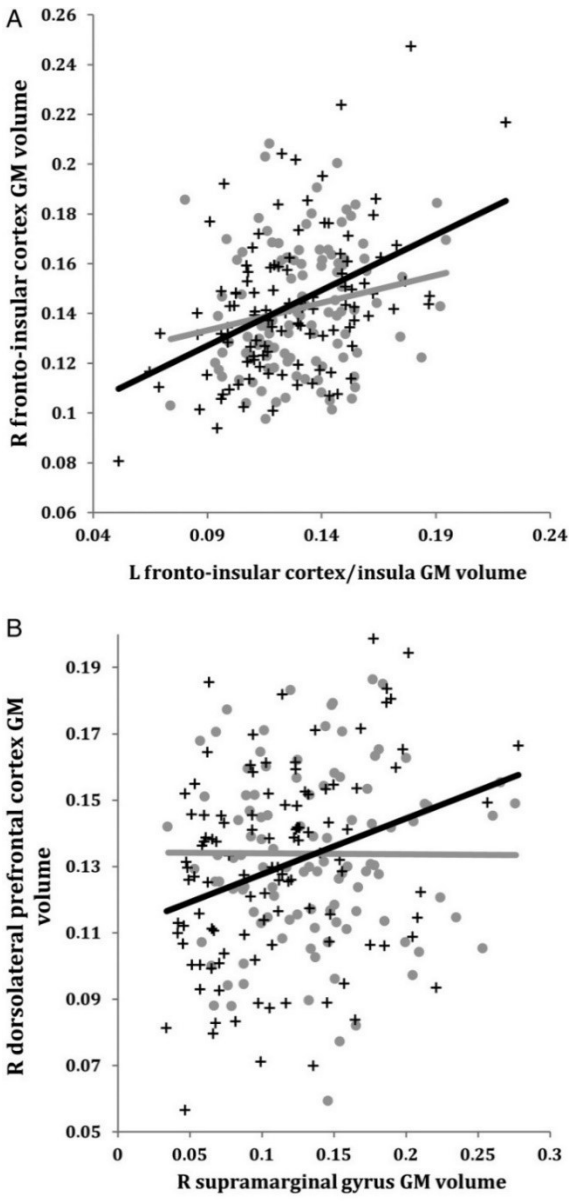
(Abbreviations: R = right; L = left; CTRL = cognitively unimpaired controls; AD = Alzheimer's disease patients; EC = entorhinal cortex; PCC = posterior cingulate cortex; FIC = frontoinsular cortex; DLPFC = dorsolateral prefrontal cortex)

Figure 3. A) Correlations between GM volumes extracted from a 4-mm radius sphere centered on the ROI and a 4-mm radius sphere centered on the peak voxel expressing decreased structural association in AD compared to CTRL. B) The voxels that expressed decreased structural association in AD compared to CTRL.



Gray dots represent CTRL and black crosses represent AD. The crosshairs are centered on the global peak. (Abbreviations: R = right; L = left; GM = gray matter; EC = entorhinal cortex; PCC = posterior cingulate cortex)

Figure 4. Correlations between GM volumes extracted from a 4-mm radius sphere centered on the ROI and a 4-mm radius sphere centered on the peak voxel showing a trend towards an increased structural association in AD compared to CTRL in the salience network (A) and the executive control network (B).



Gray dots represent CTRL and black crosses represent AD. (Abbreviations: R = right; L = left; GM = gray matter)

Supplementary material

Appendix 1:

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early Alzheimer's disease. Determination of sensitive and specific markers of very early Alzheimer's disease progression is intended to help researchers and clinicians develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date, these three protocols have recruited over 1500 adults, ages 55 to 90, consisting of cognitively normal older individuals, people with early or late mild cognitive impairment, and people with early Alzheimer's disease. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see www.adni-info.org.

Supplementary table 1. Structural covariance network for CTRL with right entorhinal cortex as seed. Max T is the maximum T statistic for each local maximum. P<0.05 based on non-stationary cluster-extent correction.

Cluster / peak regions		Stereotaxic coordinates			Extent	Max T	P-value (corr).
	Side	x	y	z			
Entorhinal cortex / Hippocampus	**R**	**27**	**-9**	**-27**	**12493**	**30.48**	**.000**
	R	21	5	-22	s.c.	8.29	
Temporal pole	R	37	11	-37	s.c.	7.31	
Fusiform cortex	R	20	-71	-13	s.c.	6.77	
Cerebellum	R	35	-81	-34	s.c.	6.31	
Pars opercularis/triangularis	R	49	21	5	s.c.	6.28	
Insula	R	36	-8	13	s.c.	5.72	
	R	43	9	-15	s.c.	5.62	
	R	46	2	-1	s.c.	5.51	
Parahippocampal gyrus	R	23	-30	-13	s.c.	5.59	
Cuneus	R	12	-47	0	s.c.	5.44	
Entorhinal cortex / Hippocampus	**L**	**-26**	**-9**	**-25**	**2301**	**9.88**	**.000**
Supplementary motor area	**R**	**6**	**6**	**54**	**4677**	**6.05**	**.000**
Cingulate cortex	L	-5	-6	48	s.c.	5.68	
	R	9	-11	50	s.c.	5.64	
Middle cingulate cortex	L	-5	-24	50	s.c.	5.47	
	R	12	0	44	s.c.	5.46	
	L	-12	24	33	s.c.	5.34	
	L	-8	9	42	s.c.	5.20	
	R	3	22	38	s.c.	4.47	
Anterior cingulate cortex	L	-12	33	21	s.c.	5.26	
Middle / posterior cingulate cortex	R	6	-30	50	s.c.	5.13	
Precuneus	L	-8	-36	56	s.c.	5.10	
Orbitofrontal cortex	**R**	**24**	**54**	**3**	**538**	**5.99**	**.000**
Cerebellum	**L**	**-21**	**-60**	**-15**	**2102**	**5.84**	**.000**
	L	-26	-74	-19	s.c.	5.61	
	L	-11	-78	-22	s.c.	5.31	

	L	-29	-87	-31	s.c.	4.99	
	L	-32	-75	-36	s.c.	4.54	
Fusiform cortex	L	-27	-56	-6	s.c.	4.99	
	L	-14	-77	-10	s.c.	4.92	
Frontal pole	**L**	**-15**	**66**	**9**	**578**	**5.64**	**.000**
Superior frontal gyrus	L	-17	57	27	s.c.	4.74	
Thalamus	**L**	**-8**	**-32**	**6**	**69**	**5.52**	**.005**
Orbitofrontal cortex	**R**	**0**	**37**	**-15**	**328**	**5.47**	**.000**
Orbitofrontal cortex	**L**	**-17**	**54**	**-16**	**115**	**5.36**	**.002**
Superior prefrontal cortex	**R**	**15**	**55**	**27**	**352**	**5.33**	**.000**
Middle occipital cortex	**R**	**45**	**-78**	**15**	**295**	**5.29**	**.000**
Occipital lobe	R	33	-84	17	s.c.	4.85	
Lateral prefrontal cortex	**R**	**31**	**1**	**53**	**342**	**5.16**	**.000**
Inferior frontal junction	**L**	**-44**	**6**	**33**	**167**	**5.04**	**.001**
Middle temporal cortex	**L**	**-57**	**-3**	**-19**	**82**	**4.87**	**.004**
Inferior frontal junction	**R**	**49**	**10**	**26**	**60**	**4.87**	**.005**
Inferior temporal cortex	**L**	**-39**	**-26**	**-19**	**108**	**4.85**	**.003**
Cuneus	**L**	**-12**	**-44**	**-6**	**128**	**4.85**	**.002**
Posterior cingulate cortex	**L**	**-8**	**-59**	**9**	**104**	**4.78**	**.003**

(Abbreviation: s.c: same cluster)

Supplementary table 2. Structural covariance network for CTRL with left posterior cingulate cortex as seed. Max T is the maximum T statistic for each local maximum. P<0.05 based on non-stationary cluster-extent correction.

Cluster / peak regions		Stereotaxic coordinates			Extent	Max T	P-value (corr).
	Side	x	y	z			
Posterior cingulate cortex	**L**	**-3**	**-35**	**36**	**7588**	**46.21**	**.000**
Precuneus	R	2	-71	36	s.c.	4.73	
Middle cingulate cortex	R	0	-2	47	s.c.	4.52	
Anterior cingulate cortex	**R**	**0**	**30**	**32**	**2314**	**6.27**	**.000**
	L	-2	42	26	s.c.	5.40	
Inferior prefrontal cortex (p. orbitalis)	**L**	**-42**	**43**	**-9**	**647**	**5.80**	**.000**
Medial orbitofrontal cortex	**L**	**-6**	**34**	**-16**	**519**	**5.51**	**.000**
Rostral orbitofrontal cortex	L	-3	22	-21	s.c.	5.58	
Angular gyrus	**L**	**-47**	**-65**	**21**	**593**	**5.39**	**.000**
	L	-45	-65	32	s.c.	4.92	
Orbitofrontal cortex	**L**	**-21**	**55**	**6**	**234**	**5.17**	**.001**
Insula	**R**	**37**	**-9**	**12**	**173**	**5.00**	**.001**
Medial prefrontal cortex	**L**	**-8**	**31**	**51**	**662**	**5.57**	**.000**
Insula	**L**	**-38**	**7**	**2**	**53**	**4.88**	**.006**
Supramarginal gyrus	**R**	**44**	**-50**	**47**	**96**	**4.83**	**.003**

(Abbreviation: s.c: same cluster)

Supplementary table 3. Structural covariance network for CTRL with right fronto-insular cortex as seed. Max T is the maximum T statistic for each local maximum. P<0.05 based on non-stationary cluster-extent correction.

Cluster / peak regions		Stereotaxic coordinates			Extent	Max T	P-value (corr).
	Side	x	y	z			
Fronto-insular / Inferior prefrontal cortex (p. orbitalis)	**R**	**36**	**27**	**-9**	**1852**	**19.64**	**.000**
	R	46	38	-10	s.c.	4.47	
Supplementary motor area	**R**	**8**	**27**	**57**	**199**	**5.60**	**.001**
Medial prefrontal cortex	**L**	**-5**	**60**	**20**	**199**	**5.30**	**.001**
Supplementary motor area	**L**	**-12**	**25**	**60**	**52**	**4.84**	**.006**
Parahippocampal cortex	**R**	**20**	**-41**	**-7**	**70**	**4.79**	**.005**
Supramarginal gyrus	**R**	**51**	**-44**	**26**	**56**	**4.75**	**.006**

(Abbreviation: s.c: same cluster)

Supplementary table 4. Structural covariance network for CTRL with right dorsolateral prefrontal cortex as seed. Max T is the maximum T statistic for each local maximum. P<0.05 based on non-stationary cluster-extent correction.

Cluster / peak regions		Stereotaxic coordinates			Extent	Max T	P-value (corr).
	Side	x	y	z			
Dorsolateral prefrontal cortex	**R**	**43**	**37**	**20**	**3848**	**26.16**	**.000**
Anterior cingulate cortex	**R**	**12**	**27**	**38**	**2517**	**6.02**	**.000**
	L	-9	46	18	s.c.	5.72	
	R	8	46	14	s.c.	5.61	
	L	-6	15	42	s.c.	5.10	
	L	-9	45	5	s.c.	5.08	
	R	2	46	0	s.c.	4.63	
Orbitofrontal cortex	L	-8	27	-12	s.c.	4.98	
Insula	**R**	**43**	**-11**	**9**	**1008**	**5.76**	**.000**
	R	38	-20	23	s.c.	4.55	
Middle / posterior cingulate cortex	**L**	**-8**	**-21**	**39**	**767**	**5.74**	**.000**
	R	6	-18	44	s.c.	5.19	
Middle cingulate cortex	R	12	4	48	s.c.	4.85	
Medial prefrontal cortex	**R**	**12**	**61**	**-6**	**625**	**5.71**	**.000**
	R	9	60	6	s.c.	5.45	
	R	11	55	26	s.c.	4.84	
Middle prefrontal cortex	**L**	**-33**	**48**	**12**	**1805**	**5.69**	**.000**
Dorsolateral prefrontal cortex	L	-39	31	30	s.c.	5.34	
Orbitofrontal cortex	**L**	**-41**	**42**	**-7**	**228**	**5.52**	**.001**
Dorsolateral prefrontal cortex	**R**	**30**	**30**	**36**	**187**	**5.35**	**.001**
Posterior cingulate cortex / precuneus	**L**	**-9**	**-48**	**48**	**163**	**5.34**	**.001**
Dorsolateral prefrontal cortex	**R**	**30**	**46**	**27**	**250**	**5.31**	**.001**
Orbitofrontal cortex	**R**	**8**	**30**	**-18**	**229**	**5.06**	**.001**
	R	11	19	-13	s.c.	4.70	
	R	11	42	-18	s.c.	4.70	
Orbitofrontal cortex	**R**	**39**	**42**	**-10**	**140**	**4.93**	**.002**
Middle temporal gyrus	**R**	**53**	**-38**	**0**	**132**	**4.78**	**.002**
Superior temporal gyrus	R	50	-36	12	s.c.	4.74	
Angular gyrus	**L**	**-45**	**-62**	**24**	**69**	**4.69**	**.005**

Medial prefrontal cortex	**L**	**-9**	**42**	**36**	**57**	**4.66**	**.006**

(Abbreviation: s.c: same cluster)

Supplementary table 5. Structural covariance network for CTRL with left entorhinal cortex as seed. Max T is the maximum T statistic for each local maximum. P<0.05 based on non-stationary cluster-extent correction.

Cluster / peak regions		Stereotaxic coordinates			Extent	Max T	P-value (corr).
	Side	x	y	z			
Entorhinal cortex / Hippocampus	**L**	**-26**	**-9**	**-27**	**4700**	**29.89**	**.000**
Medial temporal pole	L	-27	4	-40	s.c.	5.02	
Entorhinal cortex / Hippocampus	**R**	**27**	**-8**	**-27**	**5714**	**11.42**	**.000**
	R	38	-24	-12	s.c.	5.15	
Medial temporal pole	R	39	12	-40	s.c.	7.07	
Parahippocampal cortex	R	21	5	-22	s.c.	6.81	
Insular cortex	R	40	9	-16	s.c.	5.42	
Postcentral gyrus	R	58	-11	33	s.c.	5.12	
Middle temporal gyrus	R	66	-17	-10	s.c.	5.02	
	R	51	-2	-30	s.c.	4.88	
Superior temporal sulcus	R	62	-6	-13	s.c.	4.95	
Temporal pole	R	45	11	-27	s.c.	4.83	
Frontal pole	**L**	**-17**	**64**	**11**	**359**	**5.97**	**.000**
	L	-17	60	24	s.c.	4.59	
Anterior cingulate cortex	**R**	**2**	**45**	**6**	**2443**	**5.77**	**.000**
	R	3	40	20	s.c.	5.38	
	L	-12	34	20	s.c.	5.29	
	L	-11	24	35	s.c.	5.11	
	R	3	42	-7	s.c.	5.10	
Middle temporal gyrus	L	-6	10	42	s.c.	4.97	
Insula	**R**	**45**	**3**	**0**	**144**	**5.43**	**.002**
Inferior temporal cortex	**L**	**-47**	**0**	**-42**	**61**	**5.37**	**.005**
Premotor cortex	**R**	**34**	**0**	**57**	**391**	**5.22**	**.000**
Thalamus	**L**	**-6**	**-29**	**6**	**55**	**5.15**	**.006**
Frontal pole	**R**	**26**	**56**	**0**	**194**	**5.09**	**.001**
Orbitofrontal cortex	**L**	**-21**	**57**	**-12**	**168**	**5.07**	**.001**
Middle cingulate cortex	**L**	**-3**	**-3**	**48**	**188**	**5.03**	**.001**
Lateral occipital lobe	**R**	**38**	**-81**	**12**	**87**	**5.00**	**.004**

Lateral occipital lobe	**L**	**-39**	**6**	**38**	**95**	**4.97**	**.003**
Middle/posterior cingulate cortex	**R**	**0**	**-24**	**48**	**196**	**4.93**	**.001**
Pars triangularis	**R**	**55**	**21**	**6**	**75**	**4.92**	**.004**
Fusiform cortex	**R**	**18**	**-71**	**-12**	**179**	**4.88**	**.001**
	R	20	-57	-12	s.c.	4.86	
Posterior parahippocampal gyrus	**R**	**12**	**-35**	**6**	**133**	**4.73**	**.003**
Fusiform cortex	**L**	**-17**	**-44**	**2**	**50**	**4.66**	**.007**

(Abbreviation: s.c: same cluster)

Supplementary table 6. Structural covariance network for CTRL with right posterior cingulate cortex as seed. Max T is the maximum T statistic for each local maximum. P<0.05 based on non-stationary cluster-extent correction.

Cluster / peak regions		Stereotaxic coordinates			Extent	Max T	P-value (corr).
	Side	x	y	z			
Posterior cingulate cortex	**R**	**2**	**-36**	**36**	**17650**	**40.31**	**.000**
Medial prefrontal cortex	L	-2	43	30	s.c.	6.41	
	L	-8	33	50	s.c.	6.16	
	R	11	40	42	s.c.	5.60	
	R	17	58	27	s.c.	5.55	
	R	5	27	57	s.c.	5.43	
	L	-5	55	24	s.c.	5.22	
Middle cingulate cortex	L	-2	28	32	s.c.	6.28	
	R	2	13	42	s.c.	5.59	
Presupplementary motor area / medial prefrontal cortex	L	-6	21	59	s.c.	5.81	
Anterior cingulate cortex	L	-2	37	17	s.c.	5.27	
Precuneus	R	2	-71	38	s.c.	5.14	
	L	-5	-48	63	s.c.	4.56	
Superior prefrontal gyrus	L	-17	22	53	s.c.	4.92	
Posterior parahippocampal gyrus	**R**	**15**	**-39**	**2**	**1830**	**6.05**	**.000**
Thalamus	R	8	-27	8	s.c.	5.99	
Fusiform cortex	R	24	-48	-13	s.c.	5.86	
Parahippocampal gyrus	R	33	-35	-22	s.c.	5.62	
Inferior prefrontal cortex (p. orbitalis)	**L**	**-42**	**40**	**-10**	**1193**	**6.04**	**.000**
Middle prefrontal cortex	L	-36	52	-9	s.c.	4.91	
	L	-24	54	-10	s.c.	4.89	
Rostral medial prefrontal cortex	**L**	**-3**	**36**	**-16**	**1095**	**5.85**	**.000**
	L	-3	24	-21	s.c.	5.78	
Anterior cingulate cortex	R	2	46	0	s.c.	4.93	
Orbitofrontal cortex	**R**	**31**	**38**	**-19**	**1379**	**5.82**	**.000**
	R	31	27	-15	s.c.	5.41	

	R	36	53	-16	s.c.	5.05	
Rostral medial prefrontal cortex	R	14	45	-18	s.c.	5.59	
Angular cortex	**L**	**-48**	**-68**	**18**	**287**	**5.82**	**.000**
Thalamus	**L**	**-6**	**-29**	**6**	**79**	**5.52**	**.004**
Thalamus	L	-3	-18	8	s.c.	4.84	
Intraparietal sulcus	**R**	**32**	**-68**	**47**	**262**	**5.47**	**.000**
Middle prefrontal cortex	**L**	**-21**	**55**	**8**	**299**	**5.32**	**.000**
Ventral striatum	**R**	**21**	**9**	**-15**	**258**	**5.28**	**.000**
Ventral striatum	R	9	12	-10	s.c.	5.12	
Ventral striatum	L	-6	6	-6	s.c.	4.93	
Ventral striatum	L	-23	7	-13	s.c.	4.69	
Fusiform cortex	**L**	**-29**	**-39**	**-21**	**504**	**5.24**	**.000**
Fusiform cortex	L	-24	-56	-12	s.c.	5.18	
Middle temporal cortex	**R**	**65**	**-36**	**3**	**152**	**5.17**	**.001**
Fusiform cortex	**L**	**-17**	**-42**	**2**	**155**	**5.11**	**.001**
Lateral prefrontal cortex	**R**	**36**	**16**	**56**	**101**	**5.03**	**.003**
Inferior parietal lobule	**R**	**44**	**-47**	**48**	**151**	**5.01**	**.001**
Insula	**L**	**-38**	**9**	**3**	**104**	**4.96**	**.003**
Premotor cortex	**R**	**31**	**-3**	**59**	**102**	**4.95**	**.003**
Inferior frontal junction	**R**	**48**	**10**	**36**	**94**	**4.89**	**.003**
Motor cortex	**R**	**49**	**-15**	**41**	**70**	**4.86**	**.004**
Hippocampus	**L**	**-21**	**-9**	**-24**	**124**	**4.85**	**.002**
Amygdala	L	-23	3	-19	s.c.	4.52	
Insula	**R**	**40**	**-11**	**11**	**148**	**4.80**	**.002**

(Abbreviation: s.c: same cluster)

Supplementary table 7. Structural covariance network for CTRL with left fronto-insular cortex as seed. Max T is the maximum T statistic for each local maximum. P<0.05 based on non-stationary cluster-extent correction.

Cluster / peak regions		Stereotaxic coordinates			Extent	Max T	P-value (corr).
	Side	x	y	z			
Fronto-insular cortex / Inferior prefrontal cortex (p. orbitalis)	**L**	**-38**	**25**	**-10**	**842**	**15.27**	**.000**
Insula	**R**	**34**	**-9**	**18**	**96**	**5.32**	**.003**
Inferior prefrontal cortex (p. orbitalis)	**R**	**40**	**44**	**-9**	**180**	**5.29**	**.001**

(Abbreviation: s.c: same cluster)

Supplementary table 8. Structural covariance network for CTRL with left dorsolateral prefrontal cortex as seed. Max T is the maximum T statistic for each local maximum. P<0.05 based on non-stationary cluster-extent correction.

