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Hyperactivation cérébrale et réseaux fonctionnels associés chez les individus à risque de développer la maladie d'Alzheimer

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Hyperactivation cérébrale et réseaux fonctionnels associés chez les individus à risque de développer la maladie d'Alzheimer

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RÉSUMÉ

La maladie d'Alzheimer (MA) est à l'origine de la majorité des cas de démence chez les personnes âgées. Son diagnostic précoce est essentiel pour mieux comprendre les mécanismes cérébraux sous-tendant la manifestation phénotypique de la maladie et développer des interventions conséquentes. Le fait d'étudier des individus à risque de développer la MA, par exemple ceux présentant un déclin cognitif subjectif (DCS) ou un trouble cognitif léger (TCL), offre l'opportunité d'examiner les processus neuropathophysiologiques qui précèdent le stade démentiel. Cela permettrait, entre autres, d'identifier des biomarqueurs avant-coureurs de la maladie.

Cette thèse avait pour but d'investiguer la présence d'hyperactivation cérébrale chez des individus à risque de développer la MA, et d'examiner les réseaux cérébraux fonctionnels associés à l'hyperactivation. L'hyperactivation se définit par la présence de niveaux supérieurs d'activation cérébrale chez des personnes faisant partie de groupes à risque pour la MA (p.ex. DCS ou TCL), comparativement à des participants contrôles cognitivement sains. L'hyperactivation est le plus souvent mesurée par l'imagerie par résonance magnétique fonctionnelle (IRMf) en condition de réalisation de tâche. Dans cette thèse, le lecteur ou la lectrice sera d'abord exposée aux études ayant utilisé l'IRMf pour examiner les patrons d'activation cérébrale et de connectivité fonctionnelle chez les individus ayant reçu un diagnostic clinique de MA, de TCL ou présentant un DCS. Les modèles théoriques découlant de ces études seront ensuite présentés. Afin de mieux comprendre le phénomène d'hyperactivation et sa relation avec les patrons de connectivité fonctionnelle, les divers enjeux scientifiques qui demeurent à être abordés seront ensuite décrits (Chapitre 1). Trois articles exposant les études empiriques formant le corps de la thèse seront ensuite présentés. La première étude avait pour but de documenter la présence, la localisation et l'évolution longitudinale de l'hyperactivation

associée à une tâche de mémoire épisodique chez des individus qui rencontrent les critères de TCL et qui ont ultérieurement progressé vers une démence (Chapitre 2). La deuxième étude visait à déterminer la trajectoire de l'activation cérébrale associée à une tâche de mémoire associative en fonction du degré de sévérité de la maladie chez un groupe d'individus à risque de développer la MA. Elle avait également pour but de déterminer la présence d'hyperactivation chez des personnes rencontrant les critères de DCS *plus* (ou DCS^{+}), qui sont des individus présentant une plainte de mémoire ainsi que des marqueurs génétiques et/ou de neurodégénérescence pour la MA (Chapitre 3). La troisième étude avait pour but d'examiner les réseaux cérébraux fonctionnels associés aux régions montrant de l'hyperactivation chez des individus à risque de développer la MA. Elle avait également pour objectif d'évaluer comment l'hyperactivation et ces réseaux cérébraux fonctionnels sont reliés aux performances en mémoire (Chapitre 4).

Les résultats découlant de l'étude 1 ont permis de mettre en évidence la présence d'hyperactivation chez des individus présentant un TCL et ayant ultérieurement progressé vers le stade de démence. Les trouvailles de l'étude 2 indiquent qu'une fonction quadratique décrit la relation entre des indices de sévérité de la maladie et l'activation pariétale supérieure gauche chez un groupe d'individus à risque de développer la MA (DCS^{+} et TCL). Par ailleurs, des niveaux supérieurs d'activation, c'est-à-dire de l'hyperactivation, étaient retrouvés dans les hippocampes et plusieurs régions temporo-pariétales dans le groupe d'individus DCS^{+}. Une hypoactivation pariétale supérieure gauche était plutôt retrouvée chez les individus TCL. Enfin, les résultats de l'étude 3 indiquent que l'hyperactivation de régions prédéterminées est associée à la dysfonction de réseaux cérébraux fonctionnels impliqués dans les processus de mémoire associative dans le DCS^{+} et le TCL. De plus, ces interactions hyperactivation-réseaux étaient associées à une symptomatologie cognitive croissante. Les implications de cette thèse et ses limites sont abordées dans la discussion (Chapitre 5).

Mots-clés : Maladie d'Alzheimer, trouble cognitif léger, déclin cognitif subjectif, neuroimagerie, imagerie par résonance magnétique fonctionnelle, connectivité fonctionnelle, mémoire épisodique, cognition.

ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia in older adults. Its early diagnosis is essential to better understand the brain mechanisms underlying the phenotypical manifestation of the disease and develop consequent interventions. The study of individuals at risk of AD, for example those presenting with subjective cognitive decline (SCD) or mild cognitive impairment (MCI), offers the opportunity to examine the neuropathophysiological processes preceding the dementia stage. This would allow, among other things, to identify early biomarkers of the disease.

The general aim of this thesis was to determine the presence of cerebral hyperactivation and to assess functional brain networks associated with hyperactivation. Hyperactivation is defined by the presence of higher levels of brain activation in individuals at risk of AD (i.e. SCD, MCI) in comparison to cognitively healthy controls. Hyperactivation is most often measured with functional magnetic resonance imaging (fMRI) while participants perform a cognitive task. In this thesis, the reader will first be exposed to the studies which used fMRI to examine patterns of brain activation and connectivity in individuals with a clinical diagnosis of AD, MCI or presenting with SCD. Theoretical models resulting from these studies will then be presented. The scientific issues remaining to be addressed to better understand the phenomenon of hyperactivation and its relation to functional brain networks will then be described (Chapter 1). Three empirical studies forming the core of this thesis will be presented. The first study aimed to assess the presence, localization and longitudinal evolution of hyperactivation associated with an episodic memory task in individuals meeting criteria for MCI and having subsequently progressed towards dementia (Chapter 2). The second study aimed to determine the trajectory of brain activation associated with an associative memory task as a function of disease severity in a group of individuals at risk of AD. It also aimed to determine if hyperactivation is present in

participants meeting criteria for SCD *plus* (or SCD^+), who are individuals presenting with memory complaint in addition to genetic and/or neurodegeneresence markers of AD (Chapter 3). The third and last study aimed to examine patterns of functional connectivity related to regions of hyperactivation, and to assess how hyperactivation and its associated functional networks relate to memory performance in individuals at risk of AD (Chapter 4).

Results from the first study highlighted the presence of hyperactivation in individuals with MCI who subsequently progressed to the dementia stage. Findings from the second study revealed a quadratic function describing the relationship between proxies of disease severity (neurodegeneration, memory performance) and left superior parietal activation in a group of individuals at risk of AD (SCD^+ and MCI). Moreover, higher levels of activation, i.e. hyperactivation, were found in hippocampal and temporo-parietal regions in the SCD^+ group. Hypoactivation was rather found in the left superior parietal area in the MCI group. Finally, results from the third study revealed that hyperactivation of predetermined regions was associated with dysfunction of functional brain networks underlying associative memory in SCD^+ and MCI. Moreover, these hyperactivation-network interactions were associated with increasing symptomatology. The implications of this thesis and its limits are addressed in the discussion section (Chapter 5).

Key words: Alzheimer's disease, mild cognitive impairment, subjective cognitive decline, neuroimaging, functional magnetic resonance imaging, functional connectivity, episodic memory, cognition.

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LISTE DES ABRÉVIATIONS

Français

APOE : Apolipoprotéine E

CIMA-Q : Consortium pour l'identification précoce de la maladie d'Alzheimer - Québec

CMER-RNQ : Comité mixte d'éthique de la recherche du Regroupement Neuroimagerie/Québec

CRIUGM : Centre de recherche de l'Institut universitaire de gériatrie de Montréal

DCS : Déclin cognitif subjectif

FCI : Fondation canadienne pour l'innovation

FRQS : Fonds de recherche du Québec - Santé

IRM : Imagerie par résonance magnétique

IRMf : Imagerie par résonance magnétique fonctionnelle

IUGM : Institut universitaire de gériatrie

LCR : Liquide céphalo-rachidien

MA : Maladie d'Alzheimer

RQRV : Réseau québécois de recherche sur le vieillissement

RL/RI-16 : Rappel Libre/Rappel indicé à 16 items

SMAF : Système de mesure de l'autonomie fonctionnelle

TCL : Trouble cognitive léger

UNF : Unité de neuroimagerie fonctionnelle

Anglais

AD: Alzheimer's Disease

ANOVA: Analysis of variance

BA: Brodmann area

BOLD: Blood oxygen level-dependent

CIHR: Canadian Institutes of Health Research

CTL: Controls

fMRI: Functional magnetic resonance imaging

FOV: Field of view

FWE: Family-wise error

FWHM: Full width at half maximum

GE-EPI: Gradient echo echo-planar imaging

GLM: General linear model

HC: Healthy controls

ICV: Intracranial volume

LV: Latent variable

MCI: Mild cognitive impairment

MMSE: Mini-Mental State Examination

MNI: Montreal Neurological Institute

MoCA: Montreal Cognitive Assessment

MDRS: Mattis Dementia Rating Scale

MRI: Magnetic resonance imaging

NIA-AA: National Institute on Aging-Alzheimer's Association

NINCDS-ADRDA: National Institute of Neurological and Communication Disorders and Stroke – Alzheimer's Disease and Related Disorders Association

NSERC: Natural Sciences and Engineering Research Council

PLS: Partial least square analysis

QDEC: Query, Design, Estimate, Contrast

ROI: Region of interest

SCD: Subjective cognitive decline

SCD-I: Subjective Cognitive Decline Initiative Working Group

SD: Standard deviation

SPM: Statistical Parameter Mapping

SPSS: Statistical Package for the Social Sciences

VR: Virtual reality

WAIS: Weschler Adult Intelligence Scale

À maman,

toi qui es la preuve indéniable que ces maladies n'ont ni frontière, ni pitié,
et s'en prennent même à ceux et celles qui ne cherchent qu'à répandre l'amour

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CHAPITRE 1 - Introduction générale

1.1. Le continuum de la maladie d'Alzheimer

1.1.1. La démence due à la maladie d'Alzheimer

La démence est un terme qui désigne le stade généralement final d'une maladie, où les atteintes cognitives et/ou comportementales sont suffisamment sévères pour interférer avec l'autonomie fonctionnelle de l'individu atteint. La maladie d'Alzheimer (MA) est à l'origine d'environ 70% des cas de démence chez les personnes âgées, ce qui en fait la cause la plus importante de démence au sein de cette population (Alzheimer's Association, 2019; World Health Organization, 2012). Il est estimé qu'environ 747 000 canadiens et canadiennes souffriraient de la MA ou d'une autre forme de démence, engendrant des coûts directs et indirects annuels totalisant 10,4$ millions de dollars (Société Alzheimer Canada, 2019). En l'absence de traitement préventif ou curatif, ce nombre pourrait approcher le million d'ici 15 ans. Cette augmentation anticipée dans l'incidence et la prévalence de la démence souligne ainsi l'urgence de mieux identifier et comprendre ces maladies dévastatrices, particulièrement la MA, pour en éviter les effets délétères sur les plans social, sociétal et économique.

D'un point de vue pathologique, la MA se définit par la présence d'agrégations de plaques amyloïdes extracellulaires et de dégénérescences neurofibrillaires intracellulaires, et son diagnostic définitif ne peut être donné qu'à l'examen neuropathologique post-mortem (Jack et al., 2018; McKhann et al., 1984, 2011). L'accumulation de plaques amyloïdes débuterait plusieurs décennies avant l'apparition des atteintes cognitives objectivables (Insel et al., 2020a; Villemagne et al., 2013). Les sites cérébraux initialement visés par l'accumulation d'amyloïde seraient des régions néocorticales présentant une forte demande métabolique, notamment le gyrus cingulaire postérieur et les gyrus frontaux médian et orbitofrontal (Mattsson et al., 2019). Avec la progression de la maladie, l'accumulation de plaques amyloïdes s'étendrait aux autres régions néocorticales associatives (p.ex. lobes temporaux, préfrontaux, pariétaux), puis finalement aux aires sensorielles et motrices (Guo et

al., 2020; Hanseeuw et al., 2018; Mattsson et al., 2019). La présence de dégénérescences neurofibrillaires serait, quant à elle, causée par l'hyperphosporylisation de protéine tau intracellulaire et provoquerait la mort neuronale (Murray et al., 2011; Goedert & Spillantini, 2019). L'accumulation anormale de protéine tau suivrait l'accumulation de plaques amyloïdes dans la séquence temporelle des processus pathologiques de la MA et débuterait également plusieurs années avant l'apparition des symptômes cognitifs (Insel et al., 2020a). Les sites initiaux d'accumulation cette protéine seraient les régions temporales internes, notamment le cortex enthorhinal et l'hippocampe. Cette pathologie se propagerait ensuite aux régions temporales, puis à l'ensemble des aires néocorticales associatives (Braak & Braak, 1991; Jack et al., 2018; Lowe et al., 2018; Maass et al., 2017; Schöll et al., 2016). Pour des causes qui sont encore peu comprises à ce jour, l'accumulation d'amyloïde et de protéine tau entrainerait synergiquement une cascade pathologique dans le cerveau de l'individu atteint. Cette cascade menerait éventuellement à une perte neuronale et une dégradation progressive des fonctions cognitives (Aisen et al., 2010; Busche & Hyman, 2020; Jack et al., 2010;2013; Jones et al., 2016; 2017; Sperling et al., 2011).

Sur le plan clinique, il existe plusieurs présentations phénotypiques de la MA dont la classification dépend de la sphère cognitive initialement touchée. Parmi celles-ci, la forme amnésique ou ''typique'' de la maladie est de loin la plus fréquente, comparativement aux variantes ''atypiques'' (variante langagière ou aphasie primaire progressive logopénique; Gorno-Tempini, 2011; variante visuelle ou atrophie corticale postérieure; Crutch et al., 2017; variante frontale ou dysexécutive; Townley et al., 2020). La forme amnésique se déclare à un âge généralement plus avancé que les formes atypiques, et affecte initialement la mémoire épisodique (McKhann et al., 2011). Cela fait en sorte que la personne atteinte éprouve des difficultés significatives à apprendre de nouvelles informations et à se rappeler d'événements circonscrits dans un espace spatio-temporel. Avec la progression de la maladie, la

symptomatologie cognitive s'étendrait à l'ensemble des autres fonctions cognitives de haut niveau (fonctions exécutives, visuospatiales, langagières). Ces atteintes mèneraient éventuellement à une dégradation de l'autonomie fonctionnelle de l'individu, correspondant ainsi au stade de démence.

Formellement, les critères d'un diagnostic clinique de démence due à une MA du *National Institute on Aging-Alzheimer's Association* (NIA-AA; McKhann et al., 2011) requièrent 1) que les critères de démence soient remplis (c.-à-d. effet sur le travail et/ou les activités du quotidien), 2) une installation insidieuse des symptômes, 3) un historique clair de détérioration de la cognition auto-rapporté ou rapporté par un proche, 4) que l'atteinte cognitive initiale concerne l'apprentissage et le rappel d'informations pour la variante amnésique de la MA et 5) l'absence d'une étiologie alternative autre que la MA pouvant mieux expliquer le tableau clinique (p.ex. démence à corps de Lewy, délirium, maladie vasculaire, accident vasculaire cérébral, etc.). Ces critères sont similaires à ceux du Trouble Neurocognitif Majeur du *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5, American Psychiatric Association, 2013), qui sont largement utilisés dans des contextes cliniques. Toutefois, ces derniers critères sont généralement utilisés pour émettre des diagnostics cliniques et pour statuer sur leur degré de sévérité, et ne représentent donc pas les critères les plus contemporains en termes d'étiologies sous-jacentes (c.-à.-d. au niveau du diagnostic différentiel).

1.1.2. Les stades pré-démentiels de la maladie d'Alzheimer

Le fait qu'un écart de plusieurs années sépare les tout premiers changements neuropathophysiologiques de la MA et son diagnostic clinique (Donohue et al., 2017; Insel et al., 2020a; 2020b; Jack et al. 2010; 2013; Jansen et al., 2015; Villemagne et al., 2013), indique que la maladie est caractérisée par une longue phase prodromale où les symptômes cognitifs sont minimaux, voire absents. Il est ainsi crucial d'identifier les individus se situant

dans la phase pré-démentielle de la MA afin de prévenir ou retarder l'effet de la maladie sur la cognition et l'autonomie. Les individus présentant un trouble cognitif léger (TCL) ou un déclin cognitif subjectif (DCS) sont particulièrement susceptibles de développer la MA (Reisberg et al., 2008; 2010; Reisberg & Gauthier, 2008) et leur condition offre l'opportunité d'étudier les signes avant-coureurs de la maladie.

1.1.2.1. Le trouble cognitif léger

Plusieurs termes et classifications ont été formulés dès le début des années 1980 pour décrire les individus âgés présentant de faibles performances cognitives, sans toutefois répondre aux critères de démence (p.ex. « *Age-Associated Memory Impairment* », Crook et al., 1986 ; « *Mild cognitive decline* », Reisberg et al., 1982; pour une revue sur le sujet, voir Blanchet et al., 2002). Le concept du TCL a grandement évolué dans les dernières décennies (voir Gauthier et al., 2006; Petersen et al., 1999; 2001; 2004; Winblad et al., 2004). Selon les plus récents critères du NIA-AA (Albert et al., 2011), le TCL se définit par 1) la présence d'une plainte cognitive, 2) des performances cognitives se situant en-deçà de ce qui est attendu en fonction de l'âge et du niveau de scolarité à des épreuves neuropsychologiques standardisées (typiquement 1 à 1,5 écart-type sous la moyenne normative), 3) la préservation de l'autonomie fonctionnelle et 4) l'absence de démence. Le fait que les critères récents du TCL ne requièrent pas nécessairement d'atteinte de la mémoire épisodique s'explique par le fait que le processus neuropathophysiologique sous-jacent peut constituer la présence d'une autre maladie que la MA (p.ex. maladie de Parkinson, démence vasculaire, lobaire fronto-temporale, etc.) ou une forme atypique de la MA (variante dysexécutive, visuelle ou langagière). Dans le but d'identifier les individus présentant un TCL dont la pathologie sous-jaçente pourrait être une MA typique, le NIA-AA a suggéré le terme de « TCL dû à une MA » (ou *MCI due to AD* en anglais). Ce sous-type de TCL requiert qu'une des sphères cognitives

atteintes soit la mémoire épisodique (d'où l'appellation « TCL amnésique »). La présence d'autres caractéristiques peut également augmenter la probabilité d'une MA sous-jaçente. Il s'agit notamment de l'allèle ε4 du gène apolipoprotéine E (APOE4), qui constitute le plus important facteur de risque génétique pour la MA (Poirier et al., 1993), et la présence de d'amyloïde et/ou de protéine tau mesurée par l'imagerie moléculaire (tomographie par émission de positrons ; TEP) et/ou dans le liquide céphalo-rachidien (LCR).