Cluster / peak regions		Stereotaxic coordinates			Extent	Max T	P-value (corr).
	Side	x	y	z			
Dorsolateral prefrontal cortex	**L**	**-45**	**37**	**21**	**7933**	**35.14**	**.000**
Orbitofrontal cortex	L	-30	57	-1	s.c.	5.80	
Pars opercularis	L	-54	10	23	s.c.	5.43	
Ventrolateral prefrontal cortex / pars orbitalis	L	-44	46	-3	s.c.	4.72	
Inferior frontal junction	L	-45	13	35	s.c.	4.72	
Anterior cingulate cortex	**L**	**-11**	**45**	**8**	**2134**	**6.31**	**.000**
	R	2	43	-6	s.c.	5.09	
Orbitofrontal cortex	R	3	21	-18	s.c.	5.61	
	L	-9	28	-13	s.c.	4.83	
Frontal pole	L	-9	64	-4	s.c.	5.24	
	L	-5	63	12	s.c.	5.14	
Dorsolateral prefrontal cortex	**R**	**45**	**36**	**24**	**1293**	**5.83**	**.000**
	R	46	21	39	s.c.	5.68	
	R	39	16	54	s.c.	5.32	
Insula	**R**	**33**	**-17**	**14**	**1141**	**5.71**	**.000**
	R	45	-11	6	s.c.	5.18	
Precentral gyrus	**R**	**57**	**-3**	**32**	**642**	**5.61**	**.000**
	R	60	-2	17	s.c.	5.11	
Superior temporal gyrus	R	58	-3	2	s.c.	5.50	
Pars opercularis	R	57	10	24	s.c.	4.69	
Frontal pole	**R**	**11**	**64**	**-4**	**464**	**5.42**	**.000**
	R	6	63	9	s.c.	5.09	
	R	26	57	-9	s.c.	4.98	
Inferior parietal lobule	**R**	**51**	**-68**	**27**	**86**	**5.11**	**.004**
Ventral striatum	**R**	**18**	**11**	**-15**	**69**	**5.03**	**.005**
Anterior cingulate cortex	**L**	**-9**	**27**	**33**	**114**	**4.97**	**.003**
Postcentral gyrus	**R**	**54**	**-24**	**21**	**140**	**4.94**	**.002**
Medial prefrontal cortex	**R**	**9**	**57**	**33**	**55**	**4.86**	**.006**

Postcentral gyrus	**L**	**-57**	**-36**	**32**	**73**	**4.74**	**.004**
Middle cingulate gyrus	**R**	**9**	**-15**	**48**	**59**	**4.71**	**.006**

(Abbreviation: s.c: same cluster)

Supplementary table 9. Structural covariance network for Alzheimer's disease with right entorhinal cortex as seed. Max T is the maximum T statistic for each local maximum. P<0.05 based on non-stationary cluster-extent correction.

Cluster / peak regions		Stereotaxic coordinates			Extent	Max T	P-value (corr).
	Side	x	y	z			
Entorhinal cortex / Hippocampus	**R**	**27**	**-9**	**-27**	**8990**	**27.44**	**.000**
	R	33	-2	-39	s.c.	6.33	
	R	36	11	-33	s.c.	6.03	
	R	43	-1	-19	s.c.	4.99	
Parahippocampal gyrus	R	23	-39	-3	s.c.	5.02	
Entorhinal cortex / inferior temporal gyrus	R	46	-12	-30	s.c.	4.67	
Middle temporal gyrus / temporal pole	R	52	11	-27	s.c.	4.57	
Entorhinal cortex / Hippocampus	**L**	**-26**	**-12**	**-25**	**1817**	**8.68**	**.000**
	L	-32	-26	-13	s.c.	4.96	

(Abbreviation: s.c: same cluster)

Supplementary table 10. Structural covariance network for Alzheimer's disease with left posterior cingulate cortex as seed. Max T is the maximum T statistic for each local maximum. P<0.05 based on non-stationary cluster-extent correction.

Cluster / peak regions		Stereotaxic coordinates			Extent	Max T	P-value (corr).
	Side	x	y	z			
Posterior cingulate cortex	**L**	**-3**	**-35**	**36**	**6275**	**38.74**	**.000**
Precuneus	R	3	-68	30	s.c.	4.92	
Angular cortex	**L**	**-41**	**-71**	**26**	**1721**	**6.47**	**.000**
	L	-44	-60	30	s.c.	5.80	
Inferior parietal lobule	L	-36	-71	39	s.c.	5.44	
Angular cortex	**R**	**59**	**-56**	**20**	**402**	**5.63**	**.000**
Middle temporal cortex	R	47	-53	17	s.c.	4.56	
Middle temporal cortex	**L**	**-59**	**-44**	**-3**	**151**	**5.51**	**.002**
Inferior temporal sulcus	**L**	**-50**	**-60**	**-10**	**361**	**5.32**	**.000**
Fusiform cortex	L	-39	-56	-12	s.c.	4.67	
Angular cortex	**R**	**38**	**-69**	**35**	**62**	**4.92**	**.005**
Fusiform cortex	**R**	**50**	**-57**	**-10**	**95**	**4.87**	**.003**
Middle temporal cortex	**R**	**56**	**-35**	**-7**	**62**	**4.83**	**.005**

(Abbreviation: s.c: same cluster)

Supplementary table 11. Structural covariance network for Alzheimer's disease with right fronto-insular cortex as seed. Max T is the maximum T statistic for each local maximum. P<0.05 based on non-stationary cluster-extent correction.

Cluster / peak regions		Stereotaxic coordinates			Extent	Max T	P-value (corr).
	Side	x	y	z			
Fronto-insular cortex / Inferior prefrontal cortex (p. orbitalis)	**R**	**36**	**27**	**-9**	**3473**	**19.44**	**.000**
Insula	R	39	12	0	s.c.	6.03	
	R	34	-2	6	s.c.	5.43	
Orbitofrontal cortex	R	20	20	-15	s.c.	4.64	
Fronto-insular cortex / Insula	**L**	**-38**	**21**	**-7**	**1699**	**5.80**	**.000**
Insula	L	-33	-2	9	s.c.	5.69	
	L	-33	3	-16	s.c.	5.54	
	L	-35	-11	-7	s.c.	5.43	
	L	-33	9	-1	s.c.	4.96	

(Abbreviation: s.c: same cluster)

Supplementary table 12. Structural covariance network for AD with right dorsolateral prefrontal cortex as seed. Max T is the maximum T statistic for each local maximum. P<0.05 based on non-stationary cluster-extent correction.

Cluster / peak regions		Stereotaxic coordinates			Extent	Max T	P-value (corr).
	Side	x	y	z			
Dorsolateral prefrontal cortex	**R**	**43**	**37**	**20**	**9764**	**27.35**	**.000**
	R	43	34	36	s.c.	7.95	
	R	49	22	29	s.c.	7.50	
	R	27	46	35	s.c.	6.63	
	R	28	24	53	s.c.	6.16	
	R	31	30	38	s.c.	5.72	
Anterior cingulate cortex	**R**	**11**	**46**	**15**	**6143**	**7.36**	**.000**
	R	11	24	38	s.c.	7.36	
	R	11	37	27	s.c.	7.27	
	L	-9	37	24	s.c.	6.40	
	L	-8	21	38	s.c.	6.30	
	L	-8	46	-7	s.c.	4.90	
	L	-8	46	6	s.c.	4.70	
Medial prefrontal cortex	R	6	60	6	s.c.	6.88	
	R	5	57	-7	s.c.	6.26	
	L	-11	40	38	s.c.	5.23	
Middle / anterior cingulate cortex	R	6	12	44	s.c.	5.76	
Orbitofrontal cortex	R	11	43	-9	s.c.	5.26	
	L	-9	31	-15	s.c.	5.25	
Superior prefrontal cortex	R	15	58	27	s.c.	4.73	
Superior temporal gyrus	**R**	**59**	**-47**	**15**	**2945**	**6.58**	**.000**
Middle temporal gyrus	R	63	-38	3	s.c.	6.22	
	R	65	-39	-13	s.c.	4.86	
Supramarginal gyrus	R	57	-44	41	s.c.	5.29	
	R	53	-33	44	s.c.	5.22	
Inferior parietal lobule	R	45	-41	51	s.c.	5.23	
Angular gyrus	R	51	-68	27	s.c.	5.10	
Insula	**R**	**49**	**-8**	**11**	**1869**	**6.58**	**.000**
Pars opercularis	R	52	19	2	s.c.	5.26	

Postcentral gyrus	**R**	**60**	**-29**	**21**	**273**	**5.48**	**.000**
Pars orbitalis	**R**	**42**	**41**	**-18**	**292**	**5.34**	**.000**
Lateral orbitofrontal cortex	R	30	44	-10	s.c.	4.87	
Lingual gyrus	**R**	**9**	**-59**	**9**	**347**	**5.31**	**.000**
Pars triangularis	**L**	**-45**	**33**	**12**	**189**	**5.16**	**.001**
Superior temporal sulcus	**R**	**60**	**-8**	**-13**	**85**	**5.04**	**.004**
Superior frontal sulcus	**L**	**-24**	**51**	**15**	**97**	**4.91**	**.003**
Fusiform cortex	**R**	**27**	**-39**	**-18**	**64**	**4.81**	**.005**

(Abbreviation: s.c: same cluster)

Supplementary table 13. Structural covariance network for Alzheimer's disease with left entorhinal cortex as seed. Max T is the maximum T statistic for each local maximum. P<0.05 based on non-stationary cluster-extent correction.

Cluster / peak regions		Stereotaxic coordinates			Extent	Max T	P-value (corr).
	Side	x	y	z			
Entorhinal cortex / Hippocampus	**L**	**-26**	**-9**	**-27**	**6804**	**28.78**	**.000**
	L	-36	6	-25	s.c.	6.57	
Insula	L	-41	-1	-12	s.c.	5.41	
	L	-39	-5	1	s.c.	5.00	
Entorhinal cortex / Hippocampus	**R**	**26**	**-8**	**-27**	**2917**	**9.12**	**.000**

(Abbreviation: s.c: same cluster)

Supplementary table 14. Structural covariance network for Alzheimer's disease with right posterior cingulate cortex as seed. Max T is the maximum T statistic for each local maximum. P<0.05 based on non-stationary cluster-extent correction.

Cluster / peak regions		Stereotaxic coordinates			Extent	Max T	P-value (corr).
	Side	x	y	z			
Posterior cingulate cortex	**R**	**2**	**-36**	**36**	**9344**	**33.71**	**.000**
	R	9	-53	24	s.c.	6.52	
	L	-9	-56	24	s.c.	5.33	
Precuneus	R	3	-69	32	s.c.	5.65	
	R	9	-68	51	s.c.	4.94	
Lingual gyrus	R	9	-56	12	s.c.	4.94	
Inferior parietal lobule	**R**	**50**	**-36**	**45**	**3067**	**6.19**	**.000**
	R	38	-71	36	s.c.	5.61	
	R	29	-60	48	s.c.	5.25	
Angular cortex	R	59	-56	21	s.c.	5.80	
	R	45	-53	18	s.c.	5.03	
	R	50	-71	27	s.c.	5.00	
Supramarginal gyrus	R	63	-45	24	s.c.	4.88	
Middle temporal gyrus	R	57	-59	9	s.c.	4.48	
Middle temporal cortex	**R**	**63**	**-17**	**-9**	**1946**	**6.04**	**.000**
	R	59	-29	-1	s.c.	5.87	
Posterior prefrontal cortex	**R**	**30**	**19**	**53**	**289**	**5.49**	**.000**
Fusiform cortex	**R**	**38**	**-47**	**-16**	**143**	**5.46**	**.002**
Angular cortex	**L**	**-47**	**-69**	**23**	**250**	**5.36**	**.001**
Inferior parietal lobule	**L**	**-39**	**-62**	**44**	**588**	**5.32**	**.000**
Angular cortex	L	-45	-71	32	s.c.	5.06	
Inferior temporal cortex	**R**	**50**	**-63**	**-9**	**542**	**5.28**	**.000**
Inferior frontal junction / pars opercularis	**R**	**51**	**12**	**29**	**140**	**5.12**	**.002**
Superior prefrontal cortex	**L**	**-17**	**25**	**51**	**120**	**4.84**	**.002**
	L	-24	12	59	s.c.	4.48	

(Abbreviation: s.c: same cluster)

Supplementary table 15. Structural covariance network for Alzheimer's disease with left fronto-insular cortex as seed. Max T is the maximum T statistic for each local maximum. P<0.05 based on non-stationary cluster-extent correction.

Cluster / peak regions		Stereotaxic coordinates			Extent	Max T	P-value (corr).
	Side	x	y	z			
Fronto-insular cortex / Inferior prefrontal cortex (p. orbitalis)	**L**	**-38**	**25**	**-10**	**894**	**15.48**	**.000**

(Abbreviation: s.c: same cluster)

Supplementary table 16. Structural covariance network for AD with left dorsolateral prefrontal cortex as seed. Max T is the maximum T statistic for each local maximum. P<0.05 based on non-stationary cluster-extent correction.

Cluster / peak regions		Stereotaxic coordinates			Extent	Max T	P-value (corr).
	Side	x	y	z			
Dorsolateral prefrontal cortex	**L**	**-45**	**37**	**21**	**7051**	**31.69**	**.000**
	L	-35	37	38	s.c.	5.72	
Frontal pole	L	-36	55	-6	s.c.	5.40	
Dorsolateral prefrontal cortex	**R**	**43**	**48**	**9**	**3116**	**6.66**	**.000**
	R	45	18	35	s.c.	6.33	
	R	46	40	23	s.c.	5.37	
Frontal pole	R	28	59	-4	s.c.	5.86	
Orbitofrontal cortex	R	39	57	-3	s.c.	5.57	
Frontal pole	**L**	**-6**	**64**	**2**	**887**	**5.36**	**.000**
	R	6	60	8	s.c.	5.24	
Anterior cingulate cortex	L	-9	49	-6	s.c.	4.88	
Ventral striatum	**R**	**8**	**12**	**-4**	**50**	**5.03**	**.006**
Pars opercularis	**R**	**52**	**16**	**2**	**71**	**4.97**	**.005**

(Abbreviation: s.c: same cluster)

Article 3: Differential language network functional connectivity alterations in Alzheimer's disease and semantic variant of primary progressive aphasia

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Soumis à *Cortex*

Abstract

Patients with Alzheimer's disease (AD) and semantic variant primary progressive aphasia (svPPA) can present with similar language impairments. It has been hypothesized that these deficits are associated with different brain mechanisms in each disease, but no previous study has used a network approach to explore this hypothesis. The aim of this study was to compare resting-state functional magnetic resonance imaging (rs-fMRI) language network in AD, svPPA patients and cognitively unimpaired elderly adults (CTRL). Therefore, 10 AD patients, 9 svPPA patients and 11 CTRL underwent rs-fMRI. Seed-based functional connectivity analyses were conducted using regions of interest in the left anterior temporal lobe (ATL), left posterior middle temporal gyrus (pMTG) and left inferior frontal gyrus (IFG). In AD patients, the left ATL presented reduced functional connectivity with the right pMTG and the right angular gyrus, in comparison to CTRL. The left pMTG also showed reduced interhemispheric functional connectivity with its homotopic counterpart. In svPPA patients, the left ATL was functionally isolated in comparison to CTRL and AD patients, while the left pMTG, the left IFG and the other language regions remained functionally interconnected. Overall, this study suggests that language impairments in AD and svPPA are sustained by distinct disconnection across the language network. In AD, the functional disconnection of the left ATL appears to be associated with the alteration of the default-mode network. Decreased functional connectivity in the left ATL and in the left pMTG, regions respectively involved in semantics and in lexico-semantic access, support a combined semantic and lexico-semantic access impairment in AD patients. In svPPA, the functional disconnection of the left ATL was more important than in AD patients, and it was observed with many regions inside and outside of the language network. The complete functional isolation of the left ATL is consistent with the core semantic breakdown observed in svPPA patients. Finally, functional connectivity in the left ATL could serve as a neuroimaging biomarker in the differential diagnosis of these two clinical populations.

Keywords: Alzheimer's disease, semantic variant primary progressive aphasia, language network, resting-state functional magnetic resonance imaging

1. Introduction

The typical presentation of Alzheimer's disease (AD) is most often characterized by an insidious and progressive decline in episodic memory. Nevertheless, language is also frequently impaired in AD patients (Verma & Howard, 2012). While word-finding difficulties are recognized as the most prominent language deficits (McKhann et al., 2011), verbal fluency (J.R. Hodges & K. Patterson, 1995; Huff et al., 1986; Verma & Howard, 2012), and semantics (Joubert et al., 2010) are frequently impaired in AD as well. These symptoms are also the clinical hallmark of the semantic variant of primary progressive aphasia (svPPA). svPPA is characterized by impaired naming, impaired word comprehension, impaired object knowledge, and surface dyslexia/dysgraphia (Gorno-Tempini et al., 2011). A partial overlap of language symptoms, especially in language production, can therefore be observed in AD and svPPA. However, these impairments are not present in all AD patients and are overall less severe in comparison to svPPA patients (Montembeault et al., 2017; Reilly et al., 2011; Rogers & Friedman, 2008; Sajjadi, Patterson, Tomek, & Nestor, 2012).

Classic neuroanatomical models of language, mainly based on post-stroke aphasic patients, postulate that language is sustained by two main language centers, namely Broca's area (left pars triangularis/pars opercularis in the inferior frontal gyrus; IFG) and Wernicke's area (left posterior middle temporal gyrus, pMTG) (Geschwind, 1970). Although the precise function and localization of these regions have been the object of a longstanding debate, their role within the language network is widely accepted (Dronkers, Ivanova, & Baldo, 2017; Tremblay & Dick, 2016). Further studies, mainly based on observations on svPPA patients, have however revealed the critical role of the left ATL within the language network, mainly in conceptual knowledge (Chedid et al., 2016; Heilman, 1972; Hodges, Patterson, Oxbury, & Funnell, 1992; Snowden, Goulding, & Neary, 1989; M. A. Wilson et al., 2012). Although it was initially omitted from the classic language model, there is now extensive support for its inclusion as a main language center in addition to the left IFG and the left pMTG (Damasio, Tranel, Grabowski, Adolphs, & Damasio, 2004; Ferstl, Neumann, Bogler, & von Cramon, 2008; Hurley, Bonakdarpour, Wang, & Mesulam, 2015; M. M. Mesulam et al., 2013; Schwartz et al., 2009; Ueno, Saito, Rogers, & Lambon Ralph).

Consistently, the development of language symptoms in AD and svPPA are associated with a dysfunction in one or more of these three key language regions. Neuroimaging studies in

AD patients have indeed shown that language impairments are associated with changes in functional activity or hypometabolism in the left IFG (Melrose et al., 2009; Teipel et al., 2006), the left pMTG (N. Nelissen et al., 2011; Natalie Nelissen et al., 2007; Vandenbulcke et al., 2007) and the left ATL (Hirono et al., 2001; Lars, Timo, Michael, & Philipp, 2016; Zahn et al., 2004). In svPPA, studies have more consistently attributed naming and semantic impairments to dysfunction of the left ATL (Acosta-Cabronero et al., 2011; Desgranges et al., 2007; Diehl et al., 2004; M. A. Wilson et al., 2012).

However, in addition to dysfunction in specific and isolated brain regions, it is now recognized that functional disconnection within brain networks can underlie the cognitive impairments observed in neurodegenerative disorders such as AD and svPPA (Guo et al., 2013; Seeley et al., 2009). Resting-state functional magnetic resonance imaging (rs-fMRI) is one of the neuroimaging techniques that allows to investigate functional brain networks. This task-free fMRI method examines the interactions between brain regions through correlated changes in blood-oxygen-level dependent (BOLD) signal. In recent years, the language network has been studied and successfully characterized in healthy controls using this technique (Hurley et al., 2015; Tomasi & Volkow, 2012). In cognitively unimpaired elderly adults, Hurley and colleagues have confirmed that the left IFG, the left pMTG and the left ATL are functionally interconnected and form the language rs-fMRI network (Hurley et al., 2015). This suggests that rs-fMRI could be a tool of choice to better understand network-level brain alterations underlying language symptoms in clinical populations such as AD and svPPA. To our knowledge, only a very few studies have assessed functional connectivity in the language network in these populations and none has directly compared AD and svPPA patients.

In AD patients, the majority of rs-fMRI studies have focused on the default-mode network (DMN) (Buckner et al., 2005). These studies have shown a disconnection between the regions of the DMN, most frequently the hippocampus, the precuneus and the posterior cingulate cortex (for a recent review, see (Badhwar et al., 2017)). More recently, studies observed functional connectivity alterations even beyond the DMN in AD patients. This extended the interest to other brain networks such as the language network (Mascali et al., 2018; Weiler et al., 2014; Whitwell et al., 2015). The few rs-fMRI studies investigating the language network in AD patients have consistently reported lower resting-state functional connectivity in posterior temporal language regions (such as the left pMTG) (Mascali et al., 2018; Weiler et al.,

2014; Whitwell et al., 2015). Anterior frontal language regions (such as the left IFG) have yielded less consistent results, studies showing preserved (Weiler et al., 2014) or altered (Mascali et al., 2018) functional connectivity. Nonetheless, in most of these studies, language was not the main focus. Furthermore, none of them has investigated functional connectivity in the left ATL, even though recent rs-fMRI studies support its inclusion in the language network of healthy individuals (Hurley et al., 2015). Given the role of this region in language impairments in AD patients (Apostolova et al., 2008; Brambati et al., 2015; Brambati et al., 2006; Brambati et al., 2009; Domoto-Reilly et al., 2012; Grossman et al., 2004; Lars et al., 2011), it would be necessary to investigate its functional connectivity.