La présence d'un TCL augmente considérablement la probabilité de développer subséquemment une MA. En effet, il est estimé que 12% à 41% des individus présentant un TCL développeraient annuellement une démence (Geslani et al., 2005; Petersen et al., 1999; Schmidtke & Hermeneit, 2008) et certaines études montrent un taux de conversion allant jusqu'à 53% après trois ans (Okello et al., 2008; Tschanz et al., 2006). Chez les individus âgés sans trouble cognitif, ce taux serait plutôt de 4% (Tschanz et al., 2006). Cette proportion considérable d'individus avec un TCL qui développeront ultérieurement une démence suggère qu'un nombre non-négligeable de ces personnes se situerait dans la phase précoce de la MA. La phase du TCL offre donc l'opportunité d'étudier les mécanismes neuropathophysiologiques précoces de la maladie alors que les atteintes cognitives sont relativement limitées.

1.1.2.2. Le déclin cognitif subjectif

Tel que mentionné précédemment, il est reconnu que les changements pathologiques associés à la MA surviendraient plusieurs années avant l'apparition des atteintes cognitives objectivables (Insel et al., 2020a; Jansen et al., 2015; Villemagne et al., 2013). Les chercheurs et chercheuses se sont ainsi penchés sur l'étude d'individus présentant une plainte de mémoire en absence d'atteinte cognitive objectivée. Cette phase pourrait précéder celle du TCL et représenter le tout premier symptôme de la MA.

Le concept du DCS (ou *SCD* pour *subjective cognitive decline* en anglais) est apparu dans les années 1980 dans le cadre du développement du *Global Deterioration Scale* (GDS; Reisberg et al., 1988), qui est une échelle clinique visant à caractériser les individus dans la phase précoce de la MA. À l'époque, le terme « *Very mild cognitive decline* » était utilisé pour décrire les individus présentant une plainte de mémoire en absence d'atteinte cognitive objectivable. Toutefois, ce n'est que plusieurs décennies plus tard, suite à une compréhension plus approfondie du TCL, que la communauté scientifique s'est penchée sur les stades plus précoces de la MA. Il aura ainsi fallu attendre jusqu'en 2014 avant la publication de la première définition officielle du DCS par le *Subjective Cognitive Decline Initiative Working Group* (SCD-I) (Jessen et al., 2014). Selon cette définition, le DCS se définit par la présence d'une plainte cognitive auto-rapportée en absence d'une atteinte cognitive objectivable aux épreuves cliniques et neuropsychologiques traditionnelles (Jessen et al., 2014).

Plusieurs études prospectives ont mis en évidence des taux de progression vers le TCL ou vers la démence plus élevés (Adbulrab & Heun, 2008; Jessen, 2014; 2010; Slot et al., 2019; Treves et al., 2005; van Harten et al., 2018), ou un déclin progressif plus prononcé (Hohman et al., 2011; Reisberg et al., 2010) chez des individus présentant un DCS comparativement à des personnes âgées cognitivement saines et sans plainte cognitive. Selon ces études, le taux de progression vers le TCL varierait entre 10% et 15% sur une période de 3 à 5 ans, et le taux de progression vers la démence varierait de 16% à 34% sur une période de 3 ans, comparativement à environ 6% chez les individus sans plainte cognitive (Jessen et al., 2010; Wang et al., 2004; Snitz et al., 2018; Treves et al., 2005; van Harten et al., 2018). Dans la même veine, les études s'étant penchées sur la présence de biomarqueurs chez des individus avec un DCS ont rapporté des changements neuropathophysiologiques compatibles avec la MA. Notamment, une accumulation anormale de plaques amyloïdes et de protéine tau (Amariglio et al., 2012; Buckley et al., 2019; Swinford et al., 2018; Visser et al., 2009; Vogel

et al., 2017; Wolfsgruber et al., 2017), de l'hypométabolisme dans les régions temporo-pariétales en imagerie TEP (Scheef et al., 2012) et une atrophie des régions temporales (Jessen et al., 2006; Hu et al., 2019; Meiberth et al., 2015; Saykin et al., 2006) incluant l'hippocampe (Garcia-Ptacek et al., 2016; Scheef et al., 2012; Stewart et al., 2011; van der Flier et al., 2004) étaient observés chez ces individus. D'ailleurs, une étude a montré que la présence de plainte cognitive permettrait à elle seule de mieux prédire l'accumulation anormale d'amyloïde en imagerie TEP que le génotype APOE (Buckley et al., 2019). L'ensemble de ces études suggère ainsi fortement que le DCS pourrait représenter le tout premier indice clinique illustrant la présence d'une MA sous-jacente. L'étude des individus présentant un DCS, conjointement avec l'étude du TCL, pourrait donc s'avérer utile pour caractériser et mieux comprendre les mécanismes cérébraux précédant le stade de démence.

Des critères additionnels ont été émis par le SCD-I dans le but d'identifier les individus présentant un DCS et ayant une probabilité plus élevée d'être dans la phase préclinique de la MA (DCS *plus* ou DCS^{+}; Jessen et al., 2014). Ces critères impliquent que 1) la plainte de mémoire inquiète l'individu, 2) la plainte de mémoire soit récente (apparition dans les 5 dernières années), 3) les biomarqueurs associés à la MA soient présents, tels quel des niveaux anormaux d'amyloïde ou de tau en imagerie TEP ou dans le LCR, 4) une atrophie ou un amincissement cortical en imagerie par résonance magnétique (IRM) structurelle soient observés et 5) la présence de l'allèle APOE4 soit constatée. En 2020, des critères additionnels du DCS^{+} ont été ajoutés à ceux déjà établis, et ce en fonction des nouvelles données empiriques concernant le risque de progression en démence au sein de cette population (Jessen et al., 2020). Ces nouveaux critères incluent 1) la persistance de la plainte cognitive dans le temps et 2) le fait de rechercher de l'aide médicale en lien avec la plainte de mémoire.

1.2. Atteintes cognitives dans la maladie d'Alzheimer

Un très grand nombre d'études ont permis d'établir la sémiologie cognitive de la MA, particulièrement celle qui concerne la variante « amnésique » de la maladie. Les résultats de ces études ont été revues et analysées dans plusieurs grandes revues de la littérature (Belleville et al., 2014; Traykov et al., 2007). Dans l'ensemble, on rapporte une atteinte initiale et prédominante de la mémoire épisodique. Plusieurs autres fonctions cognitives deviennent atteintes avec la progression de la maladie, et l'ampleur des déficits augmente de facon graduelle avec le degré de sévérité clinique. Les fonctions cognitives qui seraient atteintes plus tardivement incluent entre autres certaines capacités langagières, les habiletés visuospatiales et le raisonnement (Jicha et al., 2010). Des modifications au niveau de la personnalité et du comportement peuvent également accompagner les stades tardifs de la maladie et pourraient même, dans certains cas, en représenter l'une des premières manifestations (Mega, Cummings, Fiorello, & Gorbein, 1996).

La fonction cognitive qui a reçu le plus grand intérêt est sans équivoque la mémoire épisodique, qui est généralement la première fonction cognitive à montrer un déclin dans le processus de la MA (Cloutier et al., 2015; Traykov et al., 2007). La mémoire épisodique se divise en trois processus : l'encodage, la consolidation et la récupération. La défaillance pure de l'encodage est une caractéristique de la MA permettant de la distinguer des autres maladies neurodégénératives. L'atteinte de ce processus mnésique fait en sorte que les patients montrent des difficultés à enregistrer des nouvelles informations et peinent à récuper ou reconnaître des informations apprises, et ce même lorsque des indices sur le contexte d'encodage sont présentés (p.ex. indices spatiaux, sémantiques) (Almkvist, 1999; Gallo et al., 2004; Moulin et al., 2004; Traykov et al., 2007). Il est proposé que les problèmes d'encodage dans la MA pourraient s'expliquer par une difficulté à lier un item à son contexte d'apprentissage, ce qui réfère au processus de « mémoire associative » (Dalla Barba, 1997;

Gallo et al., 2004; Koen & Yonelinas, 2014; Serra et al., 2007). Ce déficit pourrait être à tout le moins partiellement explicable par une atteinte précoce de l'hippocampe dans la MA (Apostolova et al., 2006; Chetelat & Baron, 2003; Desikan et al., 2009), qui est une région grandement impliquée dans les processus de mémoire associative (Stevenson et al., 2020).

Les atteintes de l'encodage en mémoire épisodique surviendraient très tôt dans le processus de la MA, et seraient d'ailleurs observables dès le stade du TCL. Notamment, plusieurs études ont comparé des participants TCL à des participants contrôles par l'entemise d'épreuves évaluant la mémoire épisodique (p.ex. encodage de paires de mots ou d'objets) opposant la mémoire associative (ou recollection) à la mémoire de l'item (ou familiarité) (Collie et al., 2002; Dudas et al., 2005; Hudon et al., 2009; Serra et al., 2007; Wolk et al., 2008). Les résultats de ces études ont montré des performances diminuées en mémoire associative chez des participants TCL comparativement à des participants contrôles, tandis que les performances en mémoire de l'item étaient préservées (Collie et al., 2002; Dudas et al., 2005; Hudon et al., 2009; Serra et al., 2007; Wolk et al., 2008). Par ailleurs, d'autres études ont également comparé des participants DCS à des participants contrôls et sans plainte de mémoire à l'aide de tâches expérimentales de mémoire associative (p.ex. d'associations nom-visage, reconnaissance de figures simples) (Koppara et al., 2015; Polcher et al., 2017). Les trouvailles de ces études ont mis en évidence de plus faibles performances chez des participants DCS relativement aux participants contrôles (p.ex. d'associations nom-visage, reconnaissance de figures simples) (Koppara et al., 2015; Polcher et al., 2017). Ces données suggèrent qu'un déclin précoce et subtil de la mémoire associative pourrait survenir même avant que les critères de TCL soient remplis.

En résumé, les atteintes de la mémoire épisodique sont caractéristiques de la MA, notamment sur le plan de l'encodage de nouvelles informations. La littérature scientifique indique plus particulièrement que l'atteinte de la mémoire associative, qui correspond à

l'encodage d'un item et son contexte d'apprentissage, serait observable très tôt dans la maladie et pourrait en représenter l'un des premiers symptômes.

1.3. Hyperactivation fonctionnelle : imagerie par résonance magnétique fonctionnelle

L'apport de la neuropsychologie est d'une importance capitale pour apprécier la nature et l'ampleur des atteintes cognitives résultant de processus neurodégénératifs. Toutefois, la contribution de marqueurs biologiques est essentielle pour identifier les individus se situant dans les stades pré-démentiels de la MA et pour mieux comprendre les processus fondamentaux de la maladie (Albert et al., 2018; Peters et al., 2014). L'IRM fonctionnelle (IRMf) est une méthode relativement peu onéreuse, non invasive et fiable qui offre l'opportunité d'étudier les mécanismes cérébraux dans les phases précoces de la MA (Clément & Belleville, 2009). Cette technique de neuroimagerie permet l'examen de l'activité cérébrale par le biais de la mesure du niveau d'oxygénation dans le sang (signal BOLD; *blood oxygen level-dependent*), un concept connu sous le terme « couplage neurovasculaire » (Iadecola, 2017). Elle s'avère ainsi particulièrement intéressante pour investiguer les patrons d'activation sous-tendant les fonctions cognitives atteintes précocément dans la maladie. Cela pourrait, entre autres, contribuer à la détection de marqueurs précoces dans les patrons d'activation cérébrale permettant l'identification d'individus à risque de progresser vers le stade démentiel. La prochaine section vise à décrire les études ayant utilisé l'IRMf et qui avaient pour but de déteminer s'il existe des patrons d'activation spécifiques aux patients avec une MA ou chez les individus à risque de développer la maladie.

Plusieurs études on fait appel à l'IRMf pour examiner les patrons d'activation sous-tendant des processus cognitifs atteints dans le continuum de la MA, et plusieurs d'entre elles se sont intéressées à l'encodage en mémoire épisodique. De façon générale, la grande majorité de ces études ont rapporté des niveaux inférieurs d'activation chez les participants avec un diagnostic clinique de MA comparativement aux participants contrôles, un

phénomène appelé « hypoactivation » (Celone et al., 2006; Golby et al., 2005; Machulda et al., 2003; Mandzia et al., 2002; Rombouts et al., 2000; Small et al., 1999). Notamment, plusieurs études ayant utilisé une tâche de mémoire associative d'associations « nom-visage » ont mis en évidence des hypoactivations chez de tels patients dans des régions connues pour être atteintes dans la MA, comme l'hippocampe et le lobe temporal médian (Celone et al., 2006; Small et al., 1999; Sperling et al., 2003). D'autres études ayant utilisé des tâches d'encodage de scènes ou de dessins simples et complexes ont rapporté des résultats semblables auprès de cette population, c'est-à-dire des hypoactivations dans les régions temporales et occipito-temporales (Golby et al., 2005; Rombouts et al., 2000). Ces observations ont généralement été interprétées par les auteurs comme une incapacité à activer les régions supportant les processus mnésiques à un niveau équivalent aux participants âgés contrôles. Il appert ainsi que les hypoactivations représenteraient un patron d'activation cérébrale caractéristique du stade démentiel de la MA.

Paradoxalement, plusieurs études menées auprès d'individus présentant un TCL ont rapporté des niveaux d'activation supérieurs à ceux observés chez des participants contrôles, un phénomène appelé « hyperactivation ». La présence d'hyperactivation a initialement été documentée dans une étude menée par Dickerson et al. (2004), où des niveaux supérieurs d'activation en IRMf ont été observés dans la formation hippocampique bilatéralement chez un groupe de 32 individus présentant un TCL alors qu'ils accomplissaient une tâche d'encodage de scènes visuelles. Fait notable, les participants qui montraient les niveaux d'activation les plus élevés étaient également ceux chez qui le déclin cognitif était le plus prononcé sur une période de 2,5 ans suivant l'examen en IRMf initial. Cela suggère que l'hyperactivation caractériserait les individus présentant un TCL et qui progresseront vers la MA par rapport à ceux qui demeureront cognitivement stables. Les auteurs ont donc évoqué l'hypothèse que la présence d'hyperactivation pourrait représenter un marqueur précoce de la

MA. Depuis cette étude inaugurale, d'autres recherches ont relevé la présence d'hyperactivation dans le TCL. Certaines études ont rapporté la présence d'une hyperactivation hippocampique lors de l'accomplissement de tâches de mémoire associative (c.-à-d. association visage-nom ou mot-image; Dickerson et al., 2005; Hämäläinen et al., 2007; Sperling et al., 2007; Putcha et al., 2011). D'autres études ayant examiné l'ensemble du cerveau chez des participants TCL ont observé que les hyperactivations étaient aussi présentes dans les régions néocorticales, notamment le cortex préfrontal. Ces hyperactivations étaient observées lors de l'accomplissement de tâches de mémoire épisodique verbale mais également de mémoire de travail (Clément & Belleville, 2012; 2012; Clément, Belleville, & Mellah, 2010; Clément, Gauthier, & Belleville, 2013). Il faut souligner que d'autres études ont plutôt observé des hypoactivations chez les individus présentant un TCL, et donc un patron d'activation similaire à ce qui est généralement observé chez des patients au stade démentiel de la MA. Ce patron d'hypoactivation était rapporté dans l'hippocampe (Johnson et al., 2006; Hanseeuw et al., 2015), les régions préfrontales (Dannhauser et al., 2008; Elgh et al, 2003) et le cortex cingulaire postérieur (Oedekoven et al., 2015) lors de tâches d'encodage en mémoire épisodique verbale, ce qui peut sembler en opposition avec les résultats précédemment soulevés.

Certaines études ont tenté d'expliquer la présence de ces résultats divergents dans la phase du TCL. Une proposition mise de l'avant stipule que le patron d'activation observé dépendrait du degré de sévérité clinique au sein de la phase du TCL (Celone et al., 2006; Clément & Belleville, 2012; Clément, Belleville & Mellah, 2010; Clément, Gauthier, & Belleville, 2013). Afin de tester cette hypothèse, Celone et al. (2006) ont comparé le niveau d'activation associé à l'accomplissement d'une tâche d'associations noms-visages chez un groupe de participants TCL, comparativement à des participants âgés contrôles et des patients se situant au stade démentiel de la MA. Les participants du groupe TCL ont été divisés en

deux sous-groupes, soit les « TCL précoces » et « TCL tardifs ». Ceux-ci ont été identifiés sur la base de leur score à l'échelle clinique *Clinical Dementia Rating* (*CDR-Sum of Boxes*; Hughes et al., 1982; Morris et al., 1993). Les résultats ont montré un plus haut niveau d'activation (c.-à-d. hyperactivation) dans un réseau fonctionnel sous-tendant la mémoire épisodique et incluant l'hippocampe chez les participants « TCL précoces » comparativement aux participants contrôles. Inversement, les participants « TCL tardifs » et ceux se situant au stade démentiel montraient des hypoactivations dans ce réseau. Ces résultats suggèrent que la présence d'hyper- et d'hypoactivation dépendrait du degré d'atteinte clinique. Clément & Belleville (2012) ont fourni des évidences empiriques allant dans le sens de cette hypothèse en examinant si certaines tâches étaient plus susceptibles de mettre en évidence des patrons d'hyperactivation cérébrale. Ils ont comparé l'activation cérébrale de participants TCL, identifiés soit comme précoces ou tardifs selon leur score à l'échelle clinique *Mattis Dementia Rating Scale* (*MDRS*; Mattis, 1976), à celle de participants contrôles lors d'une tâche d'encodage de paires de mots évaluant les processus de mémoire associative (recollection) et de mémoire de l'item (familiarité). De façon intéressante, les participants TCL précoces montraient de l'hyperactivation dans les régions spécialisées (c.-à-d. régions préfrontales bilatérales) et un recrutement de régions supplémentaires (c.-à-d. régions pariétales) lors de la condition de mémoire associative. De leur côté, les participants TCL tardifs montraient plutôt de l'hypoactivation lors de cette condition et de l'hyperactivation préfrontale et pariétale gauche lors de la condition de mémoire de l'item. Ainsi, les résultats de cette dernière étude supportent l'hypothèse que la présence d'hyperactivation dépendrait du degré de sévérité clinique et caractériserait la phase la plus précoce de la maladie. Ils indiquent également que les tâches sollicitant des processus cognitifs qui sont atteints lors d'une phase particulière de la maladie (p.ex. mémoire associative pour les premiers stades du TCL) sont celles qui sont les plus susceptibles d'évoquer des patrons d'hyperactivation durant cette phase.

Puisque que l'hyperactivation est observable au tout début de la phase du TCL, il est possible qu'elle puisse également être présente lors des phases préalables de la MA et en particulier chez les personnes présentant un DCS. Les études ayant examiné les patrons d'activation chez les individus présentant un DCS sont moins nombreuses que celles portant sur le TCL et la MA et incluent généralement des échantillons relativement modestes. Néanmoins, certaines études ont rapporté des niveaux d'activation plus élevés chez des participants DCS dans les régions hippocampiques et préfrontales lors de tâches mnésiques (Erk et al., 2011; Rodda et al., 2009) et dans les régions préfrontales, temporales et sous-corticales lors d'une tâche d'attention divisée (Rodda et al., 2011), comparativement à des participants âgés sains et sans plainte cognitive. Elles semblent donc indiquer que l'hyperactivation pourrait précéder l'apparition des atteintes cognitives mesurées à l'aide d'épreuves traditionnelles.

En bref, les études ayant utilisé l'IRMf pour investiguer les patrons d'activation lors de tâches cognitives chez des individus à risque de développer la MA ont généralement rapporté la présence d'hyperactivation, notamment dans le TCL précoce et le DCS. La présence d'hypoactivation était plutôt observée chez les individus plus sévèrement atteints sur le plan clinique, notamment dans le TCL tardif et la démence. L'activation cérébrale prendrait donc la forme d'un « U inversé » avec la progression de la maladie (Clément & Belleville, 2010; 2012; Clément, Belleville, & Mellah, 2010; Clément, Gauthier, & Belleville, 2013; Gregory et al., 2017 ; Sperling et al., 2010).

1.3.1. Lien entre hyperactivation et connectivité fonctionnelle

Le phénomène d'hyperactivation pourrait refléter des particularités au niveau de l'organisation des réseaux fonctionnels. Les récentes avancées ont montré que les maladies neurodégénératives n'affectent pas seulement des régions cérébrales spécifiques, mais également l'intégrité fonctionnelle de réseaux cérébraux multivariés et interactifs (Brown et

al., 2019; Jacobs et al., 2013; Raj et al., 2012; 2015; Seeley et al., 2009). Dans ce contexte, il est probable que les hyperactivations puissent être associés à des altérations sur le plan de la connectivité fonctionnelle. La présente section vise à présenter les études ayant utilisé des techniques d'analyse de la connectivité fonctionnelle afin d'investiguer les altérations dans les réseaux cérébraux fonctionnels dans le continuum de la MA. Elle vise également à identifier les liens possibles entre les patrons de connectivité fonctionnelle et le phénomène d'hyperactivation.

Certaines études s'étant intéressées aux patrons de connectivité fonctionnelle de régions vulnérables aux processus pathologiques de la MA ont rapporté des phénomènes d'hyperconnectivité similaires aux processus d'hyperactivation. Ce patron a notamment été décrit dans l'hippocampe et les régions temporales chez des groupes de participants TCL, que ce soit lors de la réalisation d'une tâche de mémoire (Das et al., 2013) ou au repos (Graski et al., 2019; Jie et al., 2016). D'autres études menées auprès d'individus présentant un DCS ont également rapporté des altérations dans les patrons de connectivité fonctionnelle entre des régions qui sont vulnérables à la MA, dont les hippocampes et les régions temporales (Jiang et al., 2018; Verfaillie et al., 2019; Yan et al., 2019).

Certaines études ont rapporté des patrons mixtes, incluant à la fois de l'hyperconnectivité et de l'hypoconnectivité (Bai et al., 2009a; 2009b; Berron et al., 2020; Pizzi et al., 2018; Gardini et al., 2015; Jiang et al., 2018; Wang et al., 2011). À titre d'exemple, Berron et al. (2020) ont montré des patrons d'hyperconnectivité au repos entre les régions hippocampiques et temporales chez une large cohorte de personnes TCL et présentant une charge amyloïde positive. Toutefois, cette hyperconnectivité s'accompagnait d'une diminution de la connectivité entre ces régions et les régions postérieures du réseau de mode par défaut, lequel est largement impliqué dans les processus de mémoire épisodique (Buckner et al., 2008; 2019; Chhatwal et al., 2018; Dennis & Thompson, 2014; Greicius et al., 2004;

Jones et al., 2011; Zhou et al., 2010). De plus, cette diminution de la connectivité entre les régions temporales et postérieures était associée à de plus faibles performances lors d'épreuves mnésiques, ainsi qu'à un plus grand déclin cognitif sur une période de 8 ans. Cela suggère que les altérations dans ces réseaux cérébraux fonctionnels refléteraient une pathologie croissante. Enfin, d'autres études ont plutôt observé une diminution de la connectivité fonctionnelle entre les régions temporales et le reste du cerveau chez des participants TCL (Bajo et al., 2010; Chen et al., 2016; Zhou et al., 2008). Ce type de patron de connectivité fonctionnelle est similaire à celui retrouvé chez les patients présentant une MA, où de l'hypoconnectivité a été observée au niveau des régions hippocampiques, temporales et cingulaires postérieures (Grajski et al., 2019; Montembault et al., 2019; Vipin et al., 2018; Wang et al., 2006; Zhou et al., 2008).

Dans l'ensemble, les études décrites ci-haut suggèrent une transition de l'hyperconnectivité vers une hypoconnectivité avec la progression de la maladie, similaire à ce qui est observé au niveau des patrons d'activation cérébrale. De façon importante, ces patrons d'altération dans la connectivité fonctionnelle surviendraient dans les régions vulnérables à la MA qui ont précédemment été décrites comme hyperactives (p.ex. hippocampe, lobe temporal). Cela suggère ainsi un lien entre l'hyperactivation retrouvée au niveau régional et la dysfonction des réseaux cérébraux fonctionnels. Ces relations restent toutefois peu explorées et mal comprises.

1.4. Modèles explicatifs de l'hyperactivation

Bien que cette thèse ne vise pas à élucider les causes biologiques de l'hyperactivation et des changements dans les patrons de connectivité fonctionnelle, il apparait pertinent de décrire brièvement les mécanismes explicatifs proposés pour ces phénomènes.

1.4.1. L'hypothèse compensatoire

Plusieurs auteurs ont proposé que l'hyperactivation observée dans la phase précoce de la MA serait compensatoire et refléterait des processus de plasticité cérébrale (Clément & Belleville, 2010; Clément, Belleville, & Mellah, 2010; Clément, Gauthier, & Belleville, 2013; Gregory et al., 2017; Prvulovic et al., 2010; Sperling et al., 2010). Les atteintes structurelles, qui seraient encore légères en début de maladie, diminueraient l'efficacité neuronale des régions atteintes. Cette perte d'efficacité ferait en sorte qu'un plus haut niveau d'activation ou de connectivité serait nécessaire dans les régions spécialisées pour le processus cognitif mis à l'épreuve afin de maintenir le niveau de performance. Cela mènerait à des activations supérieures à celles normalement attendues. Avec la progression de la maladie et l'augmentation des atteintes structurelles, la capacité d'activation neuronale serait diminuée. Cela ferait en sorte que la mise en place de mécanismes compensatoires ne serait plus possible, ce qui mènerait à une hypoactivation et un effondrement des capacités cognitives dans les stades plus avancés de la maladie.

Certains critères doivent être remplis pour qu'une hyperactivation/hyperconnectivité soit considérée comme compensatoire (pour une revue sur le sujet, voir Cabeza et al., 2018). D'abord, ces changements dans l'activation ou la connectivité doivent survenir en présence d'une condition réduisant les ressources neuronales pour accomplir la tâche cognitive (p.ex. une maladie neurodégénérative). Ensuite, l'hyperactivation/hyperconnectivité observée doit avoir un effet bénéfique sur les performances cognitives. Plusieurs études ont fourni des évidences empiriques en faveur de l'hypothèse compensatoire chez les individus à risque de développer la MA (Belleville et al., 2011; Clément & Belleville, 2012; Clément, Belleville, & Mellah, 2010; Clément, Gauthier, & Mellah, 2013; Erk et al. 2011; Kircher et al., 2007; Papma et al., 2017; Rodda et al., 2009). À titre d'exemple, certaines études ont montré que l'hyperactivation chez des participants TCL était accompagnée de performances équivalentes

à des participants âgés contrôles lors d'épreuves mnésiques expérimentales (Clément & Belleville, 2012; Clément, Belleville, & Mellah, 2010). Dans la même veine, d'autres recherches ont montré que le degré d'hyperactivation ou d'hyperconnectivité était positivement corrélé aux performances en mémoire (Bai et al., 2009a; 2009b; Bajo et al., 2010; Bodke et al., 2006; Clément, Gauthier, & Mellah, 2013; Kircher et al., 2007; Pampa et al., 2017). Des résultats similaires ont été observés chez des participants DCS, où un niveau supérieur d'activation préfrontale observé lors de l'accomplissement de tâches de mémoire et d'attention divisée était associé à de meilleures performances cognitives (Erk et al., 2011; Rodda et al., 2009).

1.4.2. L'hypothèse excitotoxique

L'hypothèse excitotoxique a pris source dans les modèles animaux. Cette hypothèse propose que l'hyperactivation observée dans la phase prodromale de la MA contribuerait aux processus pathologiques de la maladie par le biais d'une boucle neuropathophysiologique rétroactive (Bero et al., 2011; Busche et al., 2012; Busche & Konnerth, 2015; Busche et al., 2019; Jagust, 2009; Harris et al., 2020; Palop & Mucke, 2016; Rodriguez et al., 2019; Wu et al., 2016; Zott et al., 2018). Bien que l'événement initial demeure à déterminer, l'hyperactivation locale serait étroitement liée à l'accumulation précoce d'amyloïde soluble et de protéine tau (Bero et al., 2011; Busche et al., 2012; Busche & Konnerth, 2015; Palop & Mucke, 2016; Pasquini et al., 2019; Zott et al., 2019). Cette hyperexcitabilité aurait pour effet d'intensifier la propagation spatiale de la protéine tau aux régions fonctionnellement connectées à celles étant hyperactives, résultant en une dysfonction de ces réseaux cérébraux fonctionnels (Busche et al., 2019a; 2019b; Hallinan et al., 2019; Franzmeier et al., 2019; 2020; Ossenkoppele et al., 2019; Ovsepian et al., 2018; Rodriguez et al., 2019; Vogel et al., 2020; Wu et al., 2016). Toutefois, l'accumulation accrue de protéine tau mènerait éventuellement à une perte neuronale (Brown et al., 2019; Mutlu et al., 2017), qui serait à son

tour associée à une diminution de l'activation cérébrale et de la connectivité fonctionnelle dans les stades avancés de la maladie (Jones et al., 2016; 2017). Ainsi, tout comme l'hypothèse compensatoire, l'hypothèse excitotoxique prédit que la trajectoire de l'activation cérébrale prendrait la forme d'un « U inversé » dans le continuum de la MA. En effet, l'hyperactivation observée en début de maladie serait étroitement liée à l'accumulation débutante de plaques amyloïde et de protéine tau, tandis que l'hypoactivation dans ses stades plus tardifs serait plutôt causée par la mort neuronale découlant de l'accumulation accrue de protéine tau.

De façon générale, un rôle excitotoxique peut être attribué à l'hyperactivation si celle-ci contribue à une diminution des performances cognitives et/ou une exacerbation des processus pathologiques de la MA. Plusieurs études empiriques sont en faveur de cette hypothèse. Par exemple, Bakker et al. (2012; 2015) ont montré chez un échantillon restreint de participants atteints d'un TCL qu'une réduction de l'activation hippocampique induite via l'administration de levetiracetam, un médicament antiépileptique, menait à de meilleures performances mnésiques. D'autres études ont rapporté une corrélation négative entre l'activation hippocampique et les performances en mémoire chez des participants avec un TCL (Putcha et al., 2011) ou chez des personnes âgées asymptomatiques mais présentant un niveau anormalement élevé d'amyloïde ou de tau (Berron et al., 2019; Elman et al., 2014; Marks et al., 2017). D'autres recherches ont directement examiné le lien entre l'hyperactivation et l'hyperconnectivité et la présence de protéines associées à la MA. Ces études ont montré une association entre un plus haut degré d'activation ou de connectivité fonctionnelle et des niveaux plus élevés d'amyloïde (Foster et al., 2018; Kennedy et al., 2018; Leal et al., 2017) et de protéine tau (Adams et al., 2019; Berron et al., 2019; Franzmeier et al., 2019; 2020; Gordon et al., 2015; Huijbers et al., 2018; Vogel et al., 2020). Maass et al. (2019) ont d'ailleurs montré que la présence d'hyperactivation au sein de régions cérébrales

associées à différents processus mnésiques chevauchait la topographie spatiale d'accumulation de protéines amyloïde et tau. Ces observations indiquent que l'hyperactivation surviendrait dans les régions vulnérables des réseaux cérébraux supportant les fonctions mnésiques.

Il demeure toutefois incertain si l'hyperactivation retrouvée dans ces régions contribue aux processus pathologiques observés ou reflète plutôt des mécanismes compensatoires pour contrer leurs effets néfastes sur la cognition. En fait, les propositions compensatoires et excitotoxique ne sont pas nécessairement mutuellement exclusives. L'hyperactivation régionale et l'hyperexcitabilité des réseaux fonctionnels observées en début de maladie pourairent bel et bien représenter des phénomènes de compensation transitoires ayant pour but de maintenir les performances cognitives à un seuil optimal. Ensuite, l'hyperexcitabilité chronique pourrait contribuer à l'orchestration de la propagation spatiale de protéines pathologiques et compromettre l'intégrité des réseaux fonctionnels supportant les fonctions cognitives de haut niveau (Jones et al., 2016; 2017).

Il a aussi été proposé que les mécanismes sous-tendant l'hyperactivation pourraient différer en fonction de la région cérébrale où elle est observée (Leal et al., 2017; Marks et al., 2017). D'une part, plusieurs études et certains modèles confèrent un statut particulier à l'hippocampe, dont l'activation anormalement élevée pourrait être vectrice de processus neuropathophysiologiques (Bakker et al., 2012; 2015; Berron et al., 2019; Busche et al., 2012; 2019a; 2019b; Busche & Konnerth, 2015; Hallinan et al., 2019; Huijbers et al., 2019; Leal et al., 2017; Zott et al., 2019). D'autre part, les régions néocorticales, notamment les aires pariétales, pourraient avoir un rôle plus strictement compensatoire. En effet, certaines études ont montré que le niveau d'hyperactivation de ces régions était lié à de meilleures performances cognitives de façon tranversale chez des individus asymptomatiques présentant

une charge amyloide positive (Elman et al., 2014) ou suite à une intervention cognitive chez des individus avec un TCL (Belleville et al., 2011).

Alors que la nature compensatoire versus excitotoxique de l'hyperactivation demeure à élucider, il n'en demeure pas moins que ces deux hypothèses proposent que l'hyperactivation pourrait représenter un biomarqueur très précoce de la MA et que la forme de l'activation cérébrale prendrait la forme d'un « U inversé » avec la progression de la maladie. L'hyperactivation pourrait ainsi jouer un rôle clé dans l'identification d'individus à risque de développer la MA alors que les symptômes cognitifs sont légers ou absents.

1.5. Résumé des éléments clés qui motivent ce travail

L'état actuel des connaissances indique que plusieurs enjeux demeurent en lien avec le phénomène d'hyperactivation cérébrale et son association aux réseaux cérébraux fonctionnels chez les individus à risque de développer la MA.

D'abord, il reste à déterminer si l'hyperactivation est présente chez des individus TCL ayant bel et bien progressé vers le stade démentiel. La vaste majorité des études menées à ce jour ont utilisé un protocole tranversal pour évaluer les patrons d'activation cérébrale de personnes avec un TCL, sans effectuer de suivi clinique à long terme. Or, il est reconnu qu'une proportion relative de personnes avec un TCL ne progresseront pas vers le stade de démence et peuvent rester cognitivement stables, voire même revenir à une cognition normale (Norlund et al., 2005; Portet et al. 2006). Ces études n'ont ainsi pas été clairement en mesure d'identifier les individus TCL ayant réellement progressé vers le stade démentiel.

Le choix du devis renvoie également à la question de la trajectoire de l'activation dans le TCL. Bien que les études décrites ci-haut suggèrent qu'une transition de l'hyperactivation à l'hypoactivation surviendrait au cours de la phase du TCL, la grande majorité de ces études a été menée à l'aide de protocoles transversaux. Ce type de protocole compare les différences d'activation entre des groupes qu'on infère être à des stades différents de la maladie, mais ne

mesure pas directement le changement d'activation cérébrale à travers le temps. Les protocoles longitudinaux permettent quant à eux de mesurer le changement d'activation à travers le temps au sein d'une même groupe d'individus.