In svPPA patients, only two studies have investigated the language rs-fMRI network. Both studies demonstrated the functional isolation of the left ATL (Agosta et al., 2014; Guo et al., 2013). More specifically, this key region has been shown to be disconnected from several primary and associative cortical regions, and its reduced functional connectivity correlates with naming deficits in svPPA patients (Guo et al., 2013). Nonetheless, the functional connectivity in other parts of the language network remains unclear in these patients.

In this study, we aim to directly compare the rs-fMRI language network in AD patients, svPPA patients and cognitively unimpaired elderly adults (CTRL). In order to provide a full picture of the language network in these patients and to fill the gaps in the previous literature on this topic, regions of interest will be placed in the left IFG, left pMTG and left ATL. Given that language impairments are present in both populations, we hypothesize that significant alterations in the rs-fMRI language network will be observed in both AD and svPPA patients. We further hypothesize that functional disconnection will be predominant in the left pMTG in AD patients, and predominant in the left ATL in svPPA patients. The results of this study could support the notion that language impairments in AD and svPPA are sustained by distinct disconnection patterns across the language network. They could also contribute to the understanding of the nature of language impairments in these two patient populations.

2. Methods

2.1 Participants

This study included ten patients with a clinical diagnosis of AD, nine patients diagnosed with svPPA and eleven CTRL. These three groups were matched for age, gender, and education.

Demographics of participants are presented in Table 1. The AD and svPPA patients were recruited through the *Clinique interdisciplinaire de Mémoire du Centre hospitalier universitaire (CHU) de Québec* and referred by a behavioral neurologist with expertise in neurodegenerative diseases and cognition (R.J.L.). Diagnosis of AD was made based on the criteria of the National Institute on Aging and the Alzheimer's Association workgroup (McKhann et al., 2011). svPPA patients were diagnosed according to currently accepted criteria (Gorno-Tempini et al., 2011). General exclusion criteria were as follows: native tongue other than French, left-handedness, developmental learning disabilities, past psychiatric disorder, history of traumatic brain injury, incompatibility with magnetic resonance imaging (MRI) scanner and uncorrected hearing and/or vision problems. The study was approved by the research ethics committee of the CHU de Québec (Project #2015-1909) and written informed consent was obtained from all participants.

2.2 Neuropsychological and language assessment

All participants completed a battery of standard neuropsychological tests (previously described in (Montembeault et al., 2017)) to assess general cognitive status (Mini-Mental State Examination; (Folstein et al., 1975)), as well as a number of cognitive domains. These domains include nonverbal and verbal episodic memory (Immediate and delayed recall of the Rey Complex Figure Test (Meyers & Meyers, 1995; Osterrieth, 1944); Rey Auditory Verbal Learning Test (Rey, 1964)); language (Boston Naming Test (Kaplan et al., 1983); Free fluency, orthographic and semantic fluency (Joanette et al., 2004)), semantic associations (Pyramids and Palm Trees Test (Howard & Patterson, 1992)), verbal abstraction (Similarities subtest, WAIS-III (Wechsler, 1997)), working memory (Forward and Backward Digit-span (Wechsler, 1997)), visual perception (Benton Line Orientation test (Benton et al., 1983; Qualls et al., 2000); Benton Facial Recognition test (Benton et al., 1983)), visuoconstructional skills (copy of the Rey Complex Figure Test (Meyers & Meyers, 1995; Osterrieth, 1944); Clock-drawing Test (Rouleau et al., 1992)); and executive functioning (Trail making test A&B (Tombaugh, 2004); Stroop-Victoria Test (Regard, 1981).

2.3 Neuroimaging

2.3.1 Image acquisition

All participants underwent an MRI protocol including a high-definition T1 and resting-state fMRI brain images. The scans were obtained with a 3T Philips Achieva TX scanner at IRM

Québec-Mailloux in Quebec City. First, a volumetric magnetization prepared rapid gradient echo (MP-RAGE) sequence was used to acquire a high-resolution T1 3D structural image (TR = 8.2 ms, TE = 3.7 ms, FoV= 250 mm, flip angle = 8◦, 256×256 matrix, 180 slices/volume, slice thickness = 1mm, no gap). Secondly, a 9-minute resting-state echo-planar imaging (EPI) scan (TR = 2110 ms, TE = 30 ms, FoV=224 mm, flip angle = 70◦, 64x64 matrix, 40 transverse slices/volume, slice thickness=3.5 mm, no gap, 300 volumes) was acquired for each participant. Participants were instructed to rest quietly with their eyes opened, to think of nothing, and to remain awake.

2.3.2 Resting-state fMRI preprocessing

The functional images were pre-processed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) ran on MATLAB 7.14.0.739. (Mathworks, Natick, MA). After discarding the first ten volumes of each run, functional images were corrected for slice timing and realigned in order to account for minor head motion. Structural T1 images were coregistered to the mean of realigned functional images obtained during the previous realignment step. Coregistered structural images of all participants were then segmented. The DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) imported gray and white matter images obtained during the segmentation step were used to create a DARTEL template using the images of all participants. The flow field images obtained during the DARTEL template creation was used to warp all realigned functional images and the coregistered structural images into the MNI (Montreal Neurological Institute) space. Warped functional images were then smoothed with an 8-mm Gaussian kernel (FWHM).

2.3.3 Statistical analyses

Smoothed normalized images were entered in the CONN toolbox (v.17.f.; www.nitrc.org/projects/conn, RRID:SCR_009550) (Whitfield-Gabrieli & Nieto-Castanon, 2012). In order to remove unwanted motion, physiological and other artifactual effects from the BOLD signal, bandpass filtering (0.008 Hz < f < 0.15 Hz) and anatomical component-based noise correction method (aCompCor) were applied on the images (Behzadi, Restom, Liau, & Liu, 2007). More precisely, BOLD signal from the white matter and cerebrospinal fluid masks, as well as the six motion correction parameters and their first temporal derivatives were included as regressors. This method has shown to improve the specificity of functional connectivity estimates (Muschelli et al., 2014). Three seed ROIs, consisting of 4 mm radius spheres centered

on MNI coordinates, were used. They were located in the left ATL (-39, 15, -33), the left pMTG (-66, -42, 3) and the left IFG (-54, 24, 3) and were based on previous studies investigating language in cognitively unimpaired individuals (Binney, Embleton, Jefferies, Parker, & Lambon Ralph, 2010; Gesierich et al., 2011; Hurley et al., 2015).

Seed-to-voxel analyses were conducted using CONN. Pearson's correlation coefficient was extracted between the time course in the seed region and the time course in all other voxels in the brain. The correlation coefficients were then converted to normally distributed scores using Fisher's transformation in order to allow for second-level General Linear Model analysis (Whitfield-Gabrieli & Nieto-Castanon, 2012). First, group-level connectivity maps were derived by performing one-sample t-tests in order to detect voxels in which the time course was positively correlated with the time course in the seed ROI. Second, between groups comparisons were conducted in order to identify, for each ROI, voxels that expressed differences in correlation between each pair of groups. Age and gender were entered as control covariates in the model. All analyses were conducted with a statistical threshold of $p \leq .001$ uncorrected at height voxel-level and $p \leq .05$ false discovery rate (FDR).

3. Results

3.1 Neuropsychological and language measures

Scores of each group and between-group differences in neuropsychological and language measures are presented in Table 1. Overall, both patient groups presented significant language impairments in comparison to CTRL, and svPPA patients showed more severe language impairments in comparison with AD.

More specifically, in comparison to CTRL, AD patients were significantly impaired in naming and verbal fluency (free and semantic conditions). In comparison to CTRL, svPPA patients were impaired on all language measures, namely naming, verbal fluency, semantic associations and verbal abstraction. Finally, a significantly lower performance was observed in naming, semantic associations and verbal abstraction in svPPA patients in comparison to AD patients.

3.2 rs-fMRI networks

3.2.1 Left ATL seed

Within-group rs-fMRI networks with a seed in the left ATL for CTRL, AD and svPPA patients are visually presented in Figure 1. A detailed list of anatomical regions included in these networks are presented in Supplementary tables 1, 4 and 7 respectively.

Between-group differences in the functional connectivity of the network anchored in the left ATL are displayed in Table 2 and Figure 1. In the direct comparison between groups, decreased functional connectivity was observed in AD patients in comparison to CTRL between the left ATL and the right angular gyrus and the pMTG.

The svPPA group showed the most extensive reduced functional connectivity, both in comparison to CTRL and AD patients. In comparison to CTRL, svPPA patients presented decreased functional connectivity between the left ATL and a cluster including the left ATL and pMTG, a cluster including the right inferior orbitofrontal cortex and the right ATL, a cluster including bilateral medial frontal and anterior cingulate cortex and a cluster in the right precuneus. Finally, in comparison to AD patients, svPPA patients showed a significant decrease in functional connectivity between the left ATL and a cluster including the left pMTG, a cluster in the left thalamus and finally, a cluster in the right medial prefontal cortex.

3.2.2 Left pMTG seed.

Rs-fMRI networks with a seed in the left pMTG for CTRL, AD and svPPA patients are visually presented in Figure 2. A detailed list of anatomical regions included in these networks are presented in Supplementary tables 2, 5 and 8 respectively.

Between-group differences in the functional connectivity of the network anchored in the left pMTG are displayed in Table 3 and Figure 2. In the direct comparison between groups, decreased functional connectivity was observed in AD patients in comparison to CTRL in the left pMTG seeded network, more precisely with a cluster including the right MTG.

svPPA patients presented decreased functional connectivity in the left pMTG seeded network in comparison to CTRL and AD patients. In comparison to the CTRL, a decreased functional connectivity was observed between the left pMTG and a cluster including the left ATL (medial and lateral sections), a cluster in the right anterior inferior and middle temporal gyri and finally, a cluster in the right ATL. In comparison to AD patients, svPPA patients presented a decreased correlation between the left pMTG and a cluster in the left ATL (medial section) and middle orbitofrontal gyrus.

3.2.3 Left IFG seed.

Rs-fMRI networks with a seed in the left IFG for CTRL, AD and svPPA patients are visually presented in Figure 3. A detailed list of anatomical regions included in these networks are presented in Supplementary tables 3, 6 and 9 respectively.

No significant between-group differences were found in the left IFG seeded rs-fMRI network.

4. Discussion

In this study, we directly compared the rs-fMRI language network in AD patients, svPPA patients and cognitively unimpaired elderly adults (CTRL). Overall, language impairments and language functional network alterations were observed in both populations. These results suggest that language impairments are associated with functional disconnections across the language network. However, some differences were observed in the language profiles between AD and svPPA patients, and functional disconnection did not target the same regions in these two groups. In AD patients, the left ATL presented reduced functional connectivity with the right pMTG and the right angular gyrus, in comparison to CTRL. The left pMTG also showed reduced interhemispheric functional connectivity with its homotopic counterpart. In svPPA patients, the left ATL was functionally isolated in comparison to CTRL and AD patients, while the left pMTG, the left IFG and the other language regions remained functionally interconnected. Altogether, this study suggests that language impairments in AD and svPPA are sustained by distinct disconnection patterns across the language network. These distinct profiles have significant implications for our understanding of these two diseases as well as of the neurobiology of language.

4.1 In AD, regions of the language network present reduced interhemispheric functional connectivity, as well as reduced functional connectivity with a region of the default-mode network.

Our results in the AD group first support the notion that functional connectivity alterations are not only present within the default-mode network (DMN), but also in the language network (Mascali et al., 2018; Weiler et al., 2014; Whitwell et al., 2015). Consistently with previous studies, we observed lower resting-state functional connectivity in posterior temporal language regions, i.e. the left pMTG (Mascali et al., 2018; Weiler et al., 2014; Whitwell et al., 2015). In the present study, this region was found to be functionally

disconnected from its contralateral homologous region, the right MTG. Interestingly, it is not the first time that the role of the dynamics between left- and right-hemisphere posterior temporal regions is noted in the study of language in AD patients. First, this result has also been reported in previous rs-fMRI studies of AD patients (Weiler et al., 2014; Whitwell et al., 2015). Secondly, in a previous study by Nelissen et al. (2007), it was shown that the left posterior temporal regions had a decreased activation during an associative-semantic task, while the homologous right-hemisphere regions showed an increased activation. This right-hemisphere activity correlated positively with accuracy in a naming task, and was therefore interpreted as functional reorganisation in AD patients. Our study does not allow to interpret this decreased functional connectivity as adaptive or maladaptive. Nonetheless, the brain regions obtained by these authors (51 -9 -15; 54 -24 0) lay very close to those of our study (58 -18 -12). Furthermore, the fact that opposite patterns of activation (i.e. increased versus decreased) are observed in these two homotopic regions during the same associative-semantic task is highly coherent with the altered interhemispheric functional connectivity between these two regions demonstrated in our study. Also consistently with a previous rs-fMRI study (Weiler et al., 2014), functional connectivity in anterior language regions, i.e. the left IFG, was preserved in AD patients.

One of the novelties of our study is the investigation of the functional network derived from the left ATL, which had never been studied in AD patients. Our study shows that in AD patients, the left ATL is functionally disconnected from the right angular gyrus and the right pMTG. This is of particular interest in AD, considering that the angular gyrus is well recognized as a region of the DMN (Buckner et al., 2008; Raichle et al., 2001). As previously mentioned, the DMN is the most predominantly impaired brain network in AD (Badhwar et al., 2017; Buckner et al., 2005; Montembeault, Rouleau, Provost, & Brambati, 2016). This might suggest that the functional disconnection within the language network in AD is not totally independent from the DMN. Indeed, recent studies have revealed that there are interrelationships between the DMN and the language/semantic network in healthy individuals (Humphreys, Hoffman, Visser, Binney, & Lambon Ralph, 2015; Seghier, Fagan, & Price, 2010; Xu, Lin, Han, He, & Bi, 2016). These interrelationships are also observed in the left ATL seeded network in CTRLs in the present study. Using graph-theoretic approaches, Xu and colleagues demonstrated that the ATL was a connector hub between the DMN and a left perisylvian network, a network highly consistent with the language network described in the present study. They therefore suggested

that the left ATL plays a role in the integration of the memory-based simulation system and the language-based semantic system. However, even though a few studies have recently investigated inter-network functional connectivity in AD patients (Song et al., 2013; Zhan et al., 2016), none has focussed on the interaction between the DMN and the language network. Nonetheless, the fact that the DMN is the main targeted brain network in AD, and that it partially overlaps with regions of the language network, might contribute to the language symptoms observed in these patients.

4.2 In svPPA, the left ATL is functionally isolated, while the remaining parts of the language network remain interconnected.

In the present study, svPPA patients showed a striking functional disconnection of the left ATL with other regions within and outside the language network (bilateral temporal, frontal and parietal regions). This result is consistent with previous rs-fMRI studies (Agosta et al., 2014; Guo et al., 2013) that support the role of the left ATL as the disease-specific epicenter of svPPA (Seeley et al., 2009). In addition to being observed in comparison to CTRL, reduced functional connectivity in the left ATL was also observed in the direct comparison between svPPA and AD patients (in the left MTG, thalamus and right medial prefrontal cortex). This suggests that functional connectivity in the left ATL could represent a helpful neuroimaging biomarker for the differential diagnosis of svPPA and AD.

The originality of our study is the investigation of functional connectivity in other language key regions such as the left IFG and the left pMTG. Other than a reduced connectivity between the left pMTG and the left ATL, these two derived networks were strikingly preserved in svPPA patients. This observation has significant clinical implications, for example in the understanding of symptoms presented by svPPA patients (see section 4.5).

4.3 Language network functional connectivity alterations in svPPA and AD are consistent with white matter fiber damage.

Brain regions that present correlated changes in BOLD signal during rest are also structurally connected via white matter bundles (Michael D. Greicius, Supekar, Menon, & Dougherty, 2009; Lemaire et al., 2013; Morgan, Mishra, Newton, Gore, & Ding, 2009; Turken & Dronkers, 2011). Combining the present rs-fMRI results with previously obtained diffusion imaging results can enrich our understanding of the language brain network in AD and svPPA. On one hand, a previous meta-analysis of diffusion imaging studies in AD has shown that white

matter (WM) fiber alterations are widespread (Sexton et al., 2011). These authors reported large effect sizes (reduced fractional anisotropy and increased mean diffusivity) in the uncinate fasciculus, the superior longitudinal fasciculus and the posterior cingulum, and medium effect sizes in the splenium of the corpus callosum, as well as in temporal and parietal white matter (Sexton et al., 2011). In our study, the interhemispheric functional disconnection between homotopic pMTG appears coherent with the reduced structural connectivity within the splenium of the corpus callosum, which connects bilateral temporo-parietal regions. Future studies should investigate the association between language symptoms and WM damage in the splenium in AD patients. On the other hand, WM damage in svPPA patients is predominantly observed in the ventral tracts that pass through the temporal lobe, more precisely the inferior longitudinal fasciculus, the uncinate fasciculus and the temporal segment of the arcuate fasciculus (Acosta-Cabronero et al., 2011; Agosta et al., 2013; Agosta et al., 2010; Galantucci et al., 2011). Consistent with these observations, in our study, a functional disconnection was observed between the left ATL and the left pMTG, two regions that are located along the inferior longitudinal fasciculus. The left ATL also showed decreased functional connectivity with orbitofrontal regions, which are structurally connected by the uncinate fasciculus. Conversely, the corpus callosum and the dorsal frontoparietal tracts that do not involve the temporal lobes are relatively spared in svPPA (Acosta-Cabronero et al., 2011; Agosta et al., 2013; Agosta et al., 2010; Galantucci et al., 2011). Likewise, functional connectivity in these regions was preserved in the present study. Overall, these observations suggest a good agreement between our study using rs-fMRI and previous diffusion imaging studies. Nonetheless, future studies using multimodal neuroimaging techniques should be conducted to confirm these results.

4.4 Language network functional connectivity alterations in svPPA and AD are consistent with the language symptoms observed in these patients.

In the present study, AD and svPPA patients presented common but also differential language impairments. This might be due to the fact that both populations show different alterations of the language rs-fMRI network.

First, AD patients presented significant impairments in verbal fluency and naming tasks, and a trend towards decreased performance in semantic memory tasks. This clinical profile is consistent with previous studies investigating language in AD (Verma & Howard, 2012). It is also consistent with the reduced functional connectivity from the left pMTG ROI in our study.

The role of this brain region in lexico-semantic retrieval has been demonstrated in previous neuroimaging studies (Davey et al., 2016; Gold et al., 2006; Hickok & Poeppel, 2007; Noppeney, Phillips, & Price, 2004). Furthermore, the left ATL, involved in conceptual knowledge (Heilman, 1972; Hodges et al., 1992; Snowden et al., 1989), also showed decreased functional connectivity in AD patients. These results provide insight into the nature of language impairments in AD patients. In this regard, there has been a longstanding debate in recent years concerning the nature of language impairments (and more specifically naming impairments) in AD patients. While some authors argue that naming deficits in AD are caused by a semantic impairment (stored information is lost), others have suggested that they are caused by an impaired lexico-semantic access (access to stored information is dysfunctional) (Matthew A. Lambon Ralph, 2014). Given the fact that many studies have supported both hypotheses, some authors have suggested that naming impairments in AD patients actually reflect both mechanisms (Joubert et al., 2010; Montembeault et al., 2017; Rogers & Friedman, 2008). The rs-fMRI profile obtained in AD patients in the present study is in support of that statement, since key regions for these two mechanisms present altered functional connectivity.

Second, svPPA patients showed significant impairments on all language and semantic memory tasks, and these impairments were overall more severe than in AD patients. A similar pattern emerged in the rs-fMRI analysis: even though both groups of patients showed a functional disconnection from the left ATL in comparison to CTRLs, it was more distributed in the svPPA group and significantly more important in svPPA in the direct comparison with AD patients. These results highlight the fact that the mechanisms underlying language impairments are different in svPPA and AD. In relation to naming impairment, the profile that we observed in svPPA patients is consistent with a core semantic impairment, in which stored conceptual information is lost, which is highly consistent with previous studies (Gorno-Tempini et al., 2011; Joyal et al., 2017; Montembeault et al., 2017; Reilly et al., 2011; Rogers & Friedman, 2008; Sajjadi et al., 2012). Furthermore, the relative preservation of functional connectivity in the remaining parts of the language network is consistent with the relative sparing of other language functions sustained by these regions, such as motor speech, phonology and speech rate (Gorno-Tempini et al., 2011; S. M. Wilson et al., 2010).

4.5 Conclusion

In conclusion, the findings reported here contribute to our understanding of the functional connectivity changes that take place in AD and svPPA. This is the first study to provide a full picture of the functional connectivity in all key regions of the language network simultaneously, and to directly compare these two populations of patients. The decreased functional connectivity in the left ATL in svPPA patients in comparison to AD patients could serve as a neuroimaging biomarker in the differential diagnosis of these two clinical populations. Using a network-based approach, we were also able to highlight the fact that similar language impairments in AD and svPPA patients are associated with different brain mechanisms in each disease. In turn, the patterns of functional connectivity in each population of patients are highly suggestive of a combined impaired lexico-semantic access and semantic impairment in AD patients, and a core semantic impairment in svPPA.

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Tables

Table 1. Demographic and neuropsychological/language characteristics of CTRL, AD patients and svPPA patients.