À notre connaissance, seules deux études ont utilisé un protocole longitudinal pour examiner les patrons de changement d'activation associés à des tâches d'encodage en mémoire épisodique au cours du TCL (Huijbers et al., 2015; O'Brien et al., 2010). Les résultats de ces études ont montré qu'une hyperactivation hippocampique gauche lors du premier examen était suivie d'une diminution de l'activation et d'un déclin cognitif plus prononcé lors du suivi longitudinal. Cette observation concorde avec la proposition que l'hyperactivation de régions supportant les processus mnésiques au début du TCL est suivie d'une diminution de l'activation et d'un affaiblissement des capacités cognitives. Toutefois, ces études n'ont pas distingué les individus avec un TCL ayant ultérieurement progressé vers le stade de démence de ceux étant demeurés cognitivement stables ou dont la cognition est revenue à la normale. Elles ne permettent donc pas de conclure que la présence d'hyperactivation est spécifique au prodrome de la MA.

Une autre question est de savoir si l'hyperactivation est présente dans le stade du DCS et donc, si elle précède l'apparition des atteintes cognitives. Jusqu'à maintenant, la grande majorité des études s'étant penchées sur le phénomène d'hyperactivation portait sur le TCL et la démence. Le stade du DCS offre l'opportunité d'examiner la présence d'hyperactivation en amont du TCL, alors que les performances cognitives sont normales. Bien que certaines études aient montré des niveaux d'activation supérieurs chez des individus DCS comparativement à des groupes contrôles (Erk et al., 2011; Rodda et al., 2009; 2011), celles-ci sont composées d'échantillons modestes et ont uniquement reposé sur la plainte de mémoire auto-rapportée pour caractériser leur échantillon.

Par ailleurs, l'hypothèse voulant que l'activation suive la forme d'un « U inversé » dans le continuum de la MA est inférée sur la base de différentes études chacune évaluant des partients à différents stades de la maladie. Toutefois, cette hypothèse n'a jamais été testée directement chez un ensemble d'individus qui couvrent le spectre du prodrome de la MA en examinant, par exemple, un échantillon regroupant des personnes présentant un DCS ou un TCL. L'inclusion de participants couvrant un plus large spectre du continuum de la MA permettrait d'évaluer la forme de la courbe d'activation selon le degré de sévérité de la maladie. Cela contribuerait à définir la fenêtre temporelle où l'hyperactivation est maximale dans le continuum de la maladie.

Un dernier enjeu concerne le lien entre l'hyperactivation et l'intégrité des réseaux cérébraux fonctionnels supportant la mémoire. Plusieurs modèles animaux et certaines études menées chez l'humain suggèrent que l'hyperactivation régionale pourrait compromettre l'intégrité de réseaux cérébraux fonctionnels supportant les capacités cognitives de haut niveau (Chhatwal et al., 2018; Franzmeier et al., 2019; 2020; Jones et al., 2011; 2016; 2017; Sepulcre et al., 2017; Schultz et al., 2017). Or, les études s'étant penchées sur l'hyperactivation et la dysfonciton des réseaux cérébraux fonctionnels dans le contexte de la MA ont examiné ces deux phénomènes de façon isolée. De plus, la vaste majorité des études en connectivité fonctionnelle ont évalué les réseaux cérébraux fonctionnels à l'état de repos, ce qui est ne permet pas d'étudier les réseaux sous-tendant les atteintes cognitives (Mill et al., 2019).

1.6. Objectifs et hypothèses

L'objectif général de cette thèse était d'évaluer la présence et la trajectoire de l'hyperactivation cérébrale chez des individus à risque de développer la MA. Elle avait également pour but d'examiner la relation entre l'hyperactivation et les réseaux cérébraux fonctionnels supportant les capacités de mémoire. Pour ce faire, des groupes d'individus avec

un TCL ou un DCS, et des sujets contrôles appariés, ont été évalués à l'aide de l'IRMf alors qu'ils accomplissaient des tâches d'encodage en mémoire épisodique. La thèse comprend trois études, chacune faisant l'objet d'un article empirique. L'étude 1 comprend des individus TCL ayant ultérieurement progressé vers le stade démentiel, ainsi qu'un groupe d'individus cognitivement sains (groupe contrôle). Les deux groupes ont été évalués à l'aide d'examens par IRMf à deux reprises sur un intervalle de deux ans, ce qui a permis d'étudier le changement longitudinal dans l'activation cérébrale associée à la tâche de mémoire. Un deuxième échantillon, dont les résultats sont rapportés dans les études 2 et 3, comprend des participants avec un DCS *plus* ou DCS^{+} (Jessen et al., 2014; 2020), des individus avec un TCL, ainsi qu'un groupe contrôle composé d'individus cognitivement sains. Les individus DCS^{+} présentent une plainte de mémoire en absence d'atteinte cognitive aux épreuves cliniques traditionnelles, en plus de marqueurs de neurodégénerescence (faible volume hippocampique) et/ou génétiques (c.-à-d. gène APOE4) pour la MA. Tous les participants ont été évalués à l'aide d'un protocole transversal en IRMf afin d'évaluer les patrons d'activation cérébrale et de connectivité fonctionnelle au sein de ces groupes. Un article supplémentaire ayant été réalisé parallèlement à cette thèse est présenté en Annexe I et porte sur la validation d'un environnement en réalité virtuelle pour évaluer la mémoire auprès de personnes âgées cognitivement saines.

1.6.1. Étude 1 – *Evidence of parietal hyperactivation in individuals with MCI who progressed to dementia: A longitudinal fMRI study*

1.6.1.1. Objectifs :

L'article 1 visait à déterminer la présence, la localisation et la trajectoire longitudinale de l'hyperactivation chez des personnes avec un TCL ayant ultérieurement progressé vers le stade de démence. Pour répondre à ces objectifs, 26 personnes TCL et 14 participants âgés cognitivement sains ont pris part à un examen en IRMf lors duquel ils accomplissaient une

tâche d'encodage de paires de mots, et ce à deux reprises sur un intervalle de deux ans. Une évaluation clinique effectuée tous les deux ans a permis de distinguer les participants TCL ayant ultérieurement progressé vers une démence de ceux étant demeurés stables sur le plan cognitif.

1.6.1.2. Hypothèses :

Il était attendu que les individus présentant un TCL et ayant ultérieurement progressé vers une démence montrent de l'hyperactivation, c'est-à-dire des niveaux d'activation supérieurs à ceux des contrôles âgés cognitivement sains. Ce patron d'hyperactivation était attendu dans l'hippocampe et dans les régions corticales structurellement atteintes chez les individus TCL. Il était attendu que l'activation diminue lors du suivi longitudinal.

1.6.2. Étude 2 – *A quadratic function of activation in individuals at risk of Alzheimer's disease*

1.6.2.1. Objectifs :

Le but de l'article 2 était de d'examiner la fonction mathématique qui caractérise l'activation cérébrale en fonction du degré de sévérité clinique dans un groupe d'individus à risque de développer la MA. Cette étude visait également à déterminer si l'hyperactivation était présente dans le stade du DCS^{+}, soit avant l'apparition des atteintes cognitives. Pour ce faire, 28 individus présentant un DCS^{+} et 26 personnes avec un diagnostic de TCL amnésique, ainsi que 54 participants âgés cognitivement sains et n'étant pas porteurs de l'APOE4 (groupe contrôle) ont été recrutés. Tous les participants ont pris part à un examen d'IRMf lors duquel ils accomplissaient une tâche d'encodage en mémoire associative où ils devaient mémoriser des images ainsi que leur position spatiale.

1.6.2.2. Hypothèses :

Il était attendu qu'une fonction quadratique prenant la forme d'un « U-inversé » décrive l'activation cérébrale en fonction du degré de sévérité de la maladie. De plus, de

l'hyperactivation, c'est-à-dire des niveaux supérieurs d'activation relativement aux participants contrôles, était attendue chez les personnes avec un DCS^{+}.

1.6.3. Étude 3 – *Latent patterns of task-related functional connectivity in relation to regions of hyperactivation in individuals at risk of Alzheimer's disease*

1.6.3.1. Objectifs :

L'article 3 avait pour but d'examiner les patrons de connectivité fonctionnelle associés aux régions hyperactives chez des individus à risque de développer la MA. Elle visait également à évaluer comment l'hyperactivation et les patrons de connectivité fonctionnelle sont associés aux performances de mémoire. Cette étude a fait appel au même échantillon et à la même tâche de mémoire que ceux utilisés pour l'étude 2.

1.6.3.2. Hypothèses :

Il était attendu que l'hyperactivation soit associée à la dysfonction de réseaux cérébraux fonctionnels supportant les capacités mnésiques chez des individus à risque de développer la MA. Il était également attendu que l'hyperactivation et les patrons de connectivité fonctionnelle soient associées aux performances de mémoire.

CHAPITRE 2 – Article 1

Evidence of parietal hyperactivation in individuals with mild cognitive impairment who progressed to dementia: A longitudinal fMRI study

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Abstract

Hyperactivation, which is defined as a higher level of activation in patients compared to cognitively unimpaired older adults (controls; CTL), might represent an early signature of Alzheimer's Disease (AD). The goal of this study was to assess the presence and location of hyperactivation in individuals with mild cognitive impairment (MCI) who were later diagnosed with dementia, examine how hyperactivation changes longitudinally, and whether it is related to time before dementia. Forty participants, 26 with MCI and 14 CTL were enrolled in the study. Magnetic resonance imaging was used to measure functional activation while participants encoded word-pairs as well as cortical thickness and regional brain volume at study entry (Y0) and two years later (Y2). Clinical follow-up was completed every two years following study entry to identify progressors (pMCI), that is, individuals who later received a diagnosis of dementia. Task-related activation was assessed in pMCI in both hippocampi and in regions showing greater cortical thinning from Y0 to Y2 compared to CTLs. Hyperactivation was found in pMCI individuals in the right supramarginal gyrus. Persons with pMCI also showed hypoactivation in the left hippocampus and left pars opercularis. Both hyper- and hypoactivation were present at Y0 and Y2 and did not change longitudinally. Activation was not associated with time before dementia diagnosis. Smaller volume and thinner cortical thickness were associated with shorter time to diagnosis in the left hippocampus and left pars opercularis. In conclusion, hyperactivation was found in individuals who later progressed to dementia, confirming that it might represent an early biomarker to identify individuals in the prodromal phase of AD and that its understanding could contribute to elucidate the key brain mechanisms that precede dementia.

Keywords: Mild cognitive impairment; Alzheimer's disease; Task-related hyperactivation; Longitudinal fMRI; Episodic memory

Introduction

Alzheimer's Disease (AD) is progressive and its onset probably occurs 20 to 30 years prior to clinical diagnosis (Jansen et al., 2015; Villemagne et al., 2013). Thus, studying the prodromal phase of AD is of a tremendous importance to contribute to its early diagnosis and better understand its early effects on the brain. Persons meeting criteria for Mild cognitive impairment (MCI) have a high likelihood of progressing to dementia (Gauthier et al., 2006; Petersen et al., 1999; 2001, Winblad et al. 2004) thus, making it a suitable target population to study the early phase of the disease.

A number of studies have observed hyperactivation in MCI individuals, that is, higher level of brain activation than what is found in cognitively unimpaired older adults (controls; CTL) (Celonne et al., 2006; Clément & Belleville, 2010; 2012; Clément, Belleville, & Mellah, 2010; Clément, Gauthier, & Belleville, 2013; Putcha et al., 2011). This is in contrast with studies of persons with dementia who most often reported hypoactivation i.e., lower levels of activation in patients than in CTLs (Golby et al., 2005; Hämäläinen et al., 2007; Machulda et al., 2003; Mandzia, Black, Grady, McAndrews, & Graham, 2002; Rombouts et al., 2000; Small, Perera, DeLaPaz, Mayeux, & Stern, 1999). Thus, the presence of hyperactivation might represent an early signature of the disease. It might also reflect key mechanisms regarding how the early neuropathology of AD leads to clinical symptoms of dementia (Clément & Belleville, 2010; 2012; Clément, Belleville, & Mellah, 2010; Leal, Landau, Bell, & Jagust, 2017; Mutlu et al., 2017; Sperling et al., 2010). However, a few studies have also observed hypoactivation in MCI and therefore, it is critical to better understand the conditions that lead to hyperactivation and the reasons for such discrepancy (Johnson et al., 2006; Hampstead et al., 2011; Hanseeuw et al., 2011; Machulda et al., 2003; 2009).

The finding of both hypoactivation and hyperactivation in MCI might have a number of possible explanations. First, not all MCI progress to dementia and very few studies about hyperactivation have followed this group over time to separate progressors from stable MCI (sMCI). If hyperactivation is specific to progressors, including non-progressors might contribute to reduce or hinder the effect.

It has also been proposed that task-related activation follows a non-linear inverse U-shape trajectory with disease progression (Clément & Belleville, 2010; 2012; Gregory et al., 2017; Prvulovic et al., 2005). One account is that increased compensatory activation would occur when neural loss is mild but would no longer be possible when the neuronal insult becomes more important, producing hypoactivation and cognitive breakdown (Prvulovic et al., 2005). Another account proposes that early amyloid accumulation would increase the production and inhibit recapture of glutamate which would result in hyperactivity (Berro et al., 2011; Busche & al., 2012; Busche & Konnerth, 2015; Jagust et al., 2009). Aberrant synaptic activity would contribute to an increase in amyloid and tau production, which would lead to increased neuronal death (Esposito et al., 2013; Lee et al., 2005; Wu et al., 2016), and this whole pattern would account for the inverse U-shape activation. The hypothesis of an inverse U-shape pattern was partly supported by transversal studies from Clément and Belleville (2010; 2012), and Clément, Gauthier & Belleville (2013). They observed hyperactivation in early MCI and hypoactivation in late MCI when participants completed tasks known to be impaired in MCI (associative memory: Clément & Belleville, 2010; recollection: Clément & Belleville, 2012; working memory and divided attention: Clément, Gauthier, & Belleville, 2013). Therefore, prior findings suggest that task-related hyperactivation characterize the earliest phase of MCI and that it is followed by hypoactivation as patients progress to dementia. However, these studies relied on a transversal design where they compared groups of ‘’early’’ vs. ‘’late’’ MCI persons based on their scores

on a clinical scale. This has limitations because combining patients at different disease stages might reflect interindividual differences in activation and conceal genuine changes caused by the progression of the disease. Therefore, the effect of hyperactivation can be best assessed with longitudinal studies where intraindividual change is privileged over interindividual differences. Furthermore, only a longitudinal follow-up can exclude MCI persons who will not progress to dementia.

Very few studies used a longitudinal design to measure brain activation changes in MCI persons. Two studies reported that higher hippocampal task-related activation at baseline preceded decrease of activation and cognitive decline in MCI individuals (Huijbers et al., 2015; O'brien et al., 2015). This supports the descending phase of the inverse U-shape of activation co-occurring with cognitive breakdown. However, these studies only assessed activation in the hippocampus. To determine whether this longitudinal pattern of hyperactivation is specific to the hippocampus or whether it is also observed in cortical regions might help contribute to understanding the source of hyperactivation and its relation to cognition. Moreover, although these previous longitudinal studies involved a follow-up, they did not separate their group to examine if hyperactivation was only found in MCI individuals who later developed dementia.

In summary, hyperactivation has great potential as an early signature of AD and in accounting for the dynamic of brain changes with the disease. However, it is critical to confirm its presence in MCI later progressing to dementia and to determine its localization and temporal pattern. Thus, a first objective was to assess whether hyperactivation is present in MCI individuals who later progressed to dementia (pMCI). MCI participants received a clinical assessment over many years following recruitment which allowed to identify pMCI and examine hyperactivation in that group. A second objective was to assess whether hyperactivation is found only in the hippocampus or if it is also observed in cortical regions.

We used a region of interest (ROI) approach and assessed task-related activation only in regions showing cortical thinning over a two-year period. This approach was selected for several reasons. First, our study is based on the model that increased activation occurs in regions that suffer mild neural loss and that as the damage becomes more important, recruitment is no longer possible and hypoactivation occurs. Hence, regions with structural impairment are those that should preferentially show altered fMRI activity i.e., hyperactivation in the early disease phase followed by hypoactivation (Clément & Belleville, 2010; 2012; Gregory et al., 2017; Prvulovic et al., 2005). Based on this model, one should select brain regions according to the likelihood that they will have suffered structural impairment. This has the additional pragmatic advantage that it reduces the number of regions examined and the likelihood of type I error which might occur due to multiple comparisons. The latter is a well-recognized risk in fMRI studies inherent to voxel-wise whole-brain between-group comparisons. Additionally, the approach is consistent with influential and seminal studies which have focused on brain regions known to be structurally impaired in early AD and have found increased activation in individuals in the prodromal phase of AD (Dickerson et al., 2004; Huijbers et al., 2015; O'Brien et al., 2010; Putcha et al. 2011). Task-related activation was also assessed in the hippocampus where AD-related structural changes are known to occur very early in the disease process. A third objective was to study how hyperactivation changes over time by measuring activation twice over a two-year period. pMCI are expected to show hyperactivation, that is, larger task-related activation than CTLs in both hippocampi and in structurally-impaired cortical regions. Hyperactivation is expected to decrease with time.

A secondary objective was to assess whether task-related activation relates with time before the clinical diagnosis of dementia. This was done because even though we used a longitudinal design, different entry points might prevent us from observing activation

changes, as some individuals may be in the ascending portion of the inverse U-shape function, and others in the descending one. Examining activation as a function of time to dementia diagnosis might provide more precise information regarding the position of the participants on the MCI-to-dementia continuum. We also assessed the relationship between hippocampal volume/cortical thickness and time to diagnosis to support the validity of the measure.