	CTRLs (*n* = 11)	**AD (*n* = 10)**	**svPPA (*n* = 9)**	***p* value**	**Group comparison**
Demographics					
Gender (F/M)	4/7	5/5	2/7	NA	NA
Age (in years)	65.7 (8.1)	69.8 (8.5)	65.2 (11.2)	= .483	CTRL = AD = svPPA
Education (in years)	16.5 (3.1)	15.7 (3.0)	16.1 (4.1)	= .881	CTRL = AD = svPPA
Neuropsychological assessment					
Global cognitive status					
MMSE	28.9 (0.7)	24.9 (3.1)	25.2 (2.1)	< .001	CTRL > AD = svPPA
Episodic memory					
RCFT (Immediate recall)	19.2 (4.3)	5.5 (3.5)	9.6 (5.7)	< .001	CTRL > AD = svPPA
RCFT (Delayed recall)	20.3 (4.6)	4.8 (4.1)	8.4 (5.2)	< .001	CTRL > AD = svPPA
RAVLT (Trials 1-5)	52.9 (7.4)	29.0 (6.3)	29.5 (7.8)	< .001	CTRL > AD = svPPA
RAVLT (Immediate recall)	11.1 (2.6)	2.9 (2.6)	4.8 (2.3)	< .001	CTRL > AD = svPPA
RAVLT (Delayed recall)	10.8 (2.7)	2.1 (3.2)	4.7 (2.7)	< .001	CTRL > AD = svPPA
RAVLT (Recognition)	47.2 (1.6)	30.4 (7.3)	41.0 (5.7)	< .001	CTRL = svPPA > AD
Language and semantic memory					
Boston Naming Test	49.9 (4.4)	42.9 (9.8)	12.7 (8.7)	< .001	CTRL > AD > svPPA

Pyramids and Palm Trees Test	50.2 (1.5)	47.7 (2.4)	31.7 (12.5)	< .001	CTRL = AD > svPPA
Free Fluency	67.6 (17.3)	39.0 (14.9)	30.7 (12.0)	< .001	CTRL > AD = svPPA
Letter Fluency - P	27.0 (8.8)	19.3 (7.9)	13.2 (5.7)	< .01	CTRL = AD CTRL > svPPA AD = svPPA
Semantic Fluency - Clothing	26.3 (4.4)	13.5 (7.3)	9.1 (7.8)	< .001	CTRL > AD = svPPA
Similarities subtest - WAIS-III	18.2 (3.6)	15.1 (3.7)	6.1 (2.9)	< .001	CTRL = AD > svPPA
Visual perception					
Benton Line Orientation test	27.5 (2.2)	23.8 (7.4)	26.6 (2.4)	= .199	CTRL = AD = svPPA
Benton facial recognition test	48.0 (2.9)	45.4 (3.5)	44.4 (3.4)	= .052	CTRL = AD = svPPA
Visuoconstruction					
RCFT (copy)	32.3 (2.7)	26.6 (8.5)	29.7 (4.5)	= .095	CTRL = AD = svPPA
Clock-drawing test	9.4 (1.0)	7.5 (2.6)	7.8 (1.9)	= .067	CTRL = AD = svPPA
Clock-copy test	9.8 (0.5)	9.4 (0.8)	9.7 (0.4)	= .310	CTRL = AD = svPPA
Executive functions / working memory					
Trail making test A (s)	29.5 (5.6)	81.4 (96.3)	47.9 (13.0)	= .121	CTRL = AD = svPPA
Trail making test B (s)	60.6 (20.8)	240.1 (120.2)	113.4 (66.8)	< .001	CTRL = svPPA > AD
SVT Word-color interference task	127.4 (32.6)	237.8 (113.4)	135.1 (35.8)	< .01	CTRL = svPPA > AD
Digit span (total)	18.2 (4.3)	15.3 (2.6)	14.6 (3.7)	= .072	CTRL = AD = svPPA

(Abbreviations: MMSE = Mini-Mental State Examination; RCFT: Rey Complex Figure Test; RAVLT: Rey Auditory Verbal Learning Test; SVT = Stroop-Victoria Test)

Table 2. Between-group differences in the rs-fMRI network anchored to the left ATL ($p \leq .05$ FDR corrected).

Contrast*	Brain region	MNI coordinates			Peak T-value	p value	Cluster size (Voxels)
		x	y	z			
CTRL > AD	**R Angular gyrus**	**56**	**-62**	**24**	**5.49**	**.025**	**200**
		61	-58	28	3.70		
	R pMTG	46	-56	20	3.99		
		62	-58	10	3.56		
CTRL > svPPA	**L ATL**	**-70**	**-22**	**-8**	**5.96**	**.000**	**759**
		-64	-8	-4	4.67		
	L pMTG	-62	-44	-2	5.51		
		-66	-35	-8	4.60		
	L posterior inferior temporal gyrus	-56	-48	-16	5.17		
	R inferior orbitofrontal cortex	**26**	**18**	**-18**	**5.93**	**.001**	**367**
		40	32	-14	4.96		
	R ATL	44	24	-18	4.46		
	R Superior medial frontal gyrus	**6**	**52**	**26**	**4.80**	**.000**	**1045**
	R medial orbitofrontal gyrus	10	60	-6	4.78		
	L medial orbitofrontal gyrus	-4	60	-2	4.39		
	L anterior cingulum	-4	38	6	4.29		
	R anterior cingulum	10	54	12	4.33		
	R Precuneus	**2**	**-58**	**38**	**4.51**	**.002**	**321**
		4	-54	20	3.87		
AD > svPPA	**L MTG**	**-70**	**-24**	**-10**	**6.66**	**.001**	**436**
	L posterior inferior temporal gyrus	-54	-50	-18	5.35		
	L pMTG	-70	-40	-10	4.96		

L Thalamus	**-22**	**-28**	**8**	**5.30**	**.040**	**158**
	-8	-20	2	4.77		
R medial prefrontal cortex	**6**	**14**	**-14**	**4.95**	**.040**	**161**
	-6	10	10	4.21		

*Only contrasts in which significant differences were found are listed. (Abbreviations: L = left; R = right; ATL = anterior temporal lobe; pMTG = posterior middle temporal gyrus.)

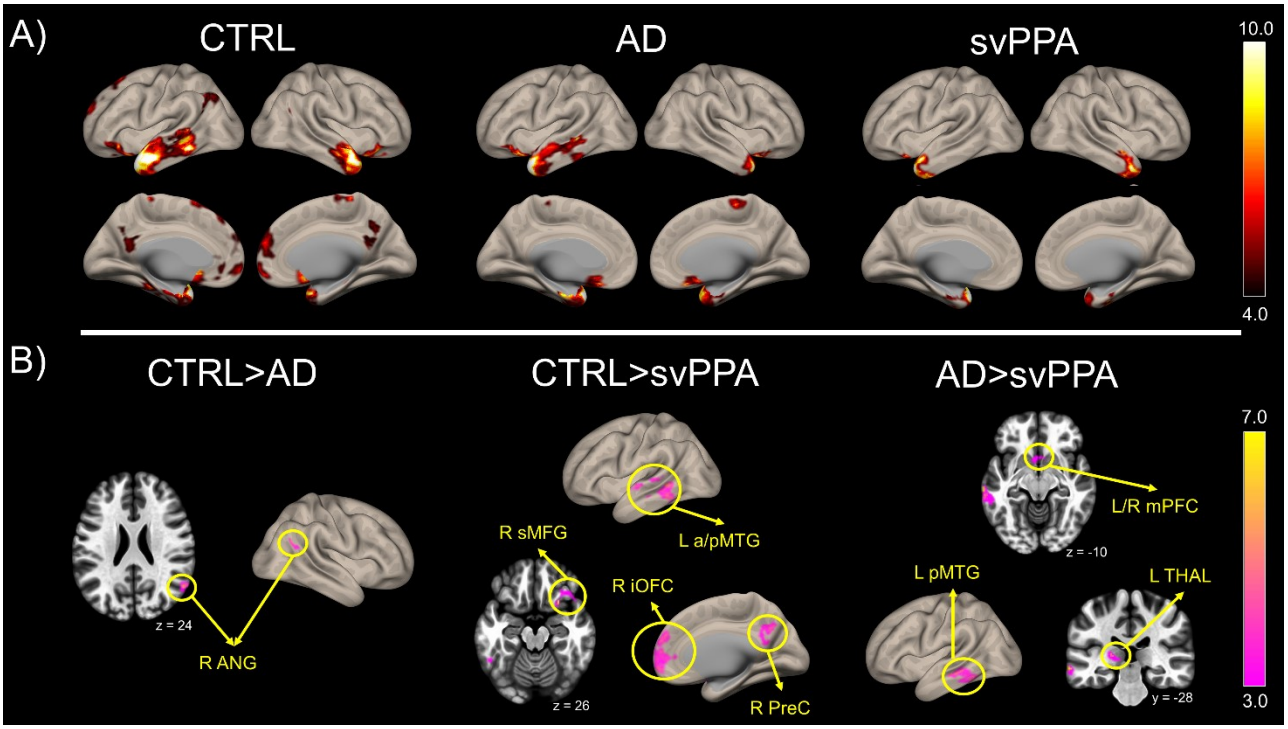
Table 3. Between-group differences in the rs-fMRI network anchored to the left pMTG ($p \leq .05$ FDR corrected).

Contrast*	Brain region	MNI coordinates			Peak T-value	p value	Cluster size (Voxels)
		x	y	z			
CTRL > AD	**R MTG**	**58**	**-18**	**-12**	**5.01**	**.010**	**246**
		70	-20	-14	4.10		
CTRL > svPPA	**L ATL**	**-24**	**24**	**-28**	7.43	**.000**	**1501**
		-44	16	-36	5.56		
		-34	2	-34	4.19		
	L ATL – medial section	-24	-2	-30	4.33		
	R anterior inferior temporal gyrus	**44**	**-4**	**-30**	**6.16**	**.000**	**697**
	R anterior MTG	56	-2	-26	5.94		
		56	-18	-16	4.67		
	R ATL	**44**	**18**	**-26**	**5.93**	**.003**	**277**
		58	10	-12	4.63		
AD > svPPA	**L ATL – medial section**	**-20**	**10**	**-28**	**7.20**	**.000**	**830**
	L ATL	-24	22	-34	**5.63**		
	L middle orbitofrontal gyrus	-22	32	-22	**6.39**		

*Only contrasts in which significant differences were found are listed. (Abbreviations: L = left; R = right; ATL = anterior temporal lobe; pMTG = posterior middle temporal gyrus.)

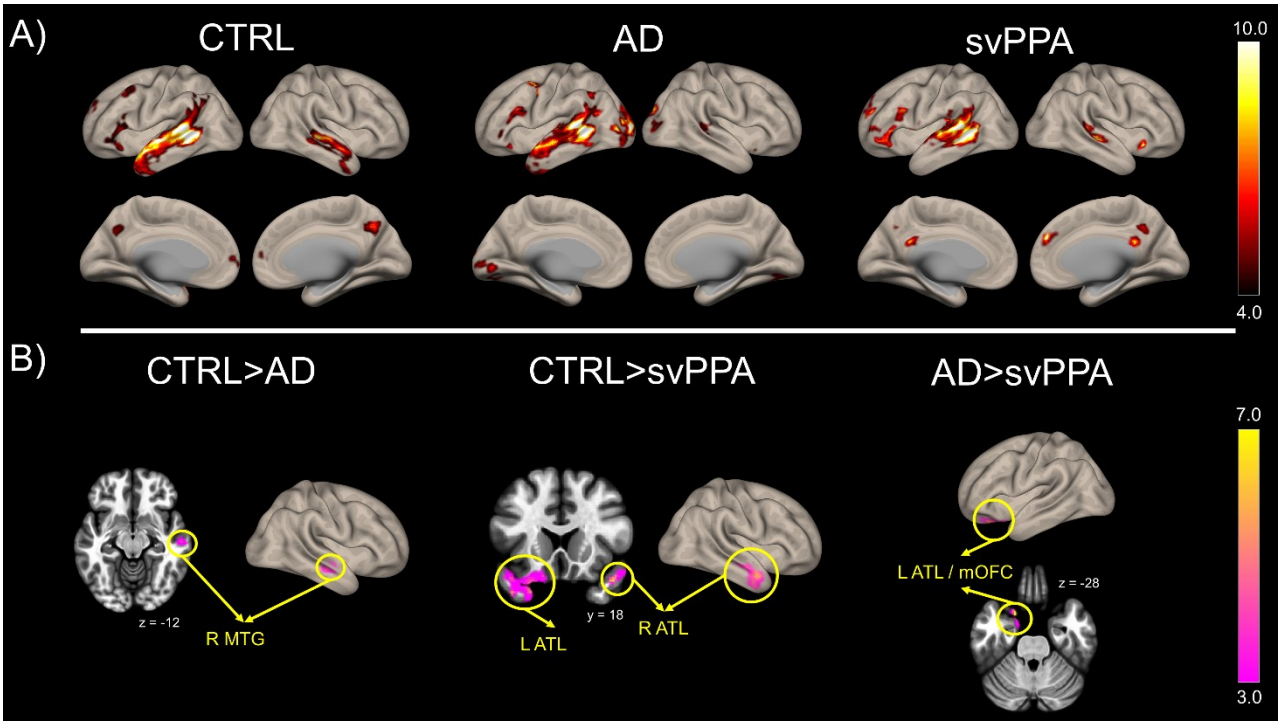
Figures

Figure 1. A) Group-specific rs-fMRI network with a seed in the left ATL in CTRL, AD patients and svPPA patients ($p \leq .05$ FDR corrected). **B)** Between-group differences in the rs-fMRI network with a seed in the left ATL.



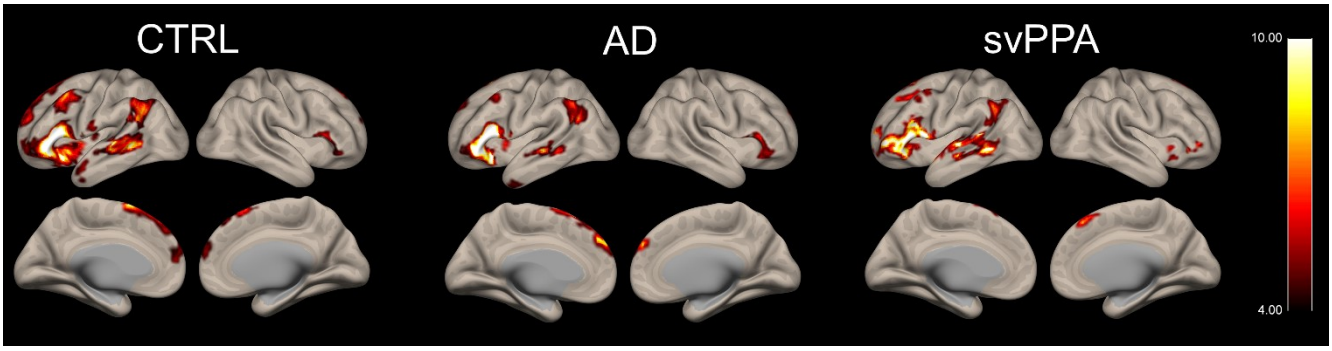
Clusters in pink-yellow represent regions of decreased connectivity from the left ATL ($p \leq .05$ FDR corrected). (Abbreviations: R = right; L = left; ANG = angular gyrus; sMFG = superior medial frontal gyrus; aMTG = anterior middle temporal gyrus; pMTG = posterior middle temporal gyrus; iOFC = inferior orbitofrontal cortex; PreC = precuneus; THAL = thalamus; mPFC = middle prefrontal cortex)

Figure 2. A) Group-specific rs-fMRI network with a seed in the left pMTG in CTRL, AD patients and svPPA patients ($p \leq .05$ FDR corrected). **B)** Between-group differences in the rs-fMRI network with a seed in the left pMTG.



Clusters in pink-yellow represent regions of decreased connectivity from the left pMTG ($p \leq .05$ FDR corrected). (Abbreviations: R = right; L = left; ATL = anterior temporal lobe; mOFC = middle orbitofrontal gyrus)

Figure 3. Group-specific rs-fMRI network with a seed in the left IFG in CTRL, AD patients and svPPA patients ($p \leq .05$ FDR corrected). No significant difference was found between groups.



Supplementary material

Supplementary table 1 : rs-fMRI network anchored to the left ATL in CTRL ($p \leq .05$ FDR corrected).

Brain region	MNI coordinates			Peak T-value	p value	Cluster size (Voxels)
	x	y	z			
ATL	**-38**	**16**	**-30**	**53.76**	**.000**	**12406**
	-52	14	-30	18.74		
Anterior MTG	-52	-2	-26	20.32		
Posterior inferior temporal gyrus	-56	-42	-12	13.42		
Anterior parahippocampal gyrus	-26	-2	-28	10.87		
Anterior MTG	52	2	-22	14.2		
Angular gyrus	**-54**	**-62**	**41**	**10.65**	**.000**	**582**
	-42	-54	28	5.52		
Inferior parietal gyrus	-36	-76	42	4.82		
pMTG	-58	-58	22	4.49		
Superior frontal gyrus	**-20**	**58**	**26**	**8.51**	**.000**	**424**
	-16	42	36	4.48		
Superior medial frontal gyrus	-12	56	14	5.43		
Paracentral lobule	**2**	**-34**	**66**	**7.97**	**.017**	**107**
Supplementary motor area	8	-20	70	5.53		
Superior frontal gyrus	**-16**	**26**	**56**	**7.75**	**.000**	**443**
Supplementary motor area	-10	12	64	7.3		
Superior medial frontal gyrus	-4	40	48	5.32		
Medial orbitofrontal gyrus	**8**	**56**	**-10**	**6.94**	**.000**	**740**
	-8	60	-4	6.04		
Anterior cingulate cortex	-8	40	-4	4.77		
	-2	36	8	4.3		
Superior medial frontal gyrus	-8	52	14	4.2		
Superior medial frontal gyrus	**4**	**56**	**22**	**6.66**	**.000**	**569**
	12	68	14	5.13		
Anterior cingulate cortex	14	50	10	5.18		
Angular gyrus	**56**	**-64**	**28**	**6.29**	**.005**	**147**
pMTG	54	-54	22	4.72		
Precuneus	**4**	**-56**	**36**	**5.19**	**.000**	**517**

	-2	-52	16	5.11
Posterior cingulate cortex	-2	-46	32	4.43

Supplementary table 2 : rs-fMRI network anchored to the left pMTG in CTRL ($p \leq .05$ FDR corrected).

Brain region	MNI coordinates			Peak T-value	p value	Cluster size (Voxels)
	x	y	z			
pMTG	**-66**	**-44**	**2**	**30.48**	**.000**	**6888**
	-52	-42	2	12.43		
	-58	-28	4	11.53		
Anterior MTG	-60	-14	-6	21.25		
	-56	0	-18	10.56		
ATL	-52	12	-18	10.03		
pMTG	**52**	**-28**	**-2**	**10.88**	**.000**	**1289**
	68	-36	-4	6.54		
Anterior MTG	52	-8	-14	7.8		
Anterior inferior temporal gyrus	54	-4	-28	6.94		
ATL	64	4	-12	4.19		
Precuneus	**6**	**-62**	**40**	**7.01**	**.000**	**416**
Cerebellum - Lobule IX	**8**	**-52**	**-30**	**6.4**	**.005**	**147**
Cerebellum - Vermis 4-5	2	-58	-18	5.6		
Cerebellum - Vermis 9	-4	-56	-32	4.88		
Superior frontal gyrus	**-16**	**60**	**26**	**6.12**	**.007**	**127**
Superior medial frontal gyrus	**-10**	**56**	**8**	**5.77**	**.008**	**121**
	14	52	8	4.88		
Anterior cingulate cortex	4	54	10	5.46		
Middle frontal gyrus	**-36**	**18**	**44**	**5.43**	**.005**	**143**

Supplementary table 3 : rs-fMRI network anchored to the left IFG in CTRL ($p \leq .05$ FDR corrected).

Brain region	MNI coordinates			Peak T-value	p value	Cluster size (Voxels)
	x	y	z			
IFG (pars triangularis)	**-56**	**24**	**4**	**48.54**	**.000**	**6232**
IFG (pars orbitalis)	-46	32	-10	12.49		
	-28	24	-14	12.16		
Insula	-40	16	-8	10.72		
Superior orbitofrontal gyrus	-28	58	-2	9.87		
Precentral gyrus	-38	12	44	9.22		
Putamen	-30	6	-2	8.86		
Middle frontal gyrus	-40	24	44	8.18		
Supplementary motor area	**-8**	**12**	**70**	**13.65**	**.000**	**2565**
	8	20	64	7.8		
Superior medial frontal gyrus	-10	38	46	8.54		
	14	40	46	8.22		
Superior frontal gyrus	-20	56	30	7.36		
pMTG	**-62**	**-44**	**-2**	**11.6**	**.000**	**2735**
	-64	-28	-2	11.18		
	-64	-56	2	8.55		
	-60	-54	24	7.99		
Angular gyrus	-52	-52	36	8.33		
	-46	-68	42	6.04		
Posterior superior temporal gyrus	-46	-42	14	6.3		
Caudate nucleus	**18**	**14**	**10**	**9.46**	**.000**	**321**
Pallidum	18	8	-2	5.8		
Cerebellum_Crus1	**36**	**-66**	**-28**	**9.23**	**.000**	**720**
	16	-74	-32	6.49		
Cerebellum_Crus2	22	-78	-46	6.99		
	18	-88	-30	5.01		
IFG (Pars opercularis)	**56**	**20**	**4**	**7.03**	**.000**	**383**
IFG (Pars triangularis)	54	22	0	7.02		
IFG (Pars orbitalis)	46	36	-10	5.25		
Anterior superior temporal gyrus	**-66**	**-10**	**8**	**5.75**	**.006**	**108**

Postcentral gyrus	-62	-10	22	5.14		
Rolandic operculum	-60	4	4	4.3		
Anterior MTG	**-50**	**-4**	**-20**	**5.61**	**.002**	**136**
Insula	**-44**	**-10**	**8**	**5.18**	**.008**	**100**

Supplementary table 4 : rs-fMRI network anchored to the left ATL in AD ($p \leq .05$ FDR corrected).

Brain region	MNI coordinates			Peak T-value	p value	Cluster size (Voxels)
	x	y	z			
ATL	**-38**	**16**	**-32**	**42.29**	**.000**	**6784**
	-46	16	-18	18.61		
Rectus	2	24	-16	9.6		
IFG (Pars orbitalis)	-32	20	-20	10.69		
Anterior parahippocampal gyrus	-22	-10	-30	10.37		
pMTG	-52	-42	-4	9.66		
IFG (Pars orbitalis)	**26**	**16**	**-20**	**16.5**	**.000**	**3335**
	28	28	-18	11.22		
ATL	44	10	-34	15.61		
Anterior parahippocampal gyrus	22	0	-22	8.83		
Supplementary motor area	**2**	**-24**	**62**	**10.58**	**.002**	**180**
Paracentral lobule	-8	-30	62	5.48		

Supplementary table 5 : rs-fMRI network anchored to the left pMTG in AD ($p \leq .05$ FDR corrected).

Brain region	MNI coordinates			Peak T-value	p value	Cluster size (Voxels)
	x	y	z			
pMTG	**-64**	**-42**	**4**	**41.18**	**.000**	**5352**
	-48	-46	2	21.28		
	-48	-20	-6	12.66		
	-54	-34	-6	9.47		
Anterior superior temporal gyrus	-52	0	-12	13.55		
Anterior MTG	-56	-16	-10	8.91		
Posterior superior temporal gyrus	-62	-30	10	9.32		
Middle occipital gyrus	**-22**	**-96**	**8**	**19.59**	**.000**	**1710**
	-42	-86	6	11.03		
Superior occipital gyrus	-18	-90	22	6.72		
Lingual gyrus	-4	-80	-2	6.61		
Inferior occipital gyrus	-38	-86	-10	6.34		
Fusiform gyrus	-22	-84	-10	5.49		
Middle frontal gyrus	**-38**	**4**	**54**	**13.27**	**.001**	**184**
Precentral gyrus	-50	-2	42	8.61		
Inferior occipital gyrus	**34**	**-84**	**-6**	**10.35**	**.000**	**510**
Cerebellum - Lobule VI	28	-70	-20	7.72		
Middle occipital gyrus	32	-88	10	5.24		
Lingual gyrus	20	-78	-4	5.79		
Superior occipital gyrus	**18**	**-90**	**24**	**9.95**	**.000**	**275**
ATL	**-42**	**18**	**-38**	**8.53**	**.000**	**673**
	-38	2	-42	7.4		
	-50	-4	-40	6.99		
IFG (Pars triangularis)	**-38**	**20**	**22**	**8.17**	**.000**	**317**
Thalamus	**-10**	**-10**	**6**	**7.19**	**.001**	**177**
Posterior superior temporal gyrus	**62**	**-32**	**8**	**7.12**	**.002**	**149**
pMTG	48	-34	4	6.54		
IFG (Pars orbitalis)	**-54**	**40**	**-2**	**6.9**	**.000**	**214**
	-40	54	-10	4.89		
Cerebellum - Crus 1	**-34**	**-80**	**-26**	**6.6**	**.020**	**82**

Cerebellum - Vermis 7	**2**	**-72**	**-32**	**6.54**	**.026**	**73**
Cerebellum - Vermis 8	-2	-60	-26	5.89		
Cerebellum - Crus 1	**20**	**-70**	**-38**	**6.41**	**.029**	**69**
Cerebellum - Lobule VI	18	-68	-26	4.63		
Putamen	**26**	**16**	**-6**	**6.39**	**.043**	**60**
Angular gyrus	**-48**	**-54**	**38**	**6.16**	**.025**	**76**

Supplementary table 6 : rs-fMRI network anchored to the left IFG in AD ($p \leq .05$ FDR corrected).

Brain region	MNI coordinates			Peak T-value	p value	Cluster size (Voxels)
	x	y	z			
IFG (Pars triangularis)	**-56**	**22**	**4**	**43.66**	**.000**	**3596**
IFG (Pars orbitalis)	-28	26	-10	20.29		
	-40	34	-6	18.03		
	-44	22	-12	11.2		
ATL	-60	10	0	10.22		
Putamen	-20	14	6	8.17		
	-22	-2	8	7.37		
Insula	-38	8	0	6.87		
Supplementary motor area	**-10**	**22**	**62**	**17.08**	**.000**	**1037**
	-8	4	74	6.64		
Superior frontal gyrus	-12	24	50	8.51		
	14	54	26	6.91		
Superior medial frontal gyrus	-8	56	34	10.42		
	-8	38	50	5.93		
	-8	60	22	5.04		
pMTG	**-52**	**-26**	**-4**	**9.57**	**.000**	**519**
	-58	-42	-8	7.81		
Anterior MTG	-54	-12	-12	4.76		
IFG (Pars orbitalis)	**58**	**26**	**-2**	**8.82**	**.000**	**794**
	44	22	-14	6.14		
IFG (Pars triangularis)	44	30	0	6.27		
Angular gyrus	**-38**	**-54**	**24**	**8.72**	**.000**	**842**
	-50	-56	38	7.07		
pMTG	-52	-54	24	7.77		
Middle frontal gyrus	**-44**	**22**	**48**	**8.43**	**.001**	**190**
Precentral gyrus	-48	6	40	5.18		
Cerebellum - Crus 1	**34**	**-76**	**-34**	**8.31**	**.000**	**250**
Cerebellum - Lobule VIII	20	-68	-40	7.21		
Pallidum	**22**	**-6**	**6**	**7.76**	**.014**	**99**
Anterior inferior temporal gyrus	**-46**	**-2**	**-40**	**5.24**	**.014**	**97**

Supplementary table 7 : rs-fMRI network anchored to the left ATL in svPPA ($p \leq .05$ FDR corrected).

Brain region	MNI coordinates			Peak T-value	p value	Cluster size (Voxels)
	x	y	z			
ATL	**-36**	**12**	**-28**	**30.4**	**.000**	**3021**
Anterior inferior temporal gyrus	-46	-2	-38	11.56		
Anterior hippocampus	-22	-4	-20	12.39		
Anterior parahippocampal gyrus	-22	-18	-20	11.88		
IFG (Pars orbitalis)	-28	20	-20	10.31		
Anterior MTG	**56**	**-8**	**-16**	**12.67**	**.000**	**1828**
	58	4	-24	12.09		
Fusiform gyrus	32	-10	-32	12.36		
Anterior inferior temporal gyrus	52	6	-36	10.3		
	38	2	-44	7.45		
ATL	40	14	-38	10.33		

Supplementary table 8 : rs-fMRI network anchored to the left pMTG in svPPA ($p \leq .05$ FDR corrected).

Brain region	MNI coordinates			Peak T-value	p value	Cluster size (Voxels)
	x	y	z			
pMTG	**-66**	**-44**	**4**	**43.12**	**.000**	**5319**
	-58	-62	12	21.78		
	-46	-30	2	9.69		
Anterior MTG	-64	-20	2	11.42		
Anterior superior temporal gyrus	-50	-12	-6	10.18		
ATL	-52	12	-10	9.6		
Anterior cingulate cortex	**8**	**46**	**28**	**12.22**	**.026**	**101**
Posterior superior temporal gyrus	**54**	**-26**	**0**	**10.37**	**.000**	**366**
Posterior cingulate cortex	**6**	**-44**	**26**	**9.53**	**.001**	**236**
	-10	-46	24	7.55		
Insula	**28**	**22**	**-8**	**9.47**	**.000**	**308**
Putamen	16	14	-10	7.37		
	28	4	-6	6.71		
Anterior hippocampus	22	-8	-16	4.73		
Superior frontal gyrus	**-26**	**50**	**22**	**8.5**	**.004**	**157**
	-14	48	38	6.24		
	-14	60	22	4.85		
IFG (Pars triangularis)	**-38**	**18**	**22**	**8.09**	**.000**	**283**
	-50	22	22	6.65		
Precuneus	**2**	**-56**	**40**	**6.49**	**.001**	**206**

Supplementary table 9 : rs-fMRI network anchored to the left IFG in svPPA ($p \leq .05$ FDR corrected).

Brain region	MNI coordinates			Peak T-value	p value	Cluster size (Voxels)
	x	y	z			
IFG (Pars triangularis)	**-54**	**22**	**2**	**44.12**	**.000**	**6815**
	-46	20	16	18.26		
IFG (Pars orbitalis)	-52	40	-2	16.73		
Middle frontal gyrus	-38	50	2	17.58		
Superior frontal gyrus	-22	54	10	10.6		
Anterior MTG	-66	-18	2	16.99		
	-68	-40	8	14.16		
ATL	-54	10	-14	11.14		
pMTG	-62	-52	-6	14.09		
Cerebellum – Crus2	**18**	**-74**	**-36**	**14.77**	**.000**	**232**
Supplementary motor area	**2**	**26**	**56**	**9.99**	**.000**	**855**
	-4	6	74	6.32		
Superior frontal gyrus	-14	24	56	8.65		
	-20	22	44	7.1		
	-18	36	44	6.84		
Middle frontal gyrus	-36	6	58	7.37		
Putamen	**28**	**8**	**-8**	**7.91**	**.000**	**249**
IFG (Pars orbitalis)	46	32	-6	7.44		
Insula	40	16	-2	6.88		

Chapitre III: Discussion Générale

1. Résumé et interprétation générale des résultats

La présente thèse comportait deux volets. Le premier volet de la thèse visait à mieux caractériser le principal déficit langagier des patients MA, soit l'anomie, ainsi qu'à clarifier ses bases cognitives et cérébrales (article #1). Le deuxième volet de la thèse visait à démontrer que la MA est un syndrome de déconnexion (article #2), et que cette déconnexion touchait également le réseau cérébral responsable du langage (article #3).

Globalement, nous avons d'abord caractérisé le profil anomique des patients MA en révélant une atteinte prédominante pour la dénomination des ESU, et particulièrement des personnes célèbres, en comparaison aux entités non uniques. L'investigation des bases cognitives et cérébrales de cette anomie a mis en relief un trouble mixte, c'est-à-dire une atteinte combinée de l'accès lexical et de la sémantique chez les patients MA. Ensuite, nous avons apporté un appui à l'hypothèse de la MA comme syndrome de déconnexion, en démontrant un profil de diminution de la connectivité structurelle dans les sous-composantes du RMD et une hausse de la connectivité structurelle dans les réseaux de la saillance et du contrôle exécutif. Finalement, il a été possible de confirmer que les atteintes de connectivité sont également présentes à l'extérieur du RMD, soit dans le réseau cérébral langagier. Les atteintes en connectivité fonctionnelle relevées dans le réseau du langage, qui ont principalement été observés dans le GTPM gauche et LTA gauche, sont également compatibles avec la nature mixte de l'anomie des patients MA.

Ainsi, dans cette discussion, nous reviendrons d'abord sur les trouvailles majeures des trois articles. Nous décrirons ensuite les implications cliniques, théoriques et méthodologiques de cette thèse. Puis, les limites des études, les contributions originales de la thèse et les avenues de recherche future seront abordées. Finalement, une conclusion générale sera énoncée.

1.1 Volet #1

1.1.1 Article #1

Le premier objectif de l'article #1 était de caractériser et de comparer le profil d'anomie des patients MA, des patients vs-APP et des sujets contrôles en évaluant leur dénomination

d'entités non uniques et d'ESU (personnes, lieux et logos célèbres). Les deux hypothèses associées à cet objectif ont été confirmées. Tout d'abord, les patients MA ont présenté une performance significativement plus faible en comparaison aux sujets contrôles, mais significativement plus élevée en comparaison aux patients vs-APP (qui présentent une détérioration progressive de la mémoire sémantique), dans toutes les tâches de dénomination. Les patients MA et vs-APP étaient également plus atteints en dénomination d'ESU en comparaison à la dénomination d'entités non uniques. Cette atteinte était particulièrement plus importante pour les personnes célèbres que les lieux ou logos célèbres, ce qui suggère une prosopoanomie dans la MA.

Le deuxième objectif de l'article #1 était de caractériser et de comparer les connaissances sémantiques portant sur les ESU à dénommer chez les patients MA, les patients vs-APP et les sujets contrôles afin de clarifier les bases cognitives de leur anomie (trouble sémantique vs. trouble d'accès lexical). Nos résultats comportementaux suggèrent une base cognitive mixte de l'anomie dans la MA. Tout d'abord, les patients MA ont montré une performance préservée au point de vue des connaissances sémantiques générales, malgré une performance déficitaire en dénomination. Toutefois, les connaissances sémantiques spécifiques chez les patients MA étaient légèrement atteintes, suggérant également une contribution sémantique. Ce profil contrastait avec celui des patients vs-APP, qui étaient atteints tant au point de vue des connaissances sémantiques générales que spécifiques, en accord avec la nature sémantique de leur anomie.

Le troisième objectif de l'article #1 était de clarifier les bases cérébrales de l'anomie des patients MA en termes d'atrophie de la matière grise (dommage au LTA gauche vs. dommage à la jonction temporo-pariétale gauche). Le profil d'anomie tel qu'évalué en dénomination de personnes célèbres chez les patients MA corrélait avec l'atrophie de la matière grise dans la jonction temporo-pariétale gauche (une région associée avec l'accès lexical), et ne corrélait pas avec l'atrophie de la matière grise dans le LTA gauche (une région associée à la sémantique). Ainsi, en combinant les résultats des analyses comportementales et de neuroimagerie, l'article #1 a permis de souligner l'apport majeur du trouble d'accès lexical dans l'anomie chez les patients MA, mais suggère tout de même un trouble de nature mixte en raison des lacunes sémantiques observées chez ces patients pour les connaissances spécifiques.

1.2 Volet #2

1.2.1 Article #2

L'objectif de l'article #2 était de caractériser et comparer la connectivité cérébrale des RCSMG (« midline core » du RMD, « medial temporal lobe subsystem » du RMD, réseau de la saillance, réseau du contrôle exécutif) d'un grand échantillon de patients MA dans les premiers stades de la maladie, en comparaison aux sujets contrôles. La première hypothèse était qu'une baisse de connectivité structurelle serait observée dans les deux sous-composantes du RMD chez les patients MA, en comparaison aux sujets contrôles. Cette hypothèse a été confirmée et les résultats ont principalement mis en relief une isolation structurelle du lobe temporal médian ainsi que du cortex cingulaire postérieur dans la MA. La deuxième hypothèse était qu'une augmentation de la connectivité structurelle serait observée dans les réseaux de la saillance et du contrôle exécutif chez les patients MA, en comparaison aux sujets contrôles. Cette hypothèse a été partiellement confirmée : malgré le fait qu'aucune différence significative n'ait émergé entre les réseaux des patients MA et des sujets contrôles, une analyse qualitative a permis de mettre en relief que les réseaux de la saillance et du contrôle exécutif étaient plus étendus en comparaison aux sujets contrôles. Dans l'ensemble, cette étude a permis d'apporter un soutien important à l'hypothèse concevant la MA en tant que syndrome de déconnexion ainsi qu'à mettre en relief les dynamiques d'augmentation/diminution de connectivité à l'aide d'une approche de neuroimagerie complémentaire.

1.2.2 Article #3

L'objectif de l'article #3 était de caractériser et comparer la connectivité cérébrale fonctionnelle du réseau du langage (investiguée avec des régions d'intérêt dans le GFI gauche, le GTPM gauche et le LTA gauche) chez les patients MA, vs-APP et les sujets contrôles. L'hypothèse était que les patients MA présenteraient principalement une diminution de la connectivité fonctionnelle du GTPM gauche, alors que les patients vs-APP présenteraient principalement une diminution de la connectivité fonctionnelle du LTA gauche. Ces hypothèses ont été confirmées, bien que l'investigation du profil de connectivité fonctionnelle chez les patients MA ait mis en relief des diminutions de connectivité fonctionnelle supplémentaires.

Tout d'abord, les patients MA présentaient une diminution de la connectivité fonctionnelle interhémisphérique entre le GTPM gauche et sa contrepartie controlatérale homotopique. Le LTA gauche présentait également une connectivité fonctionnelle réduite avec le GTPM droit et le gyrus angulaire droit. Les patients vs-APP présentaient quant à eux une isolation fonctionnelle quasi complète du LTA gauche (incluant avec le GTPM gauche), alors que le GTPM gauche, le GFI gauche et les autres régions du réseau du langage demeuraient interconnectées. Dans l'ensemble, ces résultats suggèrent que les déficits langagiers présentés par les patients MA et vs-APP semblent être accompagnés d'une déconnexion fonctionnelle dans le réseau cérébral du langage. Toutefois, ces patrons de déconnexion sont distincts entre les deux maladies et semblent compatibles avec le trouble mixte chez les patients MA (trouble d'accès lexical et trouble sémantique) et le trouble sémantique chez les patients vs-APP.

2. Implications cliniques

2.1 La caractérisation du profil anomique des patients MA et vs-APP : l'importance d'investiguer la dénomination des entités sémantiquement uniques (ESU)

Tout d'abord, l'article #1 a permis de mettre en évidence l'utilité des tâches de dénomination d'ESU dans la détection de l'anomie chez les patients MA. En effet, nos résultats suggèrent que l'anomie est plus sévère pour ce type d'entités, en comparaison aux entités non uniques, ce qui est en accord avec plusieurs études précédentes (Delazer et al., 2003; Joubert et al., 2010; Joubert et al., 2008; Semenza, Mondini, et al., 2003; Thompson et al., 2002). Un des grands intérêts des chercheurs et cliniciens spécialisés auprès des personnes âgées est d'identifier des outils cliniques de plus en plus sensibles aux troubles cognitifs, dont l'anomie, et ce dans le but de faciliter un diagnostic le plus précoce possible. À ce niveau, le test de dénomination de personnes célèbres permettait de détecter un déficit de dénomination (moins deux écart-types sous la moyenne des sujets contrôles) chez 69,2% des patients MA, en comparaison à 46,2% pour le test d'entités non uniques (*Boston Naming Test*).

En plus de permettre une meilleure détection de l'anomie chez les patients MA, l'investigation de la dénomination de plusieurs types d'ESU a permis de caractériser des profils anomiques distincts dans deux populations cliniques (MA et vs-APP), ce qui peut contribuer à un meilleur diagnostic différentiel. Afin de vérifier si les troubles de l'anomie se limitaient aux personnes célèbres ou s'ils étaient généralisés à tous les ESU, nous avons en effet investigué les lieux et logos célèbres afin de voir si certains types d'entités étaient spécifiquement atteints dans chaque maladie. Tout d'abord, sur le plan inter-groupe et pour tous les types d'entités, les patients vs-APP étaient les plus significativement atteints en comparaison aux sujets contrôles et aux patients MA, et les patients MA étaient significativement atteints en comparaison aux sujets contrôles. Sur le plan intra-groupe, les patients MA présentaient une vulnérabilité plus grande en dénomination de personnes célèbres en comparaison aux autres types d'entités, alors que les patients vs-APP étaient particulièrement atteints pour les personnes célèbres et les lieux célèbres.

2.2 La base cognitive sous-jacente de l'anomie chez les patients MA et vs-APP : l'importance d'investiguer les connaissances sémantiques

Bien que les patients MA et vs-APP diffèrent significativement en termes de la sévérité et de la spécificité de leurs déficits en dénomination dans des études de groupes, une grande hétérogénéité peut être observée chez ces patients au point de vue intra-individuel. Ceci fait en sorte que lorsque chaque patient est considéré individuellement, tel qu'en pratique clinique courante, le score à une tâche de dénomination peut tomber dans une zone grise (par exemple, chez un patient MA avec une anomie très sévère). Une des façons de surmonter ce défi clinique est d'également investiguer la base cognitive de l'anomie chez ces patients, ce que nous avons fait en investiguant les connaissances sémantiques des entités à nommer. Dans ce contexte, un patient avec un déficit de dénomination accompagné d'une performance adéquate sur le plan des connaissances sémantiques présenterait un trouble d'accès lexical, alors qu'un patient avec un déficit dans ces deux composantes présenterait un trouble de nature sémantique.

Ainsi, les résultats de l'article #1 suggèrent un trouble sémantique net chez les patients vs-APP, ceux-ci étant atteints tant au point de vue de la dénomination que des connaissances sémantiques générales et spécifiques. Les patients MA était quant à eux atteints en dénomination, mais présentaient un profil plus nuancé sur le plan des connaissances sémantiques. En effet, leurs connaissances sémantiques générales (nommer le domaine de la personne entre les arts, les sports ou la politique) étaient aussi bonnes que les sujets contrôles. Leurs connaissances sémantiques spécifiques (nommer la profession ou la raison de la célébrité précise) étaient toutefois significativement inférieures aux sujets contrôles, bien que le niveau de performance demeurait relativement adéquat en comparaison à la performance en dénomination (89,7% de bonnes réponses en connaissances sémantiques spécifiques versus 59% en dénomination). Ainsi, l'article #1 a permis de souligner l'apport majeur du trouble d'accès lexical dans l'anomie chez les patients MA, mais suggère tout de même un trouble de nature mixte en raison des lacunes sémantiques observées chez ces patients pour les connaissances spécifiques. Ces résultats sont ainsi en accord avec certains auteurs ayant suggéré l'hypothèse que l'anomie était sous-tendue par une combinaison d'un trouble sémantique et d'un trouble d'accès lexical (Balthazar et al., 2008; Delazer et al., 2003; Reilly et al., 2011; Rich et al., 2002; Salehi et al., 2017) et permettent de réconcilier les nombreuses études ayant supporté chacune des deux hypothèses.