Methods

Participants

Forty participants, 26 persons with MCI and 14 CTLs, were recruited for this study[1]. All participants were native French speakers and right-handed. Participants with MCI were recruited from memory clinics and met the criteria for single or multiple domains amnestic MCI (Petersen et al., 2001; Petersen et al., 1999; Winblad et al., 2004), in that 1) they worried about their memory, 2) they performed at least 1.5 standard deviation below age- and education-adjusted norms on neuropsychological memory tests, 3) they did not show global cognitive impairment on the basis of the Mini-Mental State Evaluation (MMSE, adjusted for age and education; Folstein, Folstein, & McHugh, 1975), and 4) they were not impaired in their activities of daily living on the basis of the Functional Autonomy Measurement System (SMAF; Hébert, Carrier, & Bilodeau, 1988) and clinical interview. At baseline and follow-up, individuals with MCI underwent a neuropsychological assessment to measure their episodic memory (RL/RI-16, free and cued word recall task (Buscke, 1984; Van der Linden & Adam, 2004), 20-min delayed recall of the Rey Complex Figure (Rey, 1959), executive functions (third plate of the Stroop-Victoria (Regard, 1981) and copy of the Rey Complex Figure), visuospatial processing (Benton Judgment of line orientation; Benton, Hamsher, Varney, & Spree, 1983), speed of information processing (Coding of the WAIS-III; Weschler, 1997), language (Boston Naming Test; Kaplan, Goodglass, & Weintraub, 1983), and global

[1] The participants were part of a larger group initially described in Clément & Belleville, 2010; 2012.

cognitive functions (Mattis Dementia Rating Scale; Mattis, 1976). They also underwent an extensive medical, neurological and neuroradiological examination to exclude the existence of any systemic, neurological, or psychiatric condition that could account for the cognitive impairments. MCI individuals received the same clinical assessment every two years following recruitment to identify whether they progressed to dementia according to the NINCDS-ADRDA (McKhann et al., 1984) and DSM-IV criteria (American Psychiatric Association, 2000). The two-year follow-up was continued for up to 6 years.

CTL older adults received an abbreviated neuropsychological assessment covering episodic memory (RL/RL-16, free and cued word recall task), speed of information processing (Coding sub-test of the WAIS-III), and global cognitive functions (MDRS, MMSE) at entry of the study to characterize their cognition. CTLs were followed over the two-year period of the study.

General procedure

At baseline (Y0), a first session was used to provide informed consent and to complete the clinical and neuropsychological assessment. One week later, participants were familiarized with the MRI procedure and task, with a simulator that imitates the MRI environment. This ensured that participants understood the task and were comfortable with the scanning procedure and environment. The MRI examination was done in a separate session which took place one week following simulation. Longitudinal follow-up (Y2) was done approximatively two years following the first MRI session (18 to 30 months later) with the same MRI and clinical procedure as for Y0. Follow-up assessments were repeated on Y4 and Y6 following initial recruitment using the clinical and neuropsychological assessment only. The study was approved by the Comité mixte d'éthique de la recherche du Regroupement Neuroimagerie/Québec (CMER-RNQ) ethic committee.

fMRI memory task

Participants were asked to memorize 16 lists of nine concrete word pairs. Following the encoding of one list, participants were shown eight word-pairs and were asked to indicate whether the pair was part of the learning list or not. Retrieval lists included four pairs that were part of the learning list and four new pairs. Half of the new pairs were made up of an old and a new word and half were made up of old words that were rearranged to make new pairs. All words were one- or two-syllables long and the different lists were matched as much as possible for mean frequency, average word length and semantic relatedness.

The task was programmed on E-prime (Psychology Software Tool, Pittsburgh, Pennsylvania) and stimuli were projected onto a mirror. Pairs were presented sequentially at a rate of 4 seconds (s) per pair. Before each block of encoding, a brief instruction to memorize the word pairs was presented. Scanning was done in two separate runs. Each run was composed of four alternating series of cross fixation (20s), encoding instructions (4s), encoding (36s), retrieval instructions (4s), and retrieval phase (40s). Only the encoding data is presented here.

Data acquisition

MRI sessions were performed using a SIEMENS 3T Magnetom TRIO System (Erlangen, Germany) at the Unité de Neuroimagerie Fonctionnelle (UNF) of the Institut universitaire de gériatrie de Montréal. The structural images were obtained with a sagittal T1-weighted three-dimensional MPRAGE sequence at the end of the scan session (Time of repetition (TR)/Time of echo (TE) = 1950/3.93 milliseconds (ms), flip angle = 15^{o}; 176 slices, voxel size = 1 x 1 x 1 millimeter (mm), field of view (FOV) = 256 mm, matrix = 256 x 256). Functional MR images were acquired using gradient-echo echo-planar imaging sequences (GE-EPI) sensitive to blood oxygen level-dependent (BOLD) contrast (TR/TE = 2000/30 ms, flip angle = 90^{o}, 31 interleaved slices, voxel size = 3.75 x 3.75 x 5 mm with a gap of 1 mm, FOV = 240 mm, matrix = 64 x 64).

MRI image processing

Longitudinal data were analyzed using the FreeSurfer 5.3 longitudinal pipeline (Reuther, Schmansky, Rosas, & Fischl, 2012), which consists in the normalization of all scans belonging to a subject into an individual template instead of individual sessions. Cortical reconstruction and volumetric segmentation (Dale, Fischl, & Sereno, 1999) included motion correction of individual T1-weighted images, removal of non-brain tissue using a hybrid watershed/surface deformation procedure, automated transformation into the Talairach stereotaxic space, segmentation of the cortical and subcortical grey and white matter volumetric structures (Desikan et al., 2006; Fischl et al., 2004), intensity normalization (Sled, Zijdenbos, & Evans, 1998), tessellation of the boundary between grey and white matter, and an automated topology correction (Ségonne et al., 2004). Individual data were inspected at each step and manual corrections were applied when necessary. The preprocessing stream was re-run for each edited step and re-examined to ensure that image quality was optimal. Hippocampal volumetric data were derived according to the Desikan-Killany atlas (Desikan et al., 2006) and were corrected as a function of the total intracranial volume (ICV; Raw hippocampal volume/Intracranial volume X 100).

fMRI image processing

Prior to preprocessing, fMRI images for each subject were first corrected for movements using "BadSlice correction" included in the "Artrepair" software (http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html). Images were then preprocessed and analyzed using Statistical Parametric Mapping (SPM12; http://www.fil.ion.ucl.ac.uk/spm). Functional data were realigned to the median image acquired in the session, and a mean image was created for each subject. Realigned volumes were then normalized into Montreal Neurological Institut (MNI) stereotaxic space and spatially smoothed with an 8mm Full width at half maximum (FWHM) Gaussian kernel. Data

were modelled with the canonical dynamic response function, and a high pass filter of 208s was used in order to exclude low-frequency variations.

Statistical analysis

Since the main focus of the paper was to assess task-related activation in pMCI, analyses were first performed on this subgroup. They were then repeated on all MCI to facilitate comparison with published data that do not separate pMCI and sMCI though the entire group is not a focus of our paper.

Behavioral performance was measured with a memory score which takes into consideration both hits and false alarms: ((hit rates/total stimuli) – (false alarm/total stimuli)). Performance was analyzed with a mixed analysis of variance (ANOVA) using Group (pMCI/all MCI, CTL) as a between-subject factor, and Time (Y0, Y2) as a within-subject factor. All behavioral analyses were done using the Statistical Package for Social Sciences (SPSS) v.25.0.

Structural brain analyses were conducted in the QDEC interface of FreeSurfer 5.3 to identify cortical regions with cortical thinning. This method was used since it is well suited to assess longitudinal cortical thickness changes between two groups and because the analysis can simplify the models to a paired analysis when there are only two time points (Reuter, Schmansky, Rosas, & Fischl, 2012). A General Linear Model (GLM) with a Monte Carlo simulation correction with a threshold set at $p < .005$ with a smoothing of 10 mm FWHM was used to test slope differences in thickness from Y0 to Y2 between CTL and MCI (pMCI/all MCI) individuals. Hippocampal volumes were extracted from FreeSurfer and exported in SPSS. Hippocampal volume was analyzed using Group (pMCI/all MCI, CTL) as a between-subject factor, and Hemisphere (left, right) and Time (Y0, Y2) as within-subject factors.

The fMRI design was a block design in order to maximize statistical power (Liu & Frank, 2004). The instruction blocks were modelled as a condition of no interest. Within-

group voxel-wise comparisons were first performed for the ‘’encoding’’ vs. ‘’cross fixation’’ contrast using random effect models at both times of measure in order to assess regions activated by the task. This was done with a threshold of $p < .05$ and family-wise correction (FWE). Functional ROI spheres were then created using the toolbox MARSeille Boîte À Région d’intérêt (Marsbar) (http://marsbar.sourceforge.net) on regions showing steeper slope in cortical thickness in pMCI compared to CTL from Y0 to Y2 on the basis of the QDEC analysis using their peak coordinates. Since MRI and fMRI analyses were done using the Talairach and MNI templates respectively, we assessed the correspondence between coordinates using the Yale BioImage Suite Package application (http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html; Lacadie et al., 2008) to build ROIs. Hippocampi ROIs were built using the PickAtlas toolbox (Maldjian, Laurienti, Kraft, & Burdette, 2003). Functional betas values obtained via ROI analyses were then extracted from MATLAB (https://www.mathworks.com/products/matlab.html) and exported in SPSS. Between-group differences in brain activation values derived from the ROIs were directly assessed with mixed ANOVAs using Group (pMCI/all MCI, CTL) as a between-subject factor, and Time (Y0, Y2) as a within-subject factor and followed by simple effects in the case of significant interactions.

To assess the relationship between task-related activation and hippocampal volume/cortical thickness, bivariate Pearson correlation were computed between ROI activation betas values, hippocampal volume, cortical thickness derived from ROIs (at Y0 and Y2) and time to diagnosis (in months, at Y0 and Y2).

Results

Clinical follow-up

Mean follow-up length in MCI individuals was 44.31 months (minimum of 24.67 months and maximum of 74.66 months). Thirteen MCI progressed to dementia. The mean

time between the first scan and diagnosis was 33.64 months (SD = 22.03 months; range: 5-72 months). None of the CTLs met criteria for MCI or AD at Y2. Seven MCI persons and 4 CTLs dropped out of the study between Y0 and Y2 and were not included in the analyses.

Sociodemographic and neuropsychological data

Participants' demographic and clinical data at Y0 are presented in Table 1 and are shown for the initial sample (n = 40) and for participants who remained in the study over the two-year follow-up (final sample; n = 29; 10 CTLs, 13 pMCI and 6 sMCI). Only the final sample was used for analyses. Independent-sample t-tests and chi-square analyses indicated that the final groups were comparable (pMCI/all MCI vs. CTL) for age, education, and gender distribution. Persons with pMCI performed significantly lower than CTLs on global clinical scales (MDRS, MMSE), as well as on measures of episodic memory (RL-RI 16 3rd free recall and delayed recall), and executive functions (coding WAIS-III. Of note, the initial versus final groups were comparable on these aforementioned measures, suggesting that the survival bias was unlikely to have impacted our findings.

Behavioral performance during fMRI

Performances on the memory task used during the fMRI scan are shown in Table 2. The analysis of the memory score in pMCI versus CTLs indicated a significant Group effect, $F(1, 19) = 34.043$, $p < .001$, $\eta^2 = .642$, with no Time, or Group x Time interaction, both $F<1$. Overall, CTLs showed better memory performance than pMCI persons. The same analysis with all MCI (sMCI + pMCI) also indicated a Group effect, $F(1, 25) = 15.398$, $p < .01$, $\eta^2 = .381$, CTLs showing better performance than all MCI, but no Time effect, $F(1, 25) = 1.494$, $p = .233$, or Group x Time interaction, $F(1, 25) = 1.042$, $p = .317$.

Structural MRI analyses

Analysis of cortical thinning for ROI selection

Comparison of pMCI and CTLs. One pMCI subject had to be discarded from neuroimaging analyses due to poor image quality. The QDEC analysis comparing CTLs to the pMCI group between Y0 and Y2 revealed five regions that showed more cortical thinning in pMCI than in CTL individuals (see Figure 2 and Table 3): the right supramarginal (BA40), right pars orbitalis (BA47), left pars opercularis (BA45), the left superior frontal gyrus (BA10) and the left lateral occipital gyrus (BA18). Thus, those regions were used as ROIs for functional analyses in addition to the hippocampi.

Comparison of all MCI and CTLs. There was no region showing cortical thinning between Y0 and Y2 when comparing the whole MCI group to CTLs

Hippocampal volume analysis

Comparison of pMCI and CTLs. The analysis of hippocampal volume (see Table 4) indicated a significant Group effect when comparing pMCI to CTLs, $F(1, 20) = 7.617$, $p < .05$, $\eta^2 = .276$, due to smaller hippocampal volumes in pMCI than CTLs. The Hemisphere effect was also significant, $F(1, 20) = 119.073$, $p < .001$, $\eta^2 = .856$, and this was qualified by a Group x Hemisphere interaction, $F(1, 20) = 4.796$, $p < .05$, $\eta^2 = .193$. The interaction was due to the fact that pMCI have larger left than right hippocampus volume, while this was not found in CTLs. None of the other effects were significant: Time effect, $F(1, 20) = 1.643$, $p = .215$, Group X Time, $F<1$, Group x Hemisphere x Time interactions, $F(1, 20) = 1.939$, $p = .179$.

Comparison of all MCI and CTLs. When comparing all MCI to CTLs, there was no Group or Time effect, nor Group x Time interaction.

fMRI analyses

Within-group whole-brain activation

Activation at Y0. The areas of activation during the memory task are presented in Table 5 and activation maps are shown in Figure 3. At Y0, all groups (CTL, pMCI, all MCI)

activated the occipital lobe bilaterally, the left inferior (pars opercularis and pars triangularis) and middle gyri, the left precuneus, and the left inferior parietal lobe. In addition to common areas of activation, CTLs activated the right inferior and superior parietal lobes and the left cerebellum. The group of pMCI additionally activated the left superior parietal lobe and the right cerebellum in addition to common areas of activation. When combined, all MCI individuals also activated the right angular gyrus, and the right inferior and superior parietal lobes, and deactivated the right superior and middle temporal lobes, the posterior cingulate and the precuneus bilaterally, in the anterior cingulate, and in the left superior and medial frontal gyri.

Activation at Y2. At Y2, all groups activated the occipital lobes bilaterally, the right cerebellum, the left inferior frontal gyrus bilaterally, the left middle frontal gyrus, the left precuneus, the left superior parietal lobe, and the supplementary motor area. In addition to common areas of activation, the pMCI group activated the right middle frontal gyrus, the inferior parietal lobe bilaterally, and the right supramarginal gyrus. When combined, MCI individuals additionally activated the left putamen, the right angular gyrus, the right inferior and superior parietal lobes, and the left inferior parietal lobe and deactivated the right superior and middle temporal lobes, the anterior, posterior and middle cingulate cortices, the precuneus bilaterally, and the superior frontal gyrus bilaterally.

Between group ROI-based activations

Comparison of pMCI and CTLs. Groups were directly compared on brain activation derived from the hippocampi and five cortical regions showing cortical thinning: the right supramarginal (BA40), right pars orbitalis (BA47), left pars opercularis (BA45), left superior frontal gyrus (BA10) and the left lateral occipital gyrus (BA18). Figure 4 shows activations in all ROIs for the pMCI and CTL groups. The analyses that assessed activation of the right supramarginal gyrus in pMCI and CTLs indicated a main Group effect, $F(1, 20) = 6.495$, $p <$

.05, η^2 = .245, due to larger activation in pMCI than in CTLs but no Time effect, or Group X Time interaction, F<1 in both cases. There was also a significant Group, $F(1, 20) = 5.508$, $p < .05$, η^2 = .216, and Time effect, $F(1, 20) = 7.786$, $p < .05$, η^2 = .280, in the left opercularis, but no interaction, F<1. pMCI showed a lower level of activation than CTLs and activation increased from Y0 to Y2 for both groups. Analysis of the left lateral occipital gyrus revealed a Time effect, $F(1, 20) = 12.019$, $p < 0.01$, η^2 = .375, as activation increased from Y0 to Y2. There was no Group effect, $F(1, 20) = 1.181$, $p = .290$, nor Group X Time interaction, $F(1, 20) = 2.523$, $p = .128$. There were no effects or interactions in the right pars orbitalis (Group and Time, F<1; Group x Time interaction, $F(1, 20) = 3.149$, $p = .093$), or in the left superior frontal gyrus (Group, Time, Group x Time interaction, all F<1).

A significant Group effect was found in the left hippocampus, $F(1, 20) = 6.834$, $p < .05$, η^2 = .255, with lower levels of activation in pMCI persons than in CTLs. There was also a Time effect, $F(1, 20) = 4.934$, $p < 0.05$, η^2 = .198, as the level of activation increased from Y0 to Y2 in both groups. There was no Group x Time interaction, F<1. The Group effect in the right hippocampus just missed significance, $F(1, 20) = 3.601$, $p = .07$, and the Time and Group x Time interaction was not significant, both F<1.

Comparison of all MCI and CTLs. When comparing activation in the whole MCI group and CTLs, the analysis indicated a significant Group effect in the left pars opercularis, $F(1, 25) = 4.952$, $p < .05$, η^2 = .160, as MCI showed less activation than CTLs, and a Time effect, $F(1, 25) = 7.558$, $p < .05$, η^2 = .225, as activation increased from Y0 to Y2, but no Group x Time interaction, F<1. A Time effect was found significant for the left lateral occipital gyrus, $F(1, 25) = 7.974$, $p < .01$, η^2 = .235, as activation increased from Y0 to Y2. There was no Group effect, $F(1, 25) = 3.856$, $p = 0.06$, nor Group X Time interaction, F<1. None of the other cortical regions showed a significant effect: the superior frontal area (Group, $F(1, 25) = 1.054$, $p = .396$, Time and Group x Time interaction, both F<1), right pars

orbitalis (Group, Time, both F<1, Group x Time interaction, F(1, 25) = 2.571, p = .124), right supramarginal gyrus (Group, F(1, 25) = 3.241, p = .08, Time and Group x Time interaction, both F<1).

The analysis of activation in the left hippocampus, indicated a significant Group, F(1, 25) = 5.285, $p < .05$, $\eta^2 = .169$, and Time effects, F(1, 25) = 4.934, $p < .05$, $\eta^2 = .198$, but no Group x Time interaction, F<1. MCI showed less activation than CTLs, and activation increased from Y0 to Y2. None of the effects were significant for activation in the right hippocampus (Group, F(1, 25) = 2.386, p = .135, Time and Group x Time interaction, both F<1).

Correlational analyses

No correlation was found significant between activation (betas values) and time to dementia (months) in any of the cortical ROIs or hippocampi (p ranging from .174 to .874; see Figure 5). However, we found negative correlations between the volume of the left hippocampus and time to dementia, r = -.547, $p < .01$, $r^2 = .30$, and between thickness of the left pars opercularis and time to dementia, r = -.534, $p < .01$, $r^2 = .29$. In both cases, smaller volume/thickness are associated with closer time to dementia.

Discussion

The innovative aspect of this paper is that we relied on a longitudinal design to assess task-related brain activation in persons with MCI. This allows for the identification of individuals with MCI who later progressed to dementia and to assess whether activation changes over a two-year period. We also examined task-related activation beyond the hippocampus to include structurally-damaged cortical regions. Our study confirms that hyperactivation is an early hallmark of AD, as we observed larger activation than CTLs in the right supramarginal gyrus of MCI who were confirmed to later progress to dementia. Interestingly, we also found hypoactivation in the left hippocampus and pars opercularis,

indicating that hyper- and hypoactivation can co-exist during the disease progression. There were no activation changes after two years, and task-related activation did not relate to time before the clinical diagnosis of dementia. This suggests that hyperactivation is relatively stable when examined over a relatively short period. In contrast, hippocampal volume and cortical thickness showed change over time, and these changes were associated with shorter time to diagnosis. Each of these main findings will be discussed in the following section in relation to our research objectives.

Our first objective was to assess whether task-related hyperactivation was found when examined in a group of pMCI individuals, that is, in individuals who were confirmed to later progress to dementia. Examining hyperactivation only in pMCI is of a great importance to understand the early mechanisms that are truly associated with neurodegenerative processes and to identify individuals that are more likely to develop dementia. Our results indicated that this was indeed the case, as hyperactivation was found to be present in pMCI. We also assessed activation using the whole MCI sample that is, including both stable and pMCI. This was done to compare our results with the literature, where most studies included MCI individuals irrespective of whether they will later progress to dementia or not. Interestingly, the right parietal hyperactivation was no longer significant when using the larger group. It is likely that including stable MCI contributes to reducing the effect, which might partly explain the discrepancies observed in the literature, where some studies failed to observe hyperactivation in MCI. Including stable MCI might indeed impede the possibility to examine task-related hyperactivation. Of note, there was a conspicuous absence of task-induced deactivation in the CTL group, a result similar to a large number of prior studies in older adults (Lustig et al., 2003; Hansen et al., 2014; Li et al., 2015; Miller et al., 2008; Persson et al., 2007). Absence of task-induced deactivation was also present in pMCI, consistent with other prior studies (Balardin et al., 2015; Petrella et al., 2007; Pihlajamaki & Sperling, 2009).

Note that a few studies did not find failure to deactivate in MCI (see Gould et al., 2006; Kochan et al., 2011). This discrepancy may be due to an effect of disease severity (Celone et al., 2006; Pihlajamaki et al., 2009; Sperling et al., 2009) or to the fact that few prior studies have examined whether their at-risk individuals actually progressed to dementia. They might thus have included a heterogeneous group of individuals. Nonetheless, it is reassuring that we did not find deactivation, as it indicates that hyperactivation cannot be merely explained by reduced deactivation in pMCI.

A second objective was to assess the location of these hyperactivations and more precisely, whether hyperactivation is present in cortical regions. Most fMRI studies reporting hyperactivation have focused on the hippocampus, so it is important to investigate whether the hyperactivation phenomenon also occurs in cortical regions. Our finding of hyperactivation in the right supramarginal gyrus indicates that hyperactivation can be found in other regions that are vulnerable to AD. Contrary to prior studies, we did not observe hippocampal hyperactivation. We rather observed hypoactivation in the left hippocampus in the pMCI group and neither hyper- nor hypoactivation difference in the right hippocampus. This is in opposition to the data reported by a number of previous studies (Dickerson et al., 2004; Huijbers et al., 2015; Miller et al., 2007; Putcha et al., 2011; O'Brien et al., 2010) where hyperactivation was reported in the hippocampus. This is not entirely incompatible with the model, however. One interpretation for the lack of hyperactivation in the hippocampus is that MCI individuals in our sample are more severely impaired than those included in previous studies. It is interesting to highlight that our pMCI were scanned on average 33 months prior to diagnosis. This is quite close to diagnosis considering that the disease progresses over about 20 years, and it is possible that hyperactivation occurs at different times for different brain regions. Importantly, few prior studies have examined pMCI separated from stable MCI and these have not reported time to diagnosis. It is therefore not possible to determine at

which stage participants were in those earlier studies. Hyperactivation might have been present in the hippocampus of our participants at some point prior to study entry. It is also possible that previous studies included a mixture or progressors and stable MCI and that stable MCI may have contributed to increase the group level of hippocampal activation given that they might not be affected by AD.

The fact that we found hyperactivation in the right parietal area is not trivial. Indeed, it is in line with a study from our team that reported that increased parietal activation was positively correlated with memory improvement following cognitive training in persons with MCI (Belleville et al., 2011). In the same vein, Elman et al. (2014) reported that larger parietal activation was associated with better cognition in older adults with high amyloid deposition. These authors have proposed that activation in this region can support compensatory mechanisms in older adults suffering from early AD. It is interesting to note that CTLs recruited the left parietal area homologous to the right parietal region recruited by MCI. Thus, it appears that pMCI recruited an alternative region that is not typically involved in the task. Interestingly, this new recruitment is controlateral to the same region recruited in the left hemisphere by CTLs. This result is consistent with studies indicating that older adults recruit regions that are controlateral to the ones recruited by younger adults (Logan & Buckner, 2001; Reuter-Lorenz et al., 2000; Stebbins et al., 2002). It is also consistent with some prior studies from our lab that found similar controlateral recruitments in MCI when compared to older CTLs (Clément & Belleville, 2010; 2012). This pattern is consistent with the hemispheric asymmetry reduction in older adults (HAROLD; Cabeza, 2002), which suggests that neural compensation occurs by recruiting brain areas that are controlateral to those normally recruited by a task. Interestingly, parietal hyperactivation in pMCI co-occurred with hypoactivation of the left hippocampus and inferior frontal gyrus, two regions activated by healthy controls and typically involved in verbal memory (Daselaar et al., 2003;

Duverne et al., 2008; Miller et al., 2008). This suggests that parietal hyperactivation may result from a shift of activation from impaired, underrecruited prefrontal areas within the memory network to more posterior regions. Hence the recruitment of alternative regions such as the right parietal area might reflect compensatory mechanisms in response to the effects of neuropathology on the function of specialized regions. We must acknowledge that performance is quite low in pMCI is spite of putative compensation processes. The presence of compensation mechanisms does not guarantee that the newly deployed or increased neural resources will totally eliminate the gap between task demands and available resources, and in fact, it is unlikely to be the case in most circumstances, especially in individuals with severe clinical impairments (Cabeza et al. 2018). Thus, there are occurrences where compensation occurs but is only partially successful and insufficient to normalize performance. It is possible that the pMCI individuals in our study recruited the right supramarginal gyrus in an "attempted/incomplete compensation", but were unable to equal their healthy counterparts' performance. There is presently no gold standard that would allow us to determine the amount of impairment expected in the presence of a given brain atrophy and hence to quantify the extent of successful compensation if any.

Our third and last objective was to assess the hyperactivation trajectory. This was done by looking at how hyperactivation changes over a two-year period and whether it interacts with group membership and by examining its relationship with clinical symptoms and time before dementia. Surprisingly, we found that both hyperactivation and hypoactivation were stable over the two-year follow-up that was used here. We have to remain prudent in interpreting this lack of longitudinal change, as it might be explained by our relatively small sample size. It might also be explained by interindividual variability in the temporality of the inverse U-shape. As patients are at different stages of the continuum, some might show increased activation whereas others might show decreased activation. However, if that was

the case, one would expect a correlation between activation and time to dementia, which was not found here. Another hypothesis is that change in task-related activation might take place on a longer timeframe than a two-year period and our test-retest length might not have been sufficient to capture. This stresses the importance to study hyperactivation on a longer period of time to better determine its trajectory and its effect on the brain and cognition. Activation in the left opercularis increased over time, but the Group effect remained significant in the absence of Group X Time interaction. This means that the increased activation is present to a similar degree in pMCI and CTLs with the result that activation in pMCI remains hypoactive when comparing their activation to that of CTLs. Importantly, hippocampal volume and volume of the left pars opercularis regions were found to be negatively correlated with time to dementia, confirming that time to dementia was a sound measure of disease severity.

Overall our results are partly consistent with the cascading network model (Jones et al., 2015; 2017). This model proposes that early disruption of tau-related networks would lead to a compensatory load shift to posterior areas that are more prone to amyloid accumulation, until these latter regions would meet amyloid saturation. Since the hippocampus is an early site of tau accumulation (Braak & Braak, 1991; Schwarz et al., 2018; Villemagne et al., 2015), hypoactivation found in this region might result from excessive tau pathology while right parietal hyperactivation might be indicative of a compensatory load shift toward more posterior regions. However, it should be acknowledged that this interpretation remains speculative since we did not measure amyloid level or tau in our study. It is also important to keep in mind that the compensatory and excitotoxic accounts might not be mutually exclusive as early compensatory increased neuronal activity might contribute to neuropathology propagation (Huijbers et al., 2015; 2018; Schultz et al., 2017).

Our study has limitations which must be recognized and addressed. Although focusing on MCI persons who progressed to dementia is a strength and reduced within-group

heterogeneity, it also negatively impacted our sample size since we only examined those who were retained at follow-up and who progressed to dementia. Also, we did not include markers of amyloid and/or tau pathology in our participants and hence cannot conclude with certainty the etiology of their cognitive symptomatology. We only used two longitudinal points which does not allow a measure of non-linear pattern of changes. Using non-linear models would have more directly tested the postulated inverse U-shape trajectory of task-related activation. We used a block design and therefore, we did not assess activation for correct vs. incorrect responses. We did not control for the potential effect of reduced behavioral performance on patterns of brain activation, as statistically controlling for group differences in performance controls for the clinical effect and therefore would result in potentially removing group effect in activation. Of note is the fact that several studies have found hyperactivation using a block design (Clément et al., 2010; Clément, Belleville, & Mellah, 2010; Clément, Gauthier, & Belleville, 2013; Erk et al., 2011; Gordon et al., 2015; Rodda et al., 2009; 2011; Yetkin et al., 2006) and therefore, we believe that such a design is appropriate to detect the presence of hyperactivation in MCI. Finally, partial volume effect could have introduced potential noise in fMRI signal.

Conclusion

To conclude, our findings show that task-related hyperactivation is present in structurally impaired regions when examining MCI individuals with a confirmed progression to dementia and that hyperactivation can co-occur with hypoactivation. Hypoactivation is deemed to reflect a failure to activate regions typically implicated in episodic memory. In turn, the hyperactivation of the right supramarginal gyrus which was found here might represent a shift in activation to compensate for the harmful consequences of neuropathology. Larger longitudinal studies with longer follow-up and additional time points will be required to underpin the complex relation between activation and cognition. Further studies will also

be needed to determine how hyperactivation can contribute to optimize prediction of future dementia in combination with other neuroimaging markers, biomarkers and/or cognition. It will also be important to prove its value as a ‘’pre-clinical” marker when cognitive symptoms are absent of very subtle in order to identify preclinical AD.

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Disclosure statement

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Table 1.1. Demographic and clinical characteristics of participants (mean, with standard deviations in parentheses) at Y0

	Initial sample				Final sample			
	CTL	MCI	pMCI	sMCI	CTL	MCI	pMCI	sMCI
Sex (f, m)	8, 6	15, 11	7, 6	3, 3	6, 4	10, 9	7, 5	3, 3
Age	67.21 (6.80)	68.32 (8.61)	69.42 (7.25)	67.00 (12.30)	65.70 (6.96)	68.61 (8.94)	69.42 (7.25)	67.00 (12.30)
Education	14.57 (3.76)	14.56 (3.92	15.17 (4.55)	14.67 (3.88)	13.80 (3.39)	15.00 (4.23)	15.17 (4.55)	14.67 (3.88)
MDRS	140.33 (2.65)	134.96 (4.99)[b]	134.00 (4.55)[c]	140.33 (2.75)	140.50 (2.88)	136.11 (5.03)[a]	134.00 (4.55)[b]	140.33 (2.75)
MMSE	29.29 (1.14)	27.57 (1.97)[b]	27.17 (2.08)[b]	29.17 (1.17)	29.40 (0.70)	27.83 (2.04)[b]	27.17 (2.08)[b]	29.17 (1.17)
SMAF	-	-1.05 (1.05)	-0.92 (1.02)	-1.00 (1.00)	-	-0.94 (0.98)	-0.92 (1.02)	-1.00 (1.00)
Boston Naming Test	-	13.22 (1.62)	12.75 (1.71)	14.33 (1.21)	-	13.28 (1.71)	12.75 (1.71)	14.33 (1.21)
Coding (WAIS-III)	11.29 (2.30)	9.57 (2.61)	9.75 (2.60)[a]	10.67 (2.25)	11.00 (2.58)	10.06 (2.46)	9.75 (2.60)	10.67 (2.25)
Benton Judgment of line orientation	-	23.78 (3.86)	23.83 (2.69)	25.67 (3.88)	-	24.44 (3.15)	23.83 (2.69)	25.67 (3.88)
Rey Osterrieth Complex Figure								
Copy (score)	-	30.59 (3.52)	31.00 (3.23)	30.92 (2.84)	-	30.97 (3.02)	31.00 (3.23)	30.92 (2.84)
Immediate recall (score)	-	10.23 (6.16)	10.58 (6.24)	13.90 (5.46)	-	11.56 (6.05)	10.58 (6.24)	13.90 (5.46)
Delayed recall (score)	-	10.57 (6.26)	10.92 (5.49)	15.08 (5.55)	-	12.31 (5.72)	10.92 (5.49)	15.08 (5.55)
Stroop (3rd plate)								
Time	-	31.40 (8.06)	31.78 (8.54)	29.13 (7.53)	-	30.90 (8.09)	31.78 (8.54)	29.13 (7.53)
Errors	-	1.22 (2.04)	1.50 (2.02)	0.50 (0.84)	-	1.17 (1.76)	1.50 (2.02)	0.50 (0.84)
RL/RI 16								
3rd immediate free recall	12.21 (2.33)	7.43 (3.40)[c]	6.92 (2.31)[c]	11.33 (2.07)	12.40 (2.67)	8.39 (3.05)[b]	6.92 (2.31)[c]	11.33 (2.07)
Delayed free recall	12.71 (2.40)	7.09 (4.01)[c]	6.33 (3.63)[c]	11.50 (1.87)	12.30 (1.00)	8.06 (3.98)[b]	6.33 (3.63)[c]	11.50 (1.87)

[a]Impairment relative to CTLs at $p < .05$; [b]Impairment relative to CTLs at $p < .01$; [c]Impairment relative to CTLs at $p < .001$

Table 1.2. Scores on the memory task (mean, with standard deviations in parentheses)

	CTL	MCI	pMCI	sMCI
T1				
Memory score	0.70 (0.22)	0.34 (0.28)[a]	0.25 (0.23)[a]	0.54 (0.29)
T2				
Memory score	0.68 (0.22)	0.26 (0.27)[a]	0.18 (0.17)[a]	0.43 (0.36)

[a]Group effect, with impairment relative to CTLs at $p < .05$.

Table 1.3. Cluster sizes, peak Talairach coordinates, and corresponding Z-scores for clusters showing a steeper cortical thickness slope from Y0 to Y2 in the pMCI group compared to CTLs with Monte Carlo simulation correction set at 0.005

	Cluster size (mm^2)	x	y	z	Z score
Right supramarginal (BA40)	326.02	52.6	-36.5	42.9	-4.162
Right pars orbitalis (BA47)	9009.80	44.3	39.2	-13.0	-8.809
Left pars opercularis (BA45)	1095.03	-53.2	21.8	9.3	-5.757
Left superior frontal gyrus (BA10)	4499.26	-7.9	58.8	-1.7	-8.438
Left lateral occipital gyrus (BA18)	284.21	-15.3	-98.7	4.0	-3.181

Table 1.4. Hippocampal volumes (corrected for intracranial volume) for the CTLs, all MCI, pMCI, and sMCI groups (mean, with standard deviations in parentheses)

	CTL	MCI	pMCI	sMCI
T1				
Left hippocampus	0.27 (0.03)	0.24 (0.06)	0.23 (0.06)	0.28 (0.04)
Right hippocampus	0.28 (0.03)	0.26 (0.05)	0.24 (0.06)	0.28 (0.04)
T2				
Left hippocampus	0.23 (0.03)	0.20 (0.06)	0.18 (0.05)	0.24 (0.04)
Right hippocampus	0.24 (0.03)	0.20 (0.06)	0.18 (0.05)	0.25 (0.04)

Table 1.5. Cluster size, peak voxel MNI coordinates, and corresponding t-values for clusers associated with encoding at Y0 and Y2 for the CTL, pMCI, and all MCI ($p < .05$, FWE corrected)