Par ailleurs, le profil des patients MA est suggestif d'une prosopoanomie, soit une anomie spécifique à la catégorie des visages (Carney & Temple, 1993; Geva, Moscovitch, & Leach, 1997; Semenza, Sartori, & D'Andrea, 2003). Il s'agit d'une condition dans laquelle la dénomination d'une personne à partir de son visage est atteinte, mais dans laquelle la perception des visages et l'accès aux connaissances sémantiques ou aux informations autobiographiques sont relativement préservées. Nous faisons l'hypothèse que la vulnérabilité sélective des patients MA aux personnes célèbres serait due au fait que parmi les ESU investigués dans cette étude, les personnes célèbres sont celles qui présentent l'association la moins fréquente avec leur référant. Par exemple, le nom de plusieurs lieux et logos célèbres inclut un nom commun décrivant leur nature (ex. tour dans Tour Eiffel). Par ailleurs, il a été démontré que l'accès aux noms propres est plus ardu (Bredart, 1993; Bredart, Brennen, & Valentine, 2002; Semenza, Nichelli, & Gamboz, 1996) et requerrait davantage de ressources métaboliques (Gorno-Tempini

& Price, 2001; Ross & Olson, 2012; Semenza, 2009). Dans le contexte de maladies neurodégénératives dont les ressources cérébrales sont limitées, cette disparité entre les ESU et les entités non uniques pourrait être amplifiée. Une autre hypothèse pour expliquer le déficit prédominant en dénomination de personnes célèbres dans la MA aurait pu être un déficit visuo-perceptif. Par exemple, il a été démontré que la perception des visages serait affectée à certains niveaux dans la MA (Lavallee et al., 2016). Néanmoins, dans notre échantillon, les patients MA ne présentaient pas de déficits en perception des visages, tel que mesuré avec le *Benton facial recognition test*. De plus, les résultats des patients MA sur le plan des connaissances sémantiques générales confirment que ceux-ci reconnaissaient les visages célèbres qui leur ont été présentés.

3. Implications théoriques

3.1 La MA comme syndrome de déconnexion et le rôle clé du RMD

Les articles #2 et #3 de cette thèse apportent également, par le biais de deux méthodes de neuroimagerie différentes, un appui considérable à l'hypothèse de la MA en tant que syndrome de déconnexion. En accord avec la théorie de la dégénérescence des réseaux, les maladies neurodégénératives, incluant la MA, cibleraient spécifiquement des réseaux fonctionnels à grande échelle qui sont formés chez les humains en santé durant leur développement (Seeley et al., 2009). Cette déconnexion au sein de réseaux déterminerait ensuite le développement et la détérioration de symptômes cognitifs avec la progression de la maladie (Palop, Chin, & Mucke, 2006; Selkoe, 2002). Dans la MA, plusieurs chercheurs spéculent que l'accumulation d'Aβ serait le déclencheur d'une série d'événements menant à des dysfonctions neuronales, à la neurodégénérescence et aux pertes cognitives (Jack, Lowe, et al., 2008; Morris et al., 2009; Walsh & Selkoe, 2007). De façon intéressante, les patients MA présentent un patron de plaques Aβ qui chevauche remarquablement les régions du RMD (Buckner et al., 2005), ce qui suggère un lien possible entre l'Aβ et la connectivité fonctionnelle de ce réseau. Plusieurs études ont tenté d'objectiver cette possibilité et ont conclu qu'en effet, la connectivité

fonctionnelle du RMD était altérée par la présence de plaques Aβ (Mormino et al., 2011; Myers et al., 2014).

Dans ce contexte, l'article #2 de cette thèse visait à investiguer la théorie de la MA en tant que syndrome de déconnexion à l'aide d'une approche de neuroimagerie de la connectivité cérébrale complémentaire, soit l'approche des RCSMG. Afin de combler certaines lacunes des études précédentes, un grand échantillon caractérisé sur le plan neuropathologique a été utilisé. Ainsi, les résultats de cette étude indiquent clairement que les patients MA, dans les premiers stades de la maladie et chez qui une présence d'Aβ est confirmée, sont caractérisés par une réduction sélective de l'association structurelle des régions formant le RMD. Nos résultats, obtenus avec une technique de connectivité structurelle, sont compatibles avec les études en connectivité fonctionnelle ayant également démontré une déconnexion du RMD dans la MA (Badhwar et al., 2017). Plus précisément, l'article #2 démontre que la déconnexion structurelle la plus prédominante dans la MA surgirait dans le sous-système du lobe temporal médian du RMD. Cette région montre une diminution de son association structurelle avec le cortex préfrontal médian ainsi qu'avec le précuneus. Bien que notre étude n'ait pas investigué spécifiquement l'impact de cette déconnexion sur le fonctionnement cognitif des patients MA, il a été suggéré que l'isolation de la région hippocampique dans la MA pourrait être à la source du symptôme principal dans la MA, soit un déficit progressif de la mémoire épisodique. En effet, une diminution de la connectivité fonctionnelle entre l'hippocampe et le cortex préfrontal médian a déjà été rapporté dans des études précédentes (Wang et al., 2006), et il semblerait que celle-ci soit associée à des déficits d'encodage et de consolidation en mémoire épisodique (Grady, Furey, Pietrini, Horwitz, & Rapoport, 2001). La déconnexion entre l'hippocampe et le précuneus a également déjà été rapportée et a même été suggérée comme un biomarqueur des premiers stades de la MA (Kim, Kim, & Lee, 2013). Bien qu'aucune étude n'ait discuté de l'impact clinique de la déconnexion entre ces deux régions spécifiquement, il est probable que celle-ci soit impliquée dans les déficits mnésiques et visuo-spatiaux des patients MA, étant donné le rôle du précuneus dans ces fonctions cognitives (Cavanna & Trimble, 2006). Finalement, une association structurelle diminuée a également été observée dans le « midline core » du RMD chez les patients MA, plus précisément entre le cortex cingulaire postérieur gauche et le gyrus orbitofrontal inférieur. L'activité cérébrale combinée de ces deux régions est associée à la mémoire à long terme (Liu, Dong, Chen, & Xue, 2013), ce qui suggère encore une

fois que les déconnexions observées dans le RMD sont associées aux symptômes principaux de la maladie.

Enfin, les mécanismes biologiques potentiels des syndromes de déconnexion sont encore un sujet de débat. Une étude par Zhou et collaborateurs apporte toutefois un soutien important à la théorie de la propagation transneuronale, selon laquelle les agents toxiques (par exemple les protéines) se propagent le long des neurones interconnectés (Zhou, Gennatas, Kramer, Miller, & Seeley, 2012).

3.2 Connectivité structurelle dans les réseaux de la saillance et du contrôle exécutif dans la MA : mécanismes compensatoires?

La spécificité du patron de déconnexion du RMD chez les patients MA a été confirmée par une tendance à une augmentation de la connectivité structurelle dans les réseaux de la saillance et du contrôle exécutif. Ce résultat semble compatible avec l'observation de plusieurs auteurs suggérant que la MA est associée avec des patrons de connectivité opposés entre le RMD (un réseau relativement postérieur) et les réseaux de la saillance et du contrôle exécutif (des réseaux relativement frontaux) (Agosta et al., 2012; Filippi et al., 2013; Zhou et al., 2010). Ce patron serait particulièrement intéressant sur le plan clinique, car les patients MA et les patients atteints de la variante comportementale de la démence frontotemporale présenteraient une double dissociation (hausse de connectivité dans le RMD et baisse de connectivité dans les réseaux frontaux chez les patients MA et le patron inverse chez les patients atteints de la variante comportementale de la démence frontotemporale). Néanmoins, très peu d'études ont investigué l'impact cognitif des hausses de connectivité dans les réseaux de la saillance et du contrôle exécutif chez les patients MA.

Ceci est particulièrement vrai pour le réseau de la saillance, dans lequel seule une étude a relevé des corrélations positives entre la connectivité fonctionnelle du réseau et un score plus élevé à un test de dépistage de la démence (Mini-Mental State Exam) (X. He et al., 2014). Ainsi, l'impact de cette hausse de connectivité sur une fonction cognitive précise demeure relativement inconnu. Chez les patients avec la variante comportementale de la démence frontotemporale, la diminution de la connectivité dans le réseau de la saillance semble toutefois associée à des

altérations de la sensibilité socio-émotionnelle (Toller et al., 2018). Il serait ainsi intéressant d'investiguer les relations entre la baisse de la connectivité dans le réseau de la saillance et la sensibilité socio-émotionnelle chez les patients MA.

Pour le réseau du contrôle exécutif, alors que certains auteurs n'ont pas identifié de corrélations significatives entre la connectivité de ce réseau et la cognition (Weiler et al., 2014), d'autres ont identifié une association positive entre une hausse de la connectivité dans le réseau du contrôle exécutif et des scores à des tâches exécutives et visuo-spatiales (Agosta et al., 2012; Gour et al., 2014). Ces observations préliminaires semblent à suggérer que ces réseaux pourraient être associés à des mécanismes compensatoires dans la MA.

3.3 Une déconnexion qui s'étend à l'extérieur du RMD : l'impact de la MA sur le réseau cérébral du langage

Bien que la majorité des études en connectivité chez les patients MA se soient focalisées sur le RMD, de plus en plus d'études suggèrent que la baisse de la connectivité n'est pas restreinte à ce réseau chez les patients MA. Ceci n'est guère surprenant considérant l'hétérogénéité de la symptomatologie de la MA, qui peut toucher le domaine mnésique, mais également exécutif, visuo-spatial et d'intérêt dans cette thèse, langagier. Il est ainsi critique de s'intéresser à la connectivité cérébrale des réseaux autres que le RMD, considérant que le champ des neurosciences tend de plus en plus à expliquer les mécanismes cérébraux sous-tendant les déficits cognitifs en termes de changement dans des réseaux cérébraux.

L'article #3 de cette thèse contribue de façon majeure à ces théories en démontrant que les patients avec MA, qui présentent des symptômes langagiers, présentent également une diminution de la connectivité structurelle au sein du réseau du langage. Ces résultats ont des implications théoriques significatives. Dans un premier temps, elles nous aident à comprendre l'impact de la MA sur l'architecture du réseau du langage, et dans un deuxième temps, elles peuvent nous éclairer sur la base sous-jacente des troubles langagiers, incluant l'anomie.

3.3.1. L'impact de la MA sur l'architecture du réseau du langage

Les résultats de l'article #3 suggèrent que la MA est associée à des altérations significatives du réseau cérébral langagier, et ce, dans deux des trois régions clés, soit le GTPM gauche et le LTA gauche, mais pas dans le GFI.

Tout d'abord, il semble que la MA affecte la connectivité fonctionnelle entre le GTPM gauche et le GTPM droit, un résultat rapporté dans deux autres études précédentes (Weiler et al., 2014; Whitwell et al., 2015), mais dont l'impact est peu compris jusqu'à maintenant. De façon intéressante, une étude en IRMf pendant la réalisation d'une tâche d'associations sémantiques auprès de patients MA a démontré que ceux-ci présentent une activité diminuée dans le GTPM gauche accompagnée d'une activité augmentée dans le GTPM droit (Nelissen et al., 2007). Cette hausse de la connectivité dans le GTPM droit corrélait par ailleurs positivement avec la performance dans une tâche de dénomination. Ainsi, une des possibilités est qu'à la suite d'une altération fonctionnelle du réseau langagier fortement latéralisé dans l'hémisphère gauche, des mécanismes compensatoires émergent dans l'hémisphère droit des patients MA. Toutefois, des études futures devraient investiguer cette hypothèse préliminaire.

De plus, les résultats de l'article #3 suggère que le LTA gauche montrait également une déconnexion fonctionnelle avec le GTPM droit, en plus d'avec le gyrus angulaire droit. Le gyrus angulaire droit est une région reconnue comme faisant partie du RMD (Buckner et al., 2005; Raichle et al., 2001) qui, tel que démontré dans l'article #2 de cette thèse, est le réseau atteint de façon prédominante dans la MA. Ceci pourrait suggérer que la déconnexion fonctionnelle du réseau langagier dans la MA n'est pas complètement indépendante du RMD. Par ailleurs, ce résultat est compatible avec le fait que le RMD et le réseau langagier sont interreliés chez les sujets contrôles (Humphreys, Hoffman, Visser, Binney, & Lambon Ralph, 2015; Seghier, Fagan, & Price, 2010; Xu, Lin, Han, He, & Bi, 2016). En effet, le LTA gauche serait une région secondaire du RMD, en plus d'être une région clé du réseau langagier. Ceci est compatible avec les réseaux obtenus dans l'article #3 chez les sujets contrôles, chez qui ces deux régions étaient significativement associées au point de vue fonctionnel. Mis ensemble, ceci suggère que les altérations du RMD pourrait être associées aux altérations du réseau langagier chez les patients MA, ce qui pourrait contribuer aux symptômes langagiers.

3.3.2 L'apport de la neuroimagerie du réseau langagier dans notre compréhension des symptômes langagiers dans la MA

La présente thèse documente l'importance de l'atrophie de la matière grise et de la connectivité fonctionnelle de la jonction temporo-pariétale gauche (incluant le GTPM) ainsi que de la connectivité fonctionnelle du LTA gauche dans la MA. En effet, dans l'article #1, les analyses de neuroimagerie ont montré que les scores de dénomination des personnes célèbres chez les patients MA corrélaient avec le volume de la matière grise dans la jonction temporo-pariétale gauche (une région associée fonctionnellement à l'accès lexical), mais pas avec le volume de la matière grise dans le LTA gauche (une région fonctionnellement associée à la sémantique). Dans l'article #3, une diminution de la connectivité fonctionnelle a été observée dans le GTPM gauche et le LTA gauche chez des patients MA avec symptômes langagiers.

Ainsi, l'investigation des bases cérébrales des troubles langagiers dans la MA, et plus principalement de l'anomie, permet également de nous éclairer au point de vue des bases cognitives. Dans l'ensemble, nos résultats comportementaux et de neuroimagerie, combinés aux nombreuses études précédentes supportant chacune des deux bases cognitives suggérées, semblent confirmer la nature mixte du trouble anomique chez les patients MA.

4. Considérations méthodologiques

4.1 Connectivité fonctionnelle et connectivité structurelle : des approches complémentaires

La popularité des approches de neuroimagerie de la connectivité cérébrale a grandement augmenté dans les dernières années, ce qui a mené à une évolution et un raffinement des techniques. Malgré tout, en raison de leur développement relativement récent et de leurs limites respectives, les résultats obtenus avec de telles techniques nécessitent d'être répliqués avec d'autres approches de neuroimagerie de la connectivité.

Tout d'abord, les RCSMG obtenus dans l'étude #2 chez les sujets contrôles montraient un bon chevauchement avec la description fonctionnelle de chacun des réseaux obtenus en IRMf-rs, ce qui est compatible avec une étude ayant comparé formellement les réseaux issus

des deux techniques (Seeley et al., 2009). Ceci peut être dû au fait que des décharges neuronales synchrones (telles qu'elles surviennent dans un réseau fonctionnel) promeuvent une synaptogénèse dans les réseaux cérébraux, tel que démontré dans des études physiologiques (Bi & Poo, 1999; Katz & Shatz, 1996). Nos résultats chez les patients MA sur le plan des RCSMG concordaient d'autant plus avec les résultats d'études précédentes en IRMf-rs, démontrant qu'il s'agit d'une technique efficace pour comprendre les patrons de connectivité dans la MA.

Dans l'étude #3 utilisant l'IRMf-rs, il peut être intéressant de comparer nos résultats avec ceux des études en imagerie de diffusion, puisqu'aucune étude n'a investigué le réseau du langage avec la technique des RCSMG. En effet, il a été démontré que les régions présentant des modulations corrélées de leur signal dépendant du niveau d'oxygène sanguin durant le repos sont également connectées structurellement par des faisceaux de matière blanche (Greicius, Supekar, Menon, & Dougherty, 2009; Lemaire et al., 2013; Morgan, Mishra, Newton, Gore, & Ding, 2009; Turken & Dronkers, 2011). Dans la MA, tel que rapporté dans la section 2.3 de l'introduction, une diminution de l'intégrité des fibres de matière blanche est prédominante dans le faisceau unciné, le faisceau longitudinal supérieur, le cingulum postérieur, le splénium du corps calleux ainsi que dans la matière blanche du lobe temporal et du lobe pariétal. Les résultats de l'article #3, dans laquelle une diminution de la connectivité fonctionnelle était prédominante entre le GTPM gauche et le GTPM droit, sont en concordance avec la diminution de l'intégrité de la matière blanche dans le splénium du corps calleux, qui connecte les régions temporo-pariétales bilatéralement. Des études futures pourraient investiguer plus précisément entre les symptômes langagiers et l'intégrité de la matière blanche dans le splénium chez les patients MA.

En conclusion, les résultats obtenus dans la présente thèse semblent à la fois concorder avec les résultats obtenus dans des études utilisant d'autres techniques de neuroimagerie et apporter de nouvelles informations sur les phénomènes de déconnexion survenant dans la MA. Il est important de considérer que chacune de ces méthodes mesure des paramètres distincts et ont ainsi un apport unique ainsi que des forces et limites propres. Par exemple, les études en RCSMG ont l'avantage de requérir seulement une image anatomique qui est acquise dans tous les types d'examens IRM. Toutefois, les études utilisant cette technique requièrent un grand nombre de sujets puisqu'il s'agit d'une technique évaluant la covariance des volumes de la matière grise au sein de la population, et non intra-individuellement. À l'inverse, les études en

IRMf-rs nécessitent une séquence IRM spécialisée, mais les études utilisant cette technique n'ont pas nécessairement besoin d'un échantillon de grande taille puisqu'elle nous fournit des indices de connectivité intra-inviduelle. Malgré tout, elle souffre de certaines limites, dont le traitement du bruit dans les données IRMf qui peuvent grandement affecter les indices de connectivité fonctionnelle.

5. Limites des études

Premièrement, une des limites de l'étude #1 est reliée au fait que les items choisis pour les tests de dénomination n'étaient pas contrôlés au point de vue de leurs caractéristiques psycholinguistiques (entre les trois tâches de dénomination d'ESU : personnes, lieux et logos célèbres). Bien que nous ayons contrôlé pour la difficulté globale de chaque tâche, c'est-à-dire que la performance était équivalente dans ces trois tâches chez les sujets contrôles, il aurait été préférable de balancer les items sur des variables psycholinguistiques telles que la fréquence, la familiarité et l'accord sur le nom. Il a été démontré que ces variables sont des prédicteurs importants de l'exactitude et de la vitesse en dénomination d'images chez les individus atteints de maladies neurodégénératives (Astell & Harley, 1998; Hirsh & Funnell, 1995; Kremin et al., 2001; Montanes, Goldblum, & Boller, 1996; Taylor, 1998; Tippett, Meier, Blackwood, & Diaz-Asper, 2007).

Deuxièmement, une des limites des études #1 et #3 concerne la petite taille de l'échantillon. Ceci est principalement attribuable à la rareté des patients avec vs-APP. Bien que nous ayons malgré tout eu la puissance statistique nécessaire pour détecter des différences significatives entre les groupes, un échantillon plus grand aurait assuré une meilleure validité externe.

Troisièmement, toujours dans les études #1 et #3, les patients MA n'étaient pas caractérisés sur le plan neuropathologique comme dans l'étude 2, dans laquelle les patients avaient subi une ponction lombaire à la recherche des biomarqueurs de la MA dans le LCR. Les critères diagnostiques de la MA suggère en effet l'utilisation des biomarqueurs pour passer d'un diagnostic de « MA probable » à « MA probable avec un niveau de certitude augmenté ». De plus, les nouvelles recommandations pour le diagnostic de la MA dans un contexte de recherche accorde une importance beaucoup plus élevée au diagnostic neuropathologique de la MA,

suggérant une définition biologique de la maladie basée entièrement sur les biomarqueurs d'Aβ, tau et de la neurodégénérescence (Jack et al., 2018).

Quatrièmement, dans les études #2 et #3, la connectivité structurelle et fonctionnelle des réseaux n'étaient pas corrélés avec les scores cognitifs. Ceci est dû au fait que la technique des RCSMG est une technique investiguant la covariance entre des volumes de matière grise sur l'ensemble de la population étudiée. Ainsi, cette technique ne fournit pas d'indice de connectivité du réseau pour chaque sujet, ne permettant pas ensuite de réaliser des analyses de corrélation. Dans l'étude 3, ceci est dû à la petite taille d'échantillon dans chaque groupe.

6. Contributions originales de la thèse

La présente thèse apporte des contributions originales dans le domaine des maladies neurodégénératives, de l'étude du langage et de la neurobiologie du langage, ainsi que sur le plan de la neuroimagerie. Plusieurs contributions ont déjà été discutées dans ce chapitre. Tout d'abord, l'article #1 est le premier à avoir étendu l'étude des ESU aux lieux et logos célèbres dans les maladies neurodégénératives et a également mené au développement de tâches de dénomination d'ESU appropriées pour les personnes âgées Québécoises et francophones. L'article #2 est le premier à utiliser la technique des RCSMG chez les patients MA et parmi les études de connectivité ayant utilisé un très grand échantillon caractérisé au point de vue des biomarqueurs du LCR. L'article #3 est le premier à investiguer l'entièreté du réseau du langage chez les patients MA et vs-APP.

Outre celles-ci, une des contributions majeures de cette thèse est le fait qu'elle a permis d'approfondir nos connaissances sur les comparaisons entre les patients MA et les patients vs-APP. Malgré le chevauchement important entre ces deux populations, tant au point de vue symptomatologique qu'au point de vue cérébral, un nombre relativement faible d'études ont directement comparé ces deux populations. Pourtant, le diagnostic différentiel peut être difficile dans certains cas. Outre l'anomie et les troubles sémantiques qui ont été discutés dans cette thèse, qui définissent la vs-APP mais qui sont également présents dans la MA, les patients vs-APP peuvent présenter certains symptômes qui sont plus fréquemment associés à la MA. Par exemple, il a été démontré que ceux-ci peuvent présenter des troubles en mémoire épisodique verbale (Eikelboom et al., 2018), des troubles praxiques (Johnen, Reul, Wiendl, Meuth, &

Duning, 2018) et même des troubles visuo-spatiaux (Watson et al., 2018). Ainsi, il est important de comparer directement ces deux maladies et de terminer les bases cognitives sous-jacentes à leurs déficits communs afin de faciliter leur diagnostic différentiel.

7. Avenues de recherches futures

Tout d'abord, peu d'études ont étudié l'anomie de façon longitudinale chez les patients MA. Ceci apparaît comme une avenue de recherche intéressante pour approfondir notre connaissance des causes cognitives de l'anomie dans la MA. Une étude récente a suggéré que la base cognitive principale de l'anomie dans les premiers stades de la maladie serait un trouble d'accès lexical, alors que le trouble sémantique serait prédominant dans les stades plus avancés de la maladie (Salehi et al., 2017). Il en est de même pour l'étude des réseaux cérébraux, que nous avons investigué auprès de patients MA dans les premiers stades de la maladie. Le peu d'études longitudinales ayant investigué ces réseaux dans la MA suggèrent que leur intégrité pourrait être modulée selon la progression de la maladie (Damoiseaux, Prater, Miller, & Greicius, 2012; Zhan et al., 2016).

Ensuite, nous avons utilisé la vs-APP comme modèle de l'anomie sémantique et comme groupe de comparaison à notre groupe de patients MA. Afin d'investiguer de façon plus exhaustive les bases cognitives possibles de l'anomie, il serait intéressant de comparer les patients MA à d'autres maladies neurodégénératives dans lesquelles les patients peuvent présenter une anomie. Entre autres, deux des formes non-amnésiques de la MA, la variante logopénique de l'aphasie primaire progressive et l'atrophie corticale postérieure, peuvent également présenter des troubles de dénomination. Toutefois, il est suggéré que l'anomie chez les patients atteints de la variante logopénique de l'aphasie primaire serait sous-tendue par un trouble d'accès lexical ainsi qu'un trouble phonologique (Leyton et al., 2017). Quant aux patients avec atrophie corticale postérieure, certains d'entre eux présenteraient une anomie pouvant être causée par un trouble d'accès lexical ou par un trouble visuo-perceptif (Crutch, Lehmann, Warren, & Rohrer, 2013; Magnin et al., 2013).

Des études récentes de notre groupe suggèrent également que l'évaluation du discours spontané pourrait être un outil de choix pour caractériser les symptômes langagiers chez les patients MA (Slegers, Filiou, Montembeault, & Brambati, 2018). Nos résultats préliminaires

montrent également que cet outil, qui possède plusieurs avantages au niveau de la validité écologique, permettrait de détecter l'anomie chez les patients MA et de les différencier des sujets vs-APP (Montembeault et al., 2017). Le développement de cette technique permettra certainement d'améliorer nos connaissances sur le langage dans la MA.

Sur le plan de la neuroimagerie, les corrélats cérébraux des symptômes langagiers dans la MA ont grandement été investigués en termes d'atrophie de matière grise dans des régions spécifiques du cerveau, ainsi qu'en termes de connectivité fonctionnelle dans l'article #3 de cette présente thèse. Malgré tout, il serait nécessaire d'utiliser des techniques telles que les RCSMG ou l'IRM de diffusion spécifiquement dans l'étude de l'anomie chez les patients MA.

Nous avons également amplement discuté de la complémentarité des approches de connectivité structurelle et fonctionnelle dans la section 6 de la discussion. Néanmoins, dans les dernières années, certaines études d'imagerie multimodale ont commencé à émerger, permettant d'investiguer différents paramètres cérébraux simultanément et au sein d'un même échantillon (Collins et al., 2017; Guo et al., 2013). Malgré les défis techniques associés à ces approches multimodales, elles seront critiques afin de mieux comprendre les interactions entre les paramètres investiguées par chacune de ces approches séparément. De plus, elles permettront certainement d'apporter un éclairage nouveau à nos connaissances sur les maladies neurodégénératives et sur le système du langage.

8. Conclusion

Dans l'ensemble, cette thèse a permis de mettre en relief l'importance de nouveaux marqueurs cognitifs (en lien avec l'anomie et la dénomination d'ESU) et cérébraux (connectivité structurelle du RMD, du réseau de la saillance et du contrôle exécutif et connectivité fonctionnelle du réseau du langage) dans la caractérisation de la MA et son diagnostic différentiel avec d'autres maladies neurodégénératives telles que la vs-APP. Étant donné l'impact au quotidien des troubles langagiers chez les patients MA et leurs proches, nous croyons qu'une meilleure caractérisation de la nature de leurs déficits contribuera au développement d'interventions auprès de ceux-ci. Par ailleurs, le développement potentiel de médicaments visant des maladies neurodégénératives spécifiques souligne l'importance d'avoir

de meilleurs outils contribuant au diagnostic différentiel et une meilleure compréhension des phénomènes de déconnexion des réseaux cérébraux qui semblent être au cœur de celles-ci.

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Annexe 1 - Clinical, Anatomical and Pathological Features in the Three Variants of Primary Progressive Aphasia: A Review

Clinical, Anatomical and Pathological Features in the Three Variants of Primary Progressive Aphasia: A Review

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Abstract

Primary progressive aphasias (PPA) are neurodegenerative diseases clinically characterized by an early and relatively isolated language impairment. Three main clinical variants, namely the nonfluent/agrammatic variant (nfvPPA), the semantic variant (svPPA) and the logopenic variant (lvPPA) have been described, each with specific linguistic/cognitive deficits, corresponding anatomical and most probable pathological features. Since the discovery and the development of diagnostic criteria for the PPA variants by the experts in the field, significant progress has been made in the understanding of these diseases. This review aims to provide an overview of the literature on each of the PPA variant in terms of their clinical, anatomical and pathological features, with a specific focus on recent findings. In terms of clinical advancements, recent studies have allowed a better characterization and differentiation of PPA patients based on both their linguistic and non-linguistic profiles. In terms of neuroimaging, techniques such as diffusion imaging and resting-state fMRI have allowed a deeper understanding of the impact of PPA on structural and functional connectivity alterations beyond the well-defined pattern of regional gray matter atrophy. Finally, in terms of pathology, despite significant advances, clinico-pathological correspondence in PPA remains far from absolute. Nonetheless, the improved characterization of PPA has the potential to have a positive impact on the management of patients. Improved reliability of diagnoses and the development of reliable in vivo biomarkers for underlying neuropathology will also be increasingly important in the future as trials for etiology-specific treatments become available.

Keywords: primary progressive aphasia, nonfluent/agrammatic variant, semantic variant, logopenic variant, language, brain connectivity

1. Introduction

In 1892, Arnold Pick (1) first described a patient with a clinical history of progressive and isolated language deficits, along with mild memory impairment and progressive social dysfunction. Around the same time, Paul Sérieux (2) described a woman who presented with a progressive loss of word comprehension and in whom, contrary to Pick's patient, memory and intelligence were initially preserved. When this patient died in 1897, Jules Déjerine examined his brain, discovering neuronal loss and cortical atrophy in bilateral temporal regions (2). More recently, Marsel Mesulam had the opportunity to examine the cell and myelin preparations of Sérieux's patient, finding no evidence of either senile plaques or neurofibrillary tangles (3). For this reason, he considered this patient the closest prototypical example of the syndrome now known as primary progressive aphasia (PPA).

In the modern literature, the first systematic description of a series of PPA cases was published in 1982 by Marsel Mesulam (4).The disorder was characterized as a "slowly progressive aphasia without generalized dementia". The six reported patients had very heterogeneous linguistic profiles, which did not completely fit the classic vascular aphasia models of Broca and Wernicke, thus suggesting the existence of several variants of PPA.

In the mid-1970s, Warrington (5), followed by Snowden (6), Hodges and their collaborators (7) described a progressive disorder of semantic memory that they termed "semantic dementia". In 1996, Grossman (8) described a different form of progressive language disorder, termed "progressive nonfluent aphasia". At the end of the 1990s, Neary and collaborators (9) proposed a classification for frontotemporal dementia (FTD, then used as a clinical term) that included semantic dementia and progressive nonfluent aphasia. However, the definition of progressive nonfluent aphasia was very broad and likely included a variety of clinical syndromes. In 2004, a third subtype of PPA was described by Gorno-Tempini and colleagues (10), the "logopenic" variant of PPA (lvPPA). In 2011, an international group of PPA investigators (11) put forth new criteria that included these three main variants. These criteria are based on clinical features, along with neuroimaging, neuropathological, and genetic data, to allow homogeneous patient classification for research purposes. In this framework, patients must first meet the general PPA criteria proposed by Mesulam, in which a difficulty with language must be 1) the most prominent clinical feature, both at symptom onset and for the initial phases of the diseases, and 2) must be the principal cause of impaired daily living

activities (12). The general clinical evaluation of PPA patients aims to identify the speech-language profile, showing impaired versus spared speech-language skills, in order to identify the variant. In addition to the clinical features, the diagnosis can be further supported by neuroimaging (atrophy, hypometabolism, hypoperfusion) and pathology. Table 1 summarizes the clinical, anatomical and biological features of the three main variants of PPA.

Although these three main variants do not account for all possible presentations of PPA, this classification is thought to capture most patients who do not a have a genetic form of the disease. It should be noted that, while correct clinical characterization allows accurate prediction of anatomical involvement, the correspondence between clinico-anatomical and molecular findings at pathology is only probabilistic. It reflects partially selective vulnerability of certain networks to certain neurodegenerative diseases (13).

Since the discovery and the development of diagnosis criteria for the PPA variants by the experts in the field in 2011, significant progress has been made in the understanding of PPA. While most neuroimaging studies on PPA had focussed on regional atrophy, recent neuroimaging studies have focused on the impact of PPA on selective brain networks sustaining different language functions. Furthermore, recent longitudinal studies have allowed a better delineation of clinical and cerebral changes associated with the progression of the disease. This review aims to provide an overview and an update of the literature on each of the PPA variant in terms of their clinical, anatomical and pathological features. More specifically, in addition to reviewing the 2011 criteria, this review will provide an update on recent findings on the linguistic/cognitive manifestations of the disease and on their assessment. The latest neuroimaging studies will be reviewed with a specific focus on disconnection aspects of the disease. Issues and controversies associated with the diagnosis of PPA will be discussed, and possible avenues will be examined in the light of the most recent research.

2. General background on pathology in PPA

From a pathological point of view, each PPA variant seems to correspond to a specific tissue pathology, and in some cases to a gene mutation. However, the clinico-pathological correspondence in PPA remains far from absolute, as will be discussed more specifically for each PPA variant in the following sections (Table 1).

One of the possible causes is the accumulation of pathological aggregates of tau protein. Tau protein is a highly soluble microtubule-associated protein (MAPT) and promotes microtubule polymerization and stabilization. Disorders in which tau pathology is considered the major contributing factor to neurodegeneration are referred to as "primary tauopathies" (e.g., fronto-temporal dementia tau related, FTD tau). Tau protein in the brain is heterogeneous due to alternative splice forms, as well as post-translational modifications, including phosphorylation (14). The terms "3R" and "4R" tau refers to the products of the alternative splicing of the MAPT gene, generating tau species with either three or four conserved ~32 amino acid repeats in the microtubule binding domain of tau protein (15). There is preferential accumulation of 3R or 4R tau in various tauopathies, providing a biochemical subclassification of the tauopathies. The MAPT gene is located on chromosome 17. Mutations in the MAPT gene induce the formation of abnormal normal tau protein inclusions, leading to abnormal functioning of these cells. Changes in tau protein induced by mutations can also decrease its effectiveness or increase its amount, which can lead to disease.

Another frequent pathological substrate is the deposits of transactive response DNA-binding protein 43 (TDP-43) which is a cellular protein encoded by the TARDBP gene. Four subtypes have been described (A, B, C, D), in some cases associated with genes mutations. For instance, type A (TDP-43-A) is associated in a proportion of cases with mutations in the progranulin (PGRN or GRN) gene (16). The PGRN gene is located on chromosome 17 and induces the production of the progranulin protein. Mutations in the PGRN gene reduce the production of progranulin and increase the neural aggregates of TDP-43. The progranulin helps cell growth, and the protein TDP-43 regulates the process of making proteins from DNA (expression). The TARDBP gene on chromosome 1, encoding the TDP-43 protein, is very rarely involved.

Finally, some patients (especially those with lvPPA) have an underlying AD pathology. AD is characterized by intracellular tau-associated neurofibrillary tangles and extracellular amyloid-β (Aβ)–associated plaques in the brain.

3. Variants of primary progressive aphasia (PPA)

3.1 Non fluent/agrammatic variant (nfvPPA)

3.1.1 Clinical manifestations

NfvPPA is a rare, early-onset neurodegenerative syndrome with a mean age of onset of approximately 60 years (17). The duration of survival is quite variable, ranging from two years in cases associated with amyotrophic lateral sclerosis to about 12 years in cases not associated with any motor disorder (18, 19).

The hallmark clinical features of nfvPPA are effortful speech and agrammatism. Effortful speech is characterized by slow, labored speech production, mainly due to a speech motor planning deficit, i.e., apraxia of speech (AOS) (20). Speech sound errors, consisting of distortions, deletions, substitutions, insertions, or transpositions of speech sounds are present. Distortions are considered as phonetic errors and are caused by AOS, while deletions, substitutions, insertions and transpositions are phonemic errors and can be caused by a motor speech impairment or a phoneme selection deficit (21, 22). However, there are some significant challenges in differentiating these two types of errors clinically, and both studies showing higher rates of phonetic errors (23, 24) or higher rates of phonemic errors (21, 22) in nfvPPA patients have been reported. Prosody is also typically affected in nfvPPA. Dysarthric features often co-occur with AOS, usually with mixed hypophonic and spastic features (20). Agrammatism is characterized by short, simple phrases and omission of grammatical morphemes. Difficulties are present in language production (e.g. omission of articles, use of incorrect morphological endings), as well as in comprehension (e.g. difficulties in understanding complex syntactic structures, such as passives and relative clauses) (25). Patients with nfvPPA often use fewer verbs compared with healthy controls, in part because verbs play a critical part in syntactically structuring a sentence. They also have difficulty with verb naming and comprehension tasks (26).

With the progression of the disease, other cognitive deficits may emerge, including a decline in attentional resources and verbal working memory, as well as executive functions, episodic memory, praxis and behavioral symptoms (27, 28). General neurological examination is normal early in the disease course but extrapyramidal signs, and in many cases, a florid progressive supranuclear palsy syndrome (PSP-s) or corticobasal syndrome (CBS), can occur later in the disease course (24, 29-34) when the disease advances to SMA and subcortical regions, which might be due to the underlying FTD-4R pathology (see section 3.1.4). In cases in which language difficulties are very early accompanied by a clear extrapyramidal syndrome (for example, a generalized rigidity or tremor), the diagnosis of PPA is excluded. In these cases,

even though the specific criteria for nfvPPA might be fulfilled, the general PPA criteria proposed by Mesulam are not fulfilled (12), given the predominance of the extrapyramidal syndrome and its impact on daily living activities. Therefore, clinically, these patients are diagnosed with PSP-s or CBS with speech/language features (35, 36). Conversely, mild deficits, such as mild limb apraxia or slowness in fine finger movements, do not exclude a diagnosis of PPA.

The current clinical criteria (11) for nfvPPA include at least one of the following core features: 1. Agrammatism in language production; 2. Effortful, halting speech with inconsistent speech sound errors and distortions (AOS); and at least 2 of 3 of the following other features: 1. Impaired comprehension of syntactically complex sentences; 2. Spared single-word comprehension; 3. Spared object knowledge.

3.1.2 Linguistic/cognitive assessment

Spontaneous speech in nfvPPA can be assessed using description of a picture, such as "The cookie theft" (37), "The picnic scene" from the Western Aphasia Battery (38), or a picture story such as "Frog, where are you?" (39). These connected speech samples may yield information about fluency, grammatical competence, and motor speech abilities, amongst others (23, 40). Previous studies have revealed that speech samples in nfvPPA are characterized speech sound errors, as well as slow rate, syntactic errors and reduced complexity (21-23). Specific tests for the motor speech component, performed by an expert speech pathologist, are also highly recommended. These may include articulatory tasks of increasing difficulty, from simple phonation and production of single syllables (e.g. puh/puh/puh) to more complex diadochokinetic tasks (e.g. puh/tuh/kuh/), repetition of multisyllabic words (e.g. impossibility), and finally, sentence repetition (e.g., (41)).

Motor speech disorders may, in some cases, prevent the accurate assessment of agrammatism. One approach is to use sentence production tasks, such as the Northwestern Anagram Test, which requires to assemble individual word cards into a meaningful sentence (42). Another approach is to assess grammatical processing in comprehension, by asking patients to point to one of two pictures after hearing an auditorily presented sentence. In this task, accurate decoding of the grammatical structure of the sentence is required to select the correct picture. Conversely, in very early stages of disease, written language (such as a written description of a picture) can often reveal early, mild grammatical errors. Specific tests for word-

comprehension and object knowledge, functions usually spared in the early phases, should also be systematically administrated.

3.1.3 Neuroimaging findings

The left inferior frontal gyrus (pars opercularis) is considered as the syndrome-specific epicentre in nfvPPA (43, 44). It is also associated with grey matter (GM) atrophy in the insula, premotor regions, SMA and striatum (figure 1) (10, 45, 46). Syntactic processing deficits observed in these patients are associated with structural and functional abnormalities in the posterior part of inferior frontal gyrus (47). Some patients can become mute early in the course of the disease. This profile is associated with GM atrophy that is more prominent in the pars opercularis, extending into the left basal ganglia (48).

A few studies reported that AOS and agrammatism can occur separately in nfvPPA, affecting different subcomponents of the same brain network (49). In cases in which AOS presents as an isolated symptom, the term of "primary progressive apraxia of speech" has been applied (PPAOS). On one hand, patients with PPAOS, might show focal imaging abnormalities in the premotor cortex. On the other hand, patients with dominant agrammatic deficits show widespread involvement of premotor, prefrontal, temporal, and parietal lobes, as well as in the caudate nucleus and the insula (49). Nevertheless, in the most common presentation of nfvPPA, motor speech deficits are prevalent, but signs of agrammatism are also present. Atrophy in these cases includes premotor and posterior inferior frontal regions, progressing along the aslant tract to the supplementary motor area (SMA) complex and eventually to the basal ganglia and supramarginal gyrus (46). nfvPPA is therefore an example of a network disorder involving the circuit of regions and connections involved in speech production.

Diffusion magnetic resonance imaging (MRI) techniques have shown that the dorsal language pathway of long-range white matter (WM) fibers connecting frontal, subcortical and parietal areas are primarily involved in neurodegeneration in nfvPPA (46, 50) (figure 2). This damage appears to be specific to this variant and is not observed in other PPA variants. WM damage in the dorsal pathway (superior longitudinal fasciculus) is also observed (figure 3) (51-53). Consistently, a recent resting state fMRI study has demonstrated decreased functional connectivity between the left inferior frontal gyrus and the posterior middle temporal gyrus in nfvPPA, even in patients in which the atrophy is not severe (54).

Longitudinal GM atrophy changes in nfvPPA occur, 1 year after the first visit, in the left posterior frontal regions (often comprising inferior middle and superior gyri), supplementary motor area, insula, striatum, inferior parietal regions and underlying WM (43, 55-57). Atrophy progresses to the supplementary motor complex region through the aslant tract. This tract is involved in the initiation and execution of movements, especially articulation. In nfvPPA, its integrity is associated with the number of distortion errors made by patients in spontaneous speech as well as with performance in a verbal fluency task (46, 58).

3.1.4 Pathology

NfvPPA is most commonly associated with a form of FTD-4R tau (45, 59-65). Other reports indicate TDP-43-A pathology in nfvPPA (45, 59, 66) and in some cases associated with progranulin (PGRN) or chromosome 9 open reading frame 72 (C9ORF72) gene mutations (67). Less frequently, AD pathology has also been reported in nfvPPA (45, 60, 61). However, a recent study investigating PPA patients with discordant amyloid status (i.e. nfvPPA with AD pathology) has suggested that most of these cases actually present mixed pathology (FTD tau pathology as primary pathologic diagnosis and AD pathology as contributing pathologic diagnosis)(68).

While progress has been made in understanding the underlying pathology in nfvPPA, some recent studies have also begun to characterize nfvPPA patients according to their underlying pathology. Clinically, it has been hypothesized that cases with predominant and isolated motor speech disorders would be associated with tau (24), while predominant agrammatism could predict TDP-43-A pathology. While similar GM damage have been observed in nfvPPA-tau and nfvPPA-TDP patients (figure 1), greater WM damage has been observed in nfvPPA-tau cases (45, 69). Recently, further involvement of temporo-parietal regions beyond GM loss in the frontal lobe has been detected in a clinically heterogeneous group of TDP-43-A cases (64).