Y0	Cluster size	x	y	z	t-value
CTL group: Encoding > Visual fixation					
Left cerebellum anterior lobe	25	0	-58	-34	8.59
Right occipital lobe (18)	721	45	-55	-13	12.41
Left occipital lobe (18)	505	-15	-85	19	9.06
Left inferior and middle frontal gyri (10, 46)	63	-39	50	8	13.06
Left inferior frontal gyrus (pars opercularis and triangularis; 6, 9, 44, 45)	122	-51	20	8	8.92
Left precuneus and inferior parietal lobes (7, 19)	73	-27	-64	38	5.93
Right inferior and superior parietal lobes (7, 19, 40)	86	24	-61	32	10.20
Left supplementary motor area (6, 8, 32)	19	9	14	47	6.60
pMCI group: Encoding > Visual fixation					
Right cerebellum posterior lobe	21	33	-64	-31	5.18
Left occipital lobe (18)	298	-24	-76	-13	9.89
Right occipital lobe (18)	197	18	-94	-1	10.67
Left inferior (pars opercularis and triangularis) and middle gyri (6, 9, 44, 45, 46)	181	-48	11	20	7.73
Left precuneus and inferior and superior parietal lobes (7, 19)	78	-27	-76	41	7.97
Left supplementary motor area (6. 8, 32)	16	-3	11	50	5.67
Whole MCI group: Encoding > Visual fixation					
Right occipital lobe (18)	557	18	-94	2	6.47
Left occipital lobe (18)	642	-24	-76	-13	6.62
Left inferior (pars opercularis and triangularis) and middle gyri (6, 9, 44, 45, 46)	381	-39	5	32	5.26
Right angular gyrus and inferior and superior parietal lobes (7, 40, 19)	102	24	-61	50	5.00
Left precuneus and inferior and superior parietal lobes (7, 19)	179	-27	-76	41	5.37
Whole MCI group: Encoding < Visual fixation					
Right superior and middle temporal lobes (39, 40)	166	51	-61	23	-4.98
Posterior cingulate cortex and precuneus bilaterally (7, 31)	658	0	-61	47	-5.19
Anterior cingulate cortex and left superior and medial frontal gyri (9, 10)	753	-15	56	23	-5.79
Y2	**Cluster size**	**x**	**y**	**z**	**t-value**
CTL group: Encoding > Visual fixation					
Right cerebellum and occipital lobes bilaterally (18)	2702	30	-85	-4	19.81
Right inferior frontal gyrus (47)	36	24	29	-10	7.16
Left inferior (pars opercularis and triangularis) and middle gyri (6, 9, 44, 45, 46)	743	-42	-1	26	20.36
Left precuneus and superior parietal lobe (7, 19)	169	-36	-43	32	11.92
Left supplementary motor area (6, 8, 32)	218	-9	11	50	8.81

pMCI group: Encoding > Visual fixation					
Right cerebellum and occipital lobe (18, 19)	670	18	-88	5	10.28
Left occipital lobe (18, 19)	704	-27	-82	-19	15.35
Left inferior gyrus (pars opercularis, triangularis, and orbitalis; 6, 9, 13, 45, 46, 47)	757	-39	26	17	11.50
Right inferior frontal gyrus (pars opercularis; 13, 45, 47)	131	42	17	5	8.92
Left frontal middle gyrus (10, 46)	53	-39	50	11	8.24
Right inferior (pars triangularis) and middle gyri (10, 46)	135	33	32	17	10.36
Right supramarginal gyrus and inferior parietal lobe (7, 40)	166	36	-49	38	8.85
Left precuneus and inferior and superior parietal lobes (7, 40)	265	-27	-61	38	8.94
Whole MCI group: Encoding > Visual fixation					
Right cerebellum and occipital lobe (18, 19)	1015	18	-88	5	5.76
Left occipital lobe (18, 19)	953	-27	-82	-19	6.42
Left inferior (pars opercularis and triangularis) and middle gyri (6, 13, 45, 46, 47)	1071	-39	26	17	6.05
Right inferior (pars opercularis and triangularis) and middle gyri (46, 47)	468	33	32	17	5.35
Left putamen	109	-21	-1	5	4.88
Right angular gyrus and inferior and superior parietal lobes (7, 40)	322	36	-49	38	5.28
Left supplementary motor area (6, 8, 32)	313	-6	11	53	5.62
Left precuneus and inferior and superior parietal lobes (7, 40)	429	-27	-61	38	5.72
Whole MCI group: Encoding < Visual fixation					
Right superior and middle temporal lobes (22, 39, 40)	145	57	-52	17	-5.28
Posterior and middle cingulate cortices and precuneus bilaterally (5, 7, 24, 31, 35)	915	-6	-40	47	-6.13
Anterior cingulate cortex and superior frontal gyrus bilaterally (9, 10)	613	-6	56	26	-6.34

Figure 1.1. Time to dementia for the 13 pMCI participants included in the study. Time 0 represents the year at which diagnosis was received for each participant. Dots indicates the Y0 and Y2 scans.

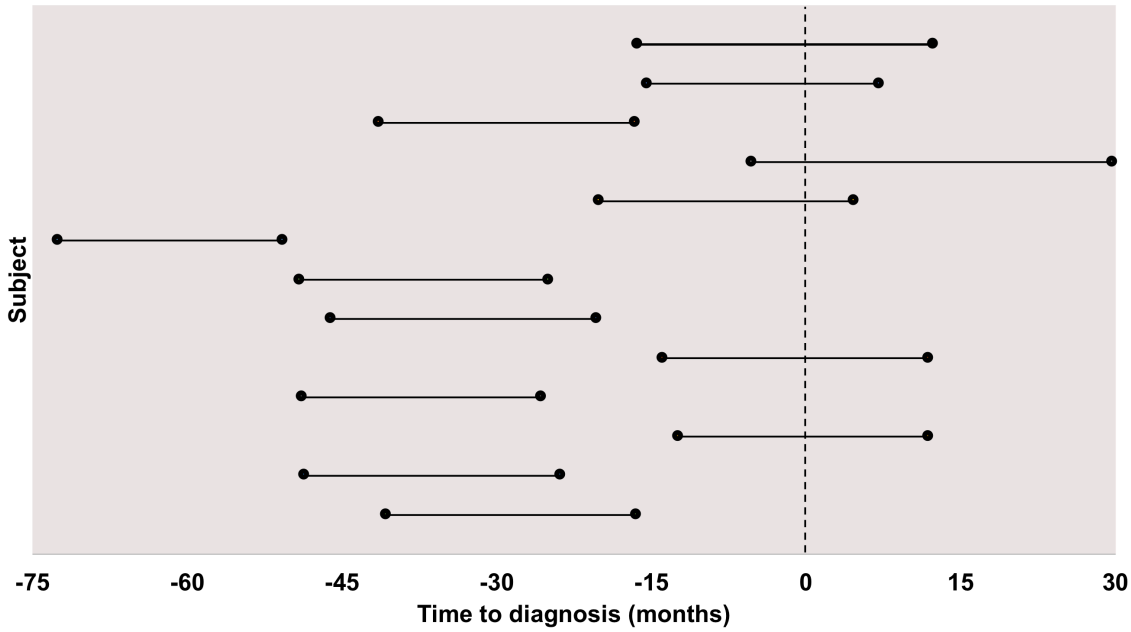


Figure 1.2. Maps showing regions with significantly different thickness slopes from Y0 to Y2 between the pMCI and CTL using the general linear model at each vertex across the entire cortical mantle. Differences are expressed in Z scores, with the blue indicating a significantly steeper slope difference in the pMCI group than in the CTL group. Maps are presented on the pial cortical surface of an average brain with sulci in dark gray color and gyris in light gray color. Non-cortical regions (i.e. thalamus, basal ganglia) were not included in the analysis.

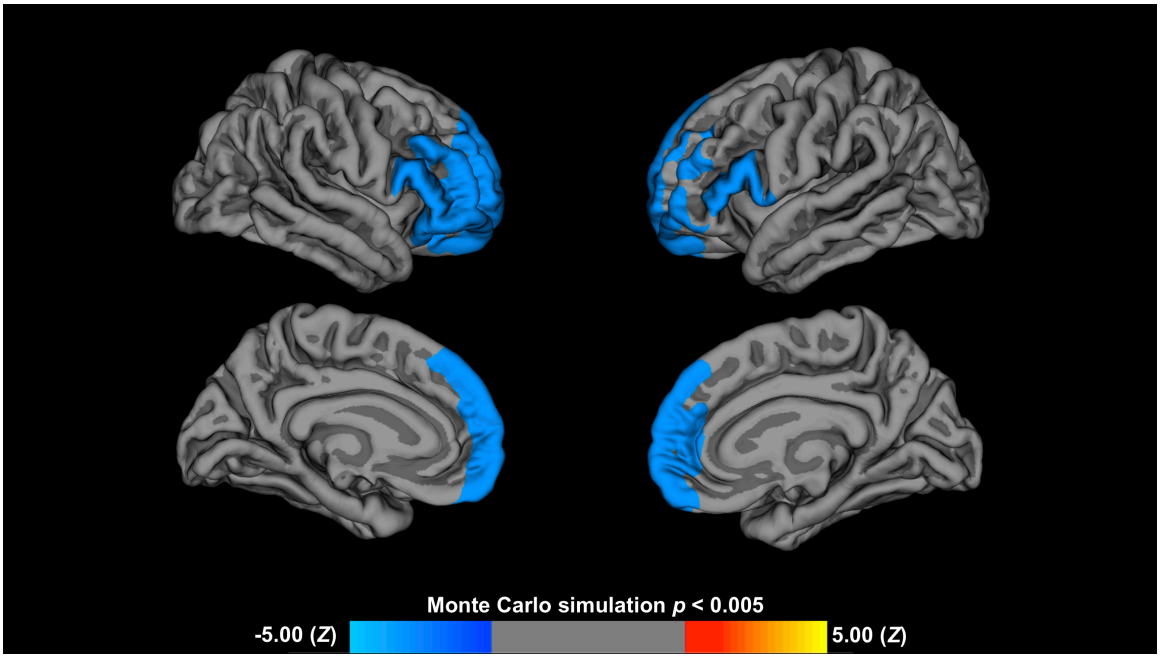


Figure 1.3. One t-test maps of activation during the encoding of word-pairs by the CTL, pMCI, and all MCI groups at Y0 and Y2. Contrasts are expressed in t scores with the orange and yellow indicating significantly higher activation than baseline and the blue indicating significantly lower activation than baseline (deactivation).

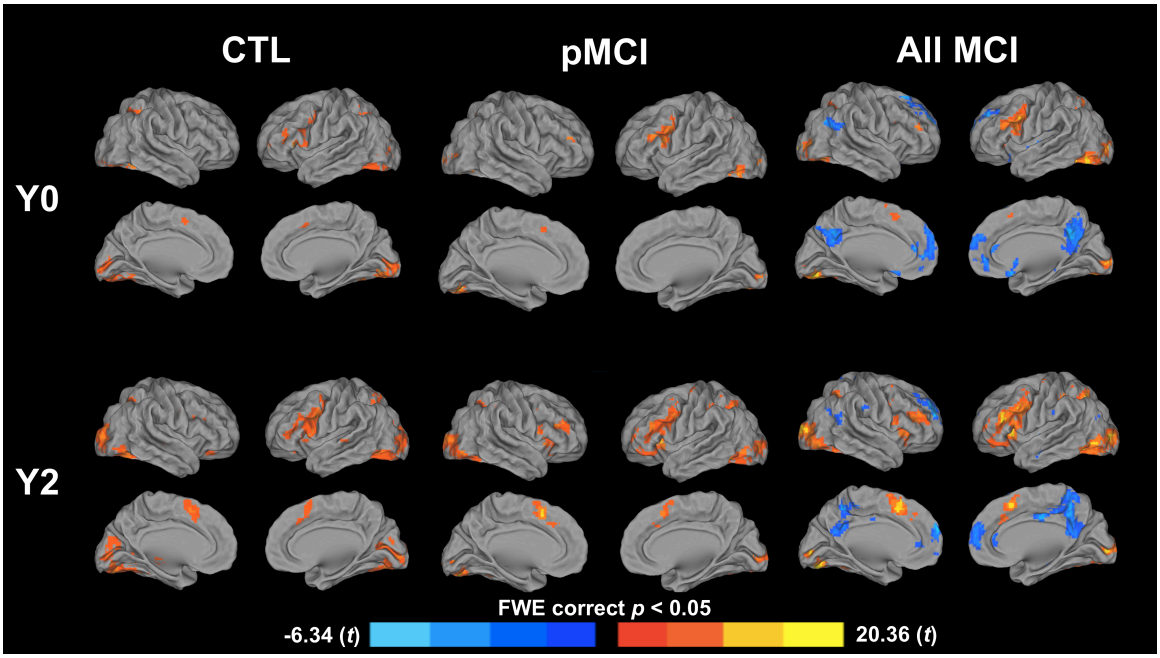


Figure 1.4. Task-related activation comparisons between CTLs and pMCI from Y0 to Y2 in the four ROIs derived from the QDEC analysis and in both hippocampi. Significant group differences were only found in the right supramarginal gyrus, left pars opercularis, and the left hippocampus, with no Time effect nor Group X Time interaction. None of these effects were significant in the right hippocampus, left superior frontal gyrus, and left pars orbitalis.

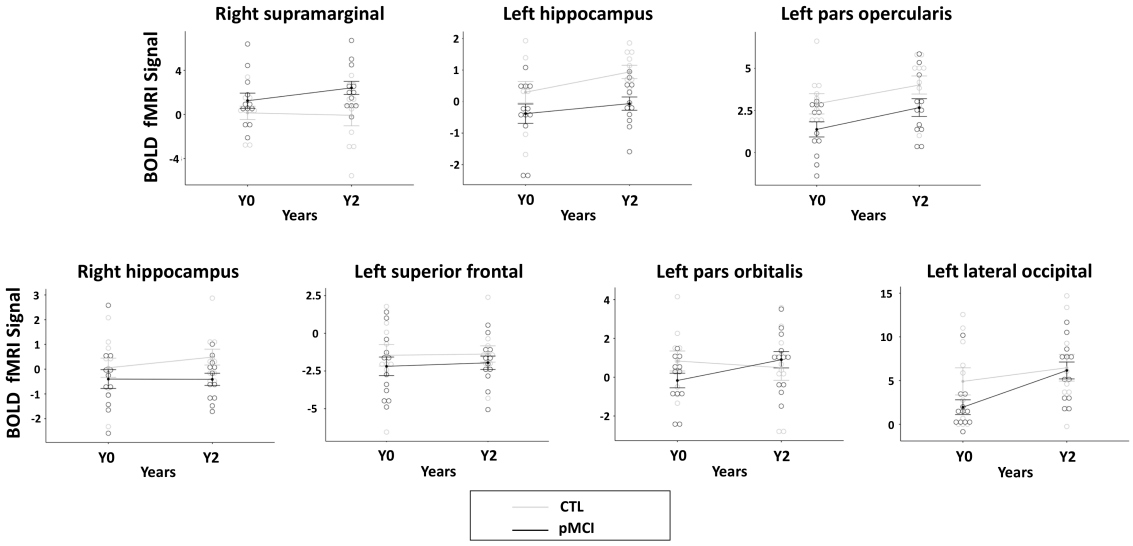
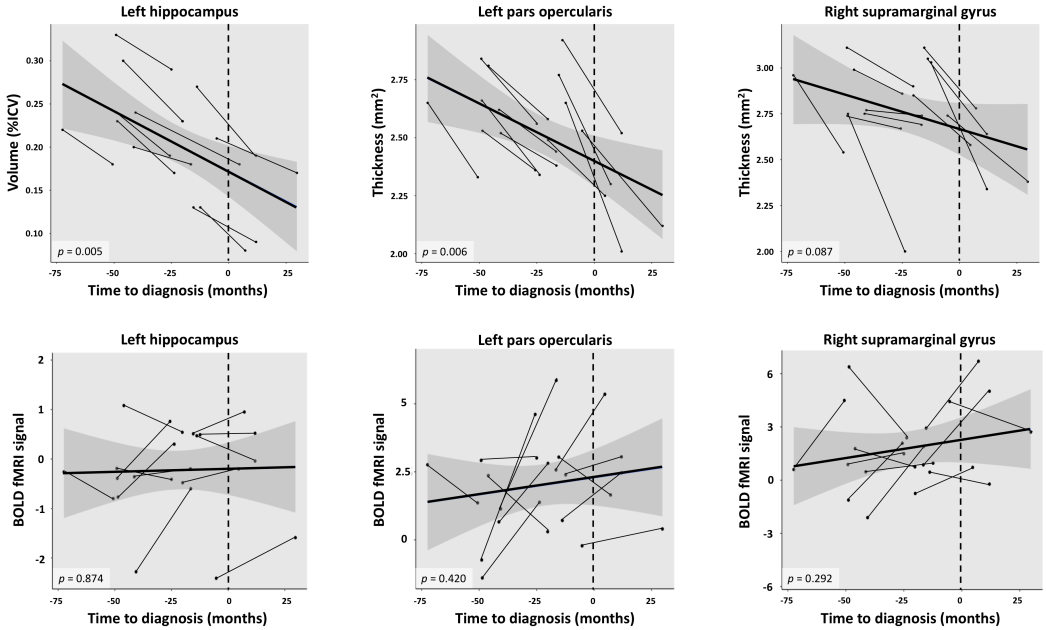


Figure 1.5. Relation between morphological measures (hippocampal volume, cortical thickness; upper row), task-related activation betas values (lower row) and time to diagnosis in regions showing group differences in task-related activation in the pMCI group. Each pMCI subject is depicted in relation to its individual time to diagnosis with its Y0 and Y2 connected by a line.



CHAPITRE 3 – Article 2

A quadratic function of activation in individuals at risk of Alzheimer's disease

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Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring (accepté)

Abstract

INTRODUCTION: It is hypothesized that brain activation forms an inverse U-shape in prodromal Alzheimer's disease (AD), with hyperactivation in the early phase, followed by hypoactivation.

METHODS: We tested this inverse U-shape hypothesis of brain activation using polynomial regression models and between-group comparisons in individuals with either subjective cognitive decline with smaller hippocampal volumes and/or an *APOE4* allele (SCD^+), or mild cognitive impairment (MCI).

RESULTS: We found that a quadratic function models the relationship between proxies of disease severity (neurodegeneration, memory performance) and left superior parietal memory-related activation. Linear negative functions model the relationship between neurodegeneration and left hippocampal/right inferior temporal activation. Group comparison between SCD^+, MCI and healthy controls indicated presence of hyperactivation in SCD^+ and hypoactivation in MCI in the left superior parietal lobule.

DISCUSSION: These findings support the presence of an inverse U-shape model of activation and provide evidence that hyperactivation might represent an early biomarker of the early AD stages.

Key Words: 1. Alzheimer's disease; 2. MCI (mild cognitive impairment); 3. SCD (subjective cognitive decline); 4. fMRI; 5. Hyperactivation; 6. Associative memory

Highlights

- A quadratic function described left parietal activation in a group at risk of AD
- Linear models rather described hippocampal and temporal activation
- We found hyperactivation in SCD^{+} and hypoactivation in MCI relative to controls

1. Introduction

There has been growing interest in hyperactivation as an early signature of Alzheimer's disease (AD). This interest stems from the observation of higher task-related fMRI activation in individuals with mild cognitive impairment (MCI) than in cognitively healthy controls (HC).[1-6] This contrasts the observation of lower level of activation, or hypoactivation, in individuals with dementia or in the late stage of MCI.[7-9] Thus, the relationship between disease progression and brain activation in the continuum of AD appears to take the form of an inverse U-shape function, with an increase in activation early in the prodromal phase followed by hypoactivation as patients progress towards dementia.[10] This suggests that hyperactivation may be an excellent candidate for an early signature of AD, although critical issues must be resolved.