NfvPPA patients with underlying FTD-4R tau can also be further divided in nfv-PPA associated with progressive supranuclear palsy (PSP) and with corticobasal degeneration (CBD) anatomopathologies (56). At initial presentation, dysarthria and relatively selective WM atrophy appear typical of nfvPPA-PSP, while greater sentence comprehension deficits appear typical of nfvPPA-CBD. While these speech/language differences dissipate at a one-year follow-up, the progression of atrophy also allow to differentiate the two subgroups (56). In nfvPPA-PSP,

atrophy spreads within the subcortical/brainstem motor system, which is consistent with greater oculomotors deficits and swallowing difficulty. In nfvPPA-CBD, atrophy progresses anteriorly in prefrontal regions, which is thought to generate greater working memory impairment and development of behavioral symptoms.

3.2 Semantic variant (svPPA)

3.2.1 Clinical manifestations

SvPPA is characterized by a progressive and multimodal loss of semantic knowledge (70). Age at onset is variable, most often between 55 and 70 years (71). The duration of the disease is also variable and can range from 2 to 15 years, although patients typically survive 7 to 8 years after onset (72, 73). Studies of the prevalence and incidence of svPPA are relatively limited, but a recent epidemiology study estimated the prevalence of FTD at 10.8/100,000, with svPPA accounting for approximately one-third of these cases (74).

These patients progressively lose the meaning of words, and they usually present with severe, progressive anomia and markedly impaired comprehension of single words (11, 30). In earlier stages, the loss of meaning of words, and subsequently, naming and single-word comprehension deficits, are more prominent for low frequency/familiarity items (e.g., “rhinoceros” vs. “dog”) (75). Often, the patients replace less frequent words with more familiar ones, typically using the superordinate category (e.g., “animal” for “cat”). Another salient aspect of the syndrome is the production of semantic paraphasias in naming (e.g., “brush” for “comb”). Anomia can also be observed in spontaneous speech that is often empty and not very informative (23, 76). In the early stages, inability to comprehend low-familiarity words can be the only symptom accompanying anomia, and patients frequently ask for the meaning of words. The progression of semantic deficits leads to impaired object recognition affecting all sensory modalities, including vision, touch, olfaction, and gustation (7, 70) (e.g., visual agnosia; (73)). The ability to correctly identify objects is strongly influenced by familiarity with the object (e.g., “fork” is more familiar than “compass”) (77). Additionally, individuals with svPPA appear to have disproportionate difficulty understanding concrete concepts relative to abstract concepts (78-80). Rarely, cases have been described with greater, or even selective, deficits for people (81) and animals (82). Some patients demonstrate impairment in the recognition of faces, which stems from a loss of person knowledge (83) that is also familiarity-dependent (84).

In contrast, episodic memory is relatively preserved in svPPA, especially when tasks with minimal conceptual loading are used (85, 86). The intact performance on traditional non-conceptually loaded episodic memory tasks converges with the performance of svPPA patients on autobiographical memory tasks. Patients typically show relatively preserved recollection of recent autobiographical memory in the context of poorer remote autobiographical memory (known as the reverse temporal gradient or step-function), reflecting increased semanticisation of past events (87, 88). SvPPA patients have also difficulties in episodic future thinking (89, 90).

The loss of word meaning is also apparent in reading. Patients do not recognize words as whole entities, but rather adopt a phonological strategy, deriving pronunciations using letter-sound conversion. As a result, irregular words are pronounced as if they are regular ("yatsht" for "yacht"), a phenomenon called surface dyslexia (91, 92). A similar pattern of selective impairment for irregular words is observed in spelling (surface dysgraphia).

Behavioral abnormalities are typically present in mid-late phases, including disinhibition, irritability and food taste changes (e.g., preference for sweet foods). Lack of empathy, mental inflexibility, and compulsions - including clockwatching and intense interest in jigsaws - are also frequently noted (93-95). Almost 50% of svPPA patients report experiencing somatic symptom disorder as misidentification and preoccupation with normal bodily sensations such as hunger, bladder filling, borborygmi, rhinorrhea, and reflux; excessive concern over the incompletely understood meaning or source of pain or other symptoms; and Cotard syndrome or the delusion that unidentified somatic symptoms signify death or deterioration (96). This inability to read and name somatic sensations, or "alexisomia," results in disproportionate and persistent concern about somatic sensations with consequent significant disability (96).

It has been demonstrated that non-right-handedness is overrepresented in svPPA patients, at nearly twice the prevalence of the general population. Left-handedness has been described as a proxy for atypical brain hemispheric lateralization (97).

The current diagnostic guidelines (11) identify anomia and single-word comprehension deficits as core features, both essential for diagnosis. At least 3 of the following other diagnostic features must also be present: 1. impaired object knowledge, particularly for low- frequency or

low-familiarity items; 2. surface dyslexia or dysgraphia; 3. spared repetition; and 4. spared speech production (grammar and motor speech).

3.2.2 Linguistic/cognitive assessment

Language assessment of svPPA includes tests of confrontation naming, in which the patient is asked to retrieve the word in response to a picture (e.g., the Boston Naming test (98)). Object and person knowledge are also examined using tests of semantic associations, gesture-object matching, and sound-picture matching tasks. The popular Pyramids and Palm Trees Test (99) is a semantic association task that measures the capacity to access detailed semantic information about words and pictures necessary for the identification of the relationships that conceptually link two perceptually and functionally distinct entities. The loss of concepts can be also tested using other types of stimuli, including sounds, foods, and odors. Famous faces and buildings naming tasks, as well as semantic knowledge tasks are also very sensitive with svPPA patients (100).

Reading and spelling of regular and irregular words are also tested in order to identify surface dyslexia and dysgraphia. Spontaneous speech should also be assessed in svPPA. Differently from nfvPPA, the spontaneous speech should not present AOS and the syntactic structure should be preserved. On the other side, svPPA present increased use of highly familiar words, anomia characterized by long pauses and use of general words (such as “thing”) for identifying the items displayed on the image.

Episodic memory tests based on non-linguistic stimuli (such as Rey Complex Figure) should be administered to exclude the presence of major episodic memory deficits, especially at early stages of the disease. Repetition and syntactic comprehension tests should be evaluated as an exclusion criterion.

3.2.3 Neuroimaging findings

The anterior temporal lobes show bilateral atrophy and hypoperfusion in svPPA and is considered as the syndrome-specific epicentre (45, 101-104) (figure 4). This focal anatomical damage makes neuroimaging a complementary tool in the diagnostic process for this PPA variant (105). The damage is usually greater in the left hemisphere at first stages of the disease (30). Typical semantic impairment is associated with greater left-sided anterior temporal atrophy/hypometabolism (106, 107), naming difficulties are correlated with superior portions of the left temporal pole (108), and finally, loss of person knowledge and behavioral changes are

associated with more extensive right temporal atrophy (109, 110). Atrophy of the hippocampus has been reported mainly involving the anterior portion, which is connected to the semantic memory system (111). On the other hand, the posterior portion, mainly connected to the episodic memory system, would be relatively spared (112). This pattern of hippocampal atrophy would explain the dissociation between semantic and episodic memory deficits in svPPA population.

Microstructural studies of WM integrity have shown damage in the ventral tracts that connect the temporal lobe to the occipital lobe and to the orbitofrontal cortex, with left side predominance (figure 3) (51). The dorsal frontoparietal tracts that do not involve the temporal lobes are spared bilaterally, except for the temporal segment of the dorsal pathway (figure 3) (51, 113, 114). This pattern is highly left lateralized compared with behavioral variant of fronto-temporal dementia which has a right predominance (115). During the progression of the disease, right-hemisphere WM bundles, in particular the uncinate, are preferentially damaged (116).

At the functional level, svPPA patients manifest extensive reduced anterior temporal lobe connectivity with primary and modality-selective cortices (117, 118). The longitudinal pattern of atrophy can be predicted by functional MRI connectivity between the temporal pole and the rest of the brain following connectional pathways within a large-scale network (119).

As the disease progresses, the atrophy involves the ventral and lateral temporal regions, as well as the contralateral temporal lobe and frontal regions (57, 120, 121). Beyond the specific metabolic signatures, additional dysfunctional patterns in the early stages can predict clinical progression: svPPA patients who present with extended bilateral patterns at baseline eventually develop behavioral disorders and a dysexecutive syndrome at follow-up (122).

3.2.4 Pathology

SvPPA is nearly always associated with underlying TDP-43-C pathological aggregates (75%–100% in clinicopathological correlation series), and for the remainder of patients, most often with FTD tau (45, 60, 62, 66, 123-126). Rarely, AD pathology has also been reported in svPPA (60, 126), although a recent study has shown that most svPPA cases with AD pathology also present TDP-43-C pathology (68). In comparison to patients with TDP-43 pathology, those with FTD tau pathology present greater atrophy of frontotemporal cortex (medial anterior temporal lobe, orbitofrontal cortex, anterior cingulate cortex), basal ganglia and connecting WM bundles (figure 4) (45). Interestingly, svPPA patients and PGRN mutation carriers are both characterized by underlying TDP-43 aggregation. In some cases, patients with PGRN mutations

can develop aphasia with semantic deficits (127). However, familial forms of pure svPPA have not been reported. In both svPPA patients and PGRN mutation carriers, an increased prevalence of specific and related autoimmune diseases has been found, suggesting a unique pattern of systemic inflammation (128). Very rarely, mutations of the C9ORF72 gene have also been described in svPPA (129).

Recent studies have tried to identify FTD pathological subtypes with the help of cerebrospinal fluid (CSF) biomarkers. Increased neurofilament light chain (NfL) levels in the CSF, which are associated with neuronal and axonal degeneration, have been reported in patients with neurodegenerative diseases, and more specifically in patients with probable TDP-43 pathology such as svPPA patients (130).

3.3 Logopenic variant (lvPPA)

3.3.1 Clinical manifestations

LvPPA has been more recently characterized (10, 131) as a distinct form of PPA, and little is known about its age at onset and disease survival. As with the other variants of PPA, the logopenic variant is considered an early onset form of dementia (132).

Patients with lvPPA typically present with word finding difficulty, along with sentence repetition deficits and, as the disease progresses, impaired sentence comprehension. Phonological impairments and, specifically, a phonological short-term memory deficit, have been suggested to be the core of the syndrome (131). In accordance with this interpretation, repetition and comprehension of single words remaining largely spared.

Prior to the current consensus criteria for diagnosis, lvPPA was often diagnosed as nfvPPA (60). Both variants can present with slow speech, frequent word-finding pauses and speech sound errors. However, patients with nfvPPA have slower speech and, conversely, those with lvPPA do not present with severe agrammatism and the distorted, effortful speech production of AOS. Speech sound errors are usually phonemic, but not phonetic (21, 23). Confrontation naming is often impaired, albeit at a lesser degree if compared to svPPA. Phonological paraphasias can occur in spontaneous speech and confrontation naming.

Usually later in the disease, episodic memory impairment (62) is often present, even though the lexical retrieval impairment observed in lvPPA patients contributes to verbal episodic memory performance (133, 134). Longitudinal studies have shown that cognitive decline is faster in lvPPA in comparison to other variants, and that this decline is not restricted

to language functioning (135). In lvPPA patients, a more accelerated decline was also observed in visuospatial abilities (136), in memory and in attention (135). This finding has been associated with the underlying AD pathology (see section 3.3.4). Poor calculation abilities (137) and limb apraxia can also occur (10). Apathy, anxiety, irritability, and agitation are often reported (138).

Recent studies have revealed that in comparison to the general population, PPA patients report higher rates of learning disabilities (and more specifically developmental dyslexia) in their early phases of life (139), and that dyslexia susceptibility genes influence brain atrophy in PPA (140). Further reports suggested that the frequency was specifically higher in lvPPA patients in comparison to the other variants, and that in these patients, learning disability is associated with earlier onset of disease, more isolated language symptoms, and more focal pattern of left posterior temporoparietal atrophy (97). Developmental dyslexia, which is the most common developmental language learning disability, can manifest with phonological disturbances and posterior temporal involvement, similarly to lvPPA. In the framework of network vulnerability hypothesis, learning disability might confer susceptibility of language network to early-onset, focal AD pathology such as lvPPA (97). However, further research is needed to confirm the higher frequency of developmental dyslexia in lvPPA specifically, since another study provided conflicting results (141).

Criteria for lvPPA (11) require that both of the following core features must be present: impaired single-word retrieval in spontaneous speech and naming along with impaired repetition of sentences and phrases. At least 3 of the following other features must be present: 1. phonological errors in spontaneous speech and naming; 2. spared single-word comprehension and object knowledge; 3. spared motor speech; and 4. absence of frank agrammatism.

3.3.2 Linguistic/cognitive assessment

The evaluation of spontaneous speech is essential in order to appreciate lvPPA patients' anomia and can be done using description of a picture as previously described. In such tasks, anomia may manifest in phonological paraphasias, hesitations and frequent pauses for word-finding. Language assessment of lvPPA also includes confrontation naming tasks such as the Boston Naming Test (98)). Oral repetition of words, pseudowords, phrases, and sentences, are usually administered in order to show the dissociation between preserved single word repetition, in opposition to the greater impairment for sentences and phrases. Moreover, phonological errors are often appreciated (142). Tests for sentence comprehension consist of matching orally

presented sentences to pictures. Patients with nfvPPA also fail on these types of tests because of the effect of grammatical complexity, whereas patients with lvPPA fail because of the effects of length and frequency.

Reading and spelling tests reveal phonological errors as well as difficulty with pseudowords, which rely upon phonological processing (91). LvPPA patients also show difficulties in verbal working memory tests, such as the digit span from the Weschler Adult Intelligence Scale (48, 143). Single-word comprehension, motor speech and agrammatism should be evaluated as exclusion criteria. Recent studies have suggested that non-linguistic features, namely visuospatial functioning (136), episodic memory and emotion processing (144), are also helpful in the differential diagnosis of lvPPA in comparison to the other variants (and specially with nfvPPA).

3.3.3 Neuroimaging findings

Anatomical damage in lvPPA is typically located in posterior superior temporal and middle temporal gyri as well as the inferior parietal lobule (10, 45). This pattern of atrophy is consistent with the classical anatomical model of the phonological loop (131). This neurodegenerative pattern is very similar to the one observed in early-onset AD (132). Naming difficulties are correlated with the left posterior temporal cortex (108). Recently, a model of the progression of atrophy in lvPPA has been suggested, showing that atrophy progresses from the disease epicentre (left posterior superior and middle temporal gyri) to ipsilateral parietal and frontal lobes and contralateral temporal lobe (145).

WM loss in association tracts in the left hemisphere has been detected (146), mainly in parietal fibers linking the parietal with frontal and posterior temporal regions (figure 3) (51). A recent longitudinal study also suggested that early WM changes in lvPPA can be observed in the left posterior inferior longitudinal fasciculus, and that these changes become widespread over a year of progression of the disease, also affecting the anterior inferior longitudinal fasciculus, the uncinate fasciculus and the superior longitudinal fasciculus (116).

In terms of functional connectivity, the working memory network (frontal regions, inferior parietal lobule, superior and middle temporal gyri) and language network (posterior superior temporal gyrus and inferior frontal lobe) have been shown to be altered in lvPPA patients in a resting-state fMRI study (147).

3.3.4 Pathology

LvPPA is most often caused by AD pathology (45, 60, 65), in as many as 95% of cases (68). It is considered one of the possible focal and early onset presentations of AD (62, 107, 132), even if other pathological profiles have been more rarely described, including Lewy body dementia (148), TDP-43 and FTD tau (60).

Cerebro-spinal fluid examination (149) and molecular imaging techniques such as PET with Pittsburgh Compound B (PIB) (107), a ligand for the amyloid, have shown the presence of amyloid in these individuals. However, in comparison to typical AD patients, lvPPA patients with AD pathology show more significant hypoperfusion in the left superior temporal gyrus (figure 5) (149).

Some authors have demonstrated the coexistence of AD pathology and argyrophilic thorny astrocyte clusters (ATAC), intensely tau immunoreactive, in the fronto-temporoparietal cortex and subcortical regions (150). They suggest that they might represent a marker of a process responsible for the prominent focal clinical manifestations in lvPPA (150). Finally, a clinical syndrome with lvPPA features but also with more global features may be predominantly linked to mutations in the GRN gene (151).

3.4 PPA unclassifiable

In addition to the three most common variants, the 2011 consensus criteria also suggest that a minority of patients might be unclassifiable (11). It might be the case in patients who present for a long time with a single language symptom or in patients who present mixed features. It was further suggested that with the progression of the disease, these patients' profiles might become clearer.

A few studies have directly investigated the extent to which the 2011 consensus criteria cover the diversity of PPA cases. While some of them found that most patients could be classified within the three suggested variants (60, 61, 68, 152), others reported higher percentage (20 to 41%) of unclassifiable PPA patients (153-155). One of the main difficulty described by these last authors is related to patients who present with a single isolated language symptom, thus fulfilling the root criteria for PPA, but not the criteria for any of the variants. The most often reported cases are the ones who present with isolated anomia, without impaired repetition of single word, sentences and phrases (therefore only partially fulfilling criteria for lvPPA). Another main difficulty reported is related to patients who present a mixed profile, thus fulfilling the criteria for more than one of the variants. Patients presenting both sentence repetition

impairments and agrammatism (therefore fulfilling criteria for both lvPPA and nfvPPA), as well as patients presenting both agrammatism and semantic impairments (fulfilling criteria for both nfvPPA and svPPA) have been observed.

Many factors could be associated with a varying proportion of unclassifiable PPA cases. First, the potential inclusion of genetic forms of PPA in studies might lead to higher number of mixed profiles. For example, it has been suggested that PGRN mutation carriers might present with a lvPPA and nfvPPA mixed profile (156). Furthermore, there is likely a high heterogeneity in tests and cutoffs used in the diagnosis of PPA across different clinical and research sites. There is a need for a use of sensitive and specific tests, and some authors have recently published assessment batteries specifically designed for the assessment of PPAs (157, 158). Most importantly, apparently similar symptoms might be due to distinct underlying causes between PPA variants, and this should be considered in tests selection and interpretation. For example, some studies have suggested that repetition deficits might be of different nature in lvPPA and nfvPPA. In lvPPA, they might be due to a disruption of the store component of the phonological loop, while in nfvPPA, impairments in speech motor planning might affect the subvocal rehearsal component of the phonological loop (159). This has also been investigated regarding the overlapping naming impairments in svPPA and lvPPA, which are thought to be respectively due to a semantic impairment versus a lexical access deficit (160, 161). Finally, more prospective studies investigating the classification of PPA patients are needed, since retrospective studies are more likely to not have had adequate or complete test batteries to apply the current criteria (68). Nonetheless, even though significant progress was made in the recent years in the understanding of PPA, these studies illustrate that there are still controversies in the diagnosis of PPA and the above-mentioned issues will need to be clarified in the next years.

4. Conclusion

In summary, each variant of PPA (nfv-, sv- and lv-PPA) is characterized by a prototypic neurolinguistic/neuropsychological, neuroimaging and neuropathological profile. The effervescence of PPA as a research field in the recent years has allowed for key discoveries in each of these domains. In terms of clinical advancements, recent studies have allowed a better characterization and differentiation of PPA patients based on both their linguistic and non-linguistic profiles. In terms of neuroimaging, techniques such as diffusion imaging and resting-

state fMRI, as well as multimodal studies, have allowed a deeper understanding of the impact of PPA on structural and functional connectivity alterations beyond the well-defined pattern of regional gray matter atrophy. Finally, in terms of pathology/genetics, despite significant advances, clinico-pathological correspondence is still far to be absolute. The improved characterization of PPA has the potential to have a positive impact on the management of individual patients. It can help to better direct patients towards appropriate therapeutic and behavioural intervention, as well as to provide adequate counselling of families and caregivers (162). Improved reliability of diagnoses and the development of reliable in vivo biomarkers for underlying neuropathology will be increasingly important as trials for etiology-specific treatments become available.

List of abbreviations

AD= Alzheimer's disease

AOS= apraxia of speech

ATAC= argyrophilic thorny astrocyte clusters

CBD = corticobasal degeneration

CBS = corticobasal syndrome

C9ORF72= chromosome 9 open reading frame 72

FTD= frontotemporal dementia

GM= grey matter

lvPPA= logopenic variant primary progressive aphasia

MAPT= microtubule-associated protein tau

MRI= magnetic resonance imaging

nfvPPA= nonfluent/agrammatic variant primary progressive aphasia

PET= positron emission tomography

PGRN= progranulin

PIB= Pittsburgh Compound B

PPA= primary progressive aphasia

PPAOS= progressive apraxia of speech

PSP = progressive supranuclear palsy

PSP-s = progressive supranuclear palsy syndrome

SMA= supplementary motor area

svPPA= semantic variant primary progressive aphasia

TDP-43= transactive response DNA-binding protein 43

WM= white matter

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Author contributions

MLGT and RM contributed to the conception of the study. RM and MM wrote the first draft of the manuscript, but all authors wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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Tables

Table 1. Clinical, anatomical and biological features of the three variants of PPA

Primary progressive aphasia variant	**Clinical**	**Anatomical**	**Most common pathology**
Non fluent/agrammatic	Effortful speech, AOS, dysarthria, agrammatism	Left inferior frontal gyrus and insula	FTD-4R tau
Semantic	Impaired retrieval and comprehension of low frequency single words, semantic deficits for objects and people, surface dyslexia/ dysgraphia	Bilateral anterior temporal lobe, usually left>right	TDP-43-C
Logopenic	Word-finding difficulty, sentence repetition/comprehension deficits and phonological dyslexia/dysgraphia	Left inferior parietal lobule and posterior superior temporal gyrus	AD

Abbreviations: AOS = Apraxia of speech; FTD= frontotemporal dementia; TDP-43= FTD characterized by abnormal precipitates of the transactive response DNA binding protein 43; AD = Alzheimer's disease