An important question is whether activation with disease progression follows an inverse U-shape as this hypothesis has never been directly assessed with statistical modeling in a single group of individuals at risk of AD. This information would contribute to identifying the time point at which higher hyperactivation occurs and thus provide important information for early diagnosis. We used polynomial regressions in a group of individuals with either subjective cognitive decline *plus* (SCD^+)[11-12] or MCI to test whether a quadratic function models the relationship between proxies of disease severity and task-related brain activation. Individuals with SCD^+ had reduced hippocampal volumes and/or an *APOE4* allele, which are biomarkers that increase the likelihood of preclinical AD.[12-13]

Another question is whether hyperactivation is present prior to the MCI phase. Group comparisons were used to assess the magnitude of activation during an associative

memory task, which was dependent on regions that are sensitive to AD[14-15]. The two clinical groups were assessed separately, in comparison to HC, to determine whether hyperactivation is present in people with SCD^{+} only, prior to the MCI phase.

2. Materials and methods

2.2. Participants

The study included data from the Consortium for the Early Identification of Alzheimer's disease-Quebec cohort (CIMA-Q http://www.cima-q.ca/en/home/).[16] The main objective of CIMA-Q is to characterize a longitudinal observational cohort consisting of over 350 community-dwelling older adults recruited via advertisements, electronic media and memory clinics from three Canadian cities (Montreal, Sherbrooke and Quebec City). Participants were either, 1) cognitively healthy, 2) exhibiting SCD, 3) suffering from MCI, or 3) diagnosed with dementia due to probable AD. CIMA-Q collects clinical, cognitive, biological, radiological and pathological data from these participants in order to, 1) establish an early diagnosis of AD, 2) provide a well-characterized cohort to the scientific community, 3) identify new therapeutic targets to prevent or slow cognitive decline and AD, and 4) support new clinical studies on these targets. For this study, 108 CIMAQ participants were included, who completed the fMRI memory examination at baseline.

This study was approved by the CIMA-Q scientific committee and the *Comité mixte d'éthique de la recherche vieillissement-neuroimagerie* of the *Centre intégré universitaire de santé et de services sociaux du Centre-Sud-de-l'Île-de-Montréal*, and all participants provided written informed consent to participate in the study.

Clinical diagnoses were made by expert consensus based on current clinical criteria. The criteria for SCD were based on the Subjective Cognitive Decline Initiative.[11-12] Study participants, 1) expressed memory complaints and worries, 2) had normal education-adjusted scores on the Logical Memory subtest of the Wechsler Memory Scale (WMS[17]; score of ≤3 for 0-7 years of education, ≤5 for 8-15 years, and ≤9 for 16 or more years), 3) had scores of >26 on the Montreal Cognitive Assessment (MoCA)[18], and 4) had a score of 0 on the Clinical Dementia Rating Scale (CDR).[19] Participants were classified as SCD^+ if they also had smaller left or right hippocampal volumes (defined as one standard deviation below the mean of study HC, corrected for intracranial volume) and/or carried at least one *APOE* e4 allele. Individuals with SCD that did not meet criteria for SCD^+ ($N = 33$) were integrated into the HC group. Criteria for MCI were based on recommendations from the National Institute on Aging-Alzheimer's Association workgroup (NIA-AA).[20] Participants met criteria for MCI if they, 1) expressed complaints about their memory, 2) showed objective memory impairment based the Logical Memory score (≤2 for 0-7 years of education, ≤4 for 8-15 years, and ≤8 for 16 or more years), 3) had a score between 20 and 25 on the MoCA, and 4) had a CDR score of 0.5. HC performed within normal ranges on clinical tests (see above for SCD), did not meet criteria for MCI or SCD, and were *APOE4* negative. All participants met safety criteria for an MRI study and were right-handed. Fasting blood sampling was conducted to determine *APOE* genotype.

Participants were included if they were age 65 and over, lived in the community or residence of an independent person, had a score of 17 or higher on the telephone-Mini Mental State Examination (T-MMSE),[21] were able to understand, read, and write in

either French or English, had sufficient auditory and visual acuity to participate in a neuropsychological assessment, and were willing to answer health-related questionnaires, undergo a physical and neuropsychological assessment, and have a blood test. Participants were excluded if they were planning on moving outside of Quebec in the next three years, or had a central nervous central system disease (e.g. subdural hematoma, active epilepsy, primary or metastatic brain cancer), intracranial brain surgery, a history of addiction to alcohol, drugs or narcotics, a daily consumption of benzodiazepines (≥1 mg of lorazepam taken daily), and/or any illness or condition that could compromise their participation in the study.

2.3. fMRI memory task and procedure

Brain activation was measured with a task designed to assess associative memory encoding (see Figure 1). The encoding phase was done in the scanner. Participants were presented with a series of items placed in one of four quadrants of a grid (top left, top right, bottom left, bottom right). They were asked to memorize the target items, which included seventy-eight (78) pictures of common objects belonging to one of six semantic categories (musical instruments, animals, fruits and vegetables, kitchen tools, sports gear and food). Thirty-nine (39) grey squares were used as control stimuli. Participants were instructed to remember the pictures and their position on the grid, and pay attention to the grey squares without having to remember their position. They were asked to press a key on a remote control whenever a stimulus occurred, whether a picture or a gray square. Stimuli were presented on a black background of a computer screen. They were presented for three seconds with a 500- to 18500-millisecond inter-stimulus interval. Instructions were displayed on the screen prior to the task. This phase lasted about 10 minutes.

Following the encoding phase, participants left the scanner and were invited to a separate room for the retrieval phase. The 78 studied pictures and 39 new ones were presented one at a time in the center of a computer screen. Studied and new items were presented in a random order. Participants were asked to determine if an item had been studied during the encoding phase by pressing the Yes/No response key. When an item was identified as having been studied, participants were asked to determine where it was located on the grid by pressing the corresponding key on a different keypad. Participants had an unlimited amount of time to respond. The retrieval phase lasted approximately 10 minutes

Insert Figure 1 about here

2.4. Neuroimaging data acquisition

The core CIMA-Q protocol is referred to as the *Canadian Dementia Imaging Protocol* (www.cdip-pcid.ca). All brain images were acquired from either Siemens Healthcare (TrioTim and Prisma Fit) or Philips Medical Systems (Achieva and Ingenia) scanners with a magnetic field of 3 Tesla (more details about the acquisition parameters can be found in Supplementary Materials). The protocol sequences for image acquisition were harmonized between manufacturers/software configurations to optimize commonality, and quality control procedures were performed monthly to ensure across-scan comparability (see[22]).

2.5. Neuroimaging data processing and analysis

2.5.1. Task-related fMRI

Functional data was processed using Statistical Parametric Mapping version 12 software, (SPM12) implemented in MATLAB 9.4. The first four volumes were discarded

for every participant to avoid artefact contamination. All functional images were first converted into analyze format and unwarped. They were then realigned to the median image acquired in the session, and a mean image was created. Realigned volumes were co-registered to their corresponding T_1-MRI image, corrected for within-run movement, normalized into the MNI stereotaxic space with a voxel size of 3 mm^3, and spatially smoothed with an 8 mm full-width at half-maximum Gaussian Kernel. Images were high-passed filtered (128 seconds) to remove low-frequency signal drifts.

fMRI data was analyzed in an event-related design and only participants with a minimum of 12 events per contrast were considered. Within-group voxel-wise comparisons were performed for all three groups for the associative memory contrast, which consisted in the subtraction of activation associated with the control items (grey squares) from those associated with the successful encoding of an item and its position. This was done with a family-wise correction (FWE) set at $P < 0.05$ at the cluster and peak levels. Analyses focused on both hippocampi and regions from the cortical signature of AD.[23] Masks were built using the PickAtlas toolbox,[24] and subject-wise betas values were extracted using MarsBar[25] implemented in MATLAB.

2.5.2. Anatomical MRI

Cortical reconstruction and volumetric segmentations were performed using *FreeSurfer 5.3* (http://freesurfer.net).[26] Two types of data were obtained: 1) raw hippocampal volumes (used to defined SCD^+), and 2) normative morphological data (hippocampal volumes, cortical thickness). This latter type of data was obtained by comparing them to large-scale normative cohorts and converted into Z scores correcting for age, sex, estimated total intracranial volume, scanner manufacturer, magnetic field

strength, and interactions between these terms, as per the normative data and procedure defined by [27-28] (used for regression analyses).

Data on white matter lesions (WML) were also obtained and used as covariates, as white matter damage has been shown to cause blood-oxygen-level-dependant (BOLD) signal alterations unrelated to true change in neuronal activity (for a review, see[29]). WML were derived from the segmentation of the T_1-weighted and FLAIR volumes using a patch-based method[30] implemented in *volbrain* (http://volbrain.upv.es/) and expressed as the percentage of total brain volume.

2.6. Statistical analyses

Statistical analyses were conducted with *R* software packages (http://www.R-project.org). Participants whose T_1 ($n = 5$) or fMRI activation images ($n = 4$) failed quality control based on visual inspection of motion artefacts in the brain activations by an image analyst (SM) and the first author (NCL) were excluded from analyses. There were a few outliers identified when examining performance on the associative memory test ($n = 2$) and left superior parietal lobule fMRI activity ($n = 1$). Since these observations accounted for less of 5% than total observations, the winsorization procedure was applied.[31] Kolmogorov-Smnirnov tests were then conducted for normality for each variable included in the analyses. All variables of interest were normally distributed and showed appropriate residual distribution, except for the associative memory score ($P = 0.01$), which revealed a slightly positive asymmetric distribution. Hence a non-parametrical test was used to compare groups on this score. All analyses involved scanning site, age, sex, and WML as a covariances of nuisance.

2.6.1. Behavioral analysis

An associative memory score was computed as follows: *correct source* (*wrong source* + *false alarm*), where *correct source* refers to the number of responses in which both the item and its position were correctly identified. *Wrong source* refers to the number of responses where the item was recognized but not its position, and *false alarm* refers to the number of responses where a new image was falsely recognized.

Group differences on associative memory were assessed using a Kruskall-Wallis one-way ANOVA with group (HC, SCD^+, MCI) as a between-subject factor and the associative memory score as the dependent variable. Post-hoc comparisons were performed using the Mann-Whitney U-test.

2.6.2. Polynomial analyses

Polynomial regression analyses were computed in a single group combining individuals with SCD^+ and MCI. Within-group linear and quadratic regressions models were assessed with intercept, mean-centered measures of neurodegeneration (i.e. linear) and their squared term (i.e. quadratic) as independent variables, and task-related activation as the dependent variable. The significance of *F* change was assessed between linear and quadratic models to determine which model explained the higher proportion of variance. Measures of neurodegeneration included a composite score derived from mean thickness values in the cortical signature of AD[23] and left and right hippocampal volumes. Beta values extracted from ROI analyses were used as measures of task-related activation. Of note, normative *Z*-scores were used as measures of neurodegeneration for these analyses (see[28-29]) in order to reduce the impact of the measures used for the definition of SCD^+ (raw hippocampal volumes corrected for intracranial volume).

A similar procedure was used to examine the function modelling the relationship between memory performance and brain activation. An intercept, mean-centered associative memory performance score (i.e. linear) and its squared term (i.e. quadratic) were entered in the models as independent variables with task-related activation (beta values) as the dependent variable.

2.6.3. Task-related activation analysis

Task-related activation group differences during the associative contrast were then performed by conducting one-way ANOVAs with group (SCD^+, MCI, HC) as a between-subject factor on beta values derived from functional regions of interests (ROIs), and a Tukey test for *post* hoc comparisons.

3. Results

3.1. Clinical and demographic characterization

Demographic and clinical data are shown in Table 1. All groups had similar education levels. However, there were proportionally more females in the HC group compared to the SCD^+ and MCI groups, and participants with MCI were significantly older than HC. MCI individuals had lower MoCA scores than both HC and SCD^+, and lower Logical Memory scores than HC but not SCD^+.

Insert Table 1 about here

3.2. Behavioral performance

Analysis of post-scan memory performance revealed a group effect on the associative memory score. Participants with MCI performed more poorly than HC, whereas SCD^+ did not differ from HC or MCI (see Table 1).

3.3. Polynomial regressions

A significant quadratic function was found for the relationship between cortical thickness in the AD signature regions and activation in the left superior parietal lobule (see Figure 3 and Table 3). The assessment of *F* change between models indicated that the quadratic function explained a significantly larger proportion of variance than the linear function. The linear model was significant when examining the relationship between left hippocampal volume and activation of the left hippocampus, and between left hippocampal volume and activation of the right inferior temporal lobule. In both cases, a smaller volume was associated with higher levels of activation. The difference in *F* change was not significant, suggesting that a linear function was a better fit than a quadratic one.

The analyses of the relationship between associative memory performance and brain activation revealed a significant quadratic model between the associative memory score and left superior parietal activation (see Table 3). The *F* change was significant, indicating that the quadratic model explained a significantly larger proportion of variance than the linear one. There was also a significant linear and positive model between associative memory performance and activation in the left middle temporal lobe, with a higher level of activation associated with superior memory performance. There was no other significant model.

3.4. Task-related activations

Within-group task-related activation maps for the associative memory contrast are presented in Figure 2, where the three groups are shown separately. Table 2 and Figure 2 present group comparisons of activation related to associative memory encoding. Higher levels of activation were found in participants with SCD^{+} compared to HC and

participants with MCI. Higher activation levels in SCD^+ occurred in the left and right hippocampi, left and right middle temporal lobes, left superior parietal lobule, right inferior temporal lobe and right precuneus. Participants with MCI showed a lower level of activation in the left superior parietal lobule compared to those with those with SCD^+ and HC. In addition, individuals with SCD^+ showed greater activation in the left and right inferior frontal lobes than individuals with MCI but not HC. There were no other significant group differences.

Insert Table 3 about here

Insert Figure 3 about here

4. Discussion

The main goal of this study was to characterize hyperactivation by identifying the function that best fits the relationship between proxies of disease severity and memory-related activation in a group of individuals at risk of AD. A quadratic inverse U-shape function modeled the relationship between activation in the left superior parietal lobule and proxies of disease severity. Linear models accounted for the relationship between activation in the left hippocampus, and the right inferior temporal and left hippocampal volume. Evidence of hyperactivation was found in individuals with SCD^+ in the hippocampi and several cortical regions, including the middle temporal lobes bilaterally, the left superior parietal lobule, right inferior temporal lobe and right precuneus.

Activation in the left superior parietal region is described by a quadratic function when using cortical thickness or associative memory performance as a proxy for disease severity. Furthermore, group comparisons in this region indicates hyperactivation in individuals with SCD^+ and hypoactivation in those with MCI. This supports the

hypothesis of early hyperactivation followed by hypoactivation at later stages of AD. Activation in the left hippocampus and right inferior temporal regions was better described by a negative linear relationship when related to hippocampal volume. Figure 3 shows that this is due to increased activation as volume is reduced. Thus, the functions appear to reflect activation in the ascending portion of the inverse U-shape.

This study's results have many far-reaching implications. The finding of hyperactive brain regions in individuals with SCD^{+} suggests that hyperactivation may represent a sensitive marker for the phase that precedes the occurrence of measurable cognitive impairment. It thus has potential as a marker to identify individuals, who are cognitively intact but at risk of future progression to dementia. This finding is consistent with other studies, which report similar results using smaller sample sizes and a behaviorally-defined group of individuals with SCD.[33-35] However, this is the first study to find hyperactivation in individuals with SCD with biomarker features (i.e. *APOE4* allele and hippocampal volume) that increase the likelihood of pathophysiological processes of AD. In the presence of a mild neurodegeneration, a high level of activation may be consistent with a higher risk of progression in cognitively intact older adults complaining about their memory. Furthermore, while some studies investigated fMRI dynamics in relation to amyloid and tau[36-37], this is the first study to link a quadratic trajectory of brain activation with neurodegeneration, a recognized proxy of clinical severity[38-39] and time to dementia.[5].

Although this study was not designed to address the cause of hyperactivation, this issue should be briefly addressed here, as it is debated in the literature. The compensatory view posits that increased activation may reflect protective brain plasticity. [1-5, 40] In

contrast, the excitotoxic view suggests that abnormally high levels of activation would accelerate AD-related pathophysiologic processes and contribute to cognitive impairment. [41-47] The two opposing views may not be mutually exclusive as compensatory hyperactivation and pathologically-driven hyperactivation may occur at different points in time or in different regions. This study's finding of a positive relationship between memory and activation in the left superior parietal region but not in the hippocampus could indeed reflect different mechanisms in the hippocampus versus cortical regions as has been suggested.[48-49] However, this is hypothetical and should investigated in future studies.

Some limitations must be recognized. The sample is relatively small, although it is larger than most previous studies on this issue. It is nonetheless noteworthy that CIMA-Q is one of the rare cohorts that includes task-related activation data. This study is transversal, and longitudinal follow-up will be needed to determine if hyperactivation can be used to predict progression to dementia. Although the BOLD signal reflects neuronal activity, it is an indirect measure and other factors may modify the relationship between true neuronal activity and the observed BOLD signal. Finally, it was not possible to access tau or amyloid brain imaging for this study's participants. There is a possibility that some of the study participants may not meet criteria for biologically defined AD according to the recent NIA-AA A/T/N research framework. [50]. However, our results fit the aforementioned models and studies that assessed the relationships between AD biomarkers and changes in fMRI activation and connectivity.

In conclusion, novel findings are reported to support the presence of very early and transient hyperactivation in people at risk of AD. We show that activation increases

linearly in some regions and follows an inverse U-shape in others, when examined as a function of disease severity. Overall, the results suggest that hyperactivation is present in the early stages of the disease such as in individuals who have genetic and/or brain markers of AD and meet criteria for SCD, and has potential as a biomarker indicating future progression to AD. However, future studies are needed to determine the value of hyperactivation as a predictor of dementia in comparison to other markers and to better understand the pathophysiology that underlies hyperactivation in early AD.

Acknowledgments

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Conflicts

Authors report no conflict of interest in relation to this study.

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Table 2.1. Demographic, clinical, genetic and behavioural characteristics of participants

	HC	SCD^{+}	MCI	P-values
Participants, N	54	28	26	-
Age (Mean, SD)	71.54 (4.56)	73.23 (5.21)	75.73 (5.01)	P = .002
Sex, M/F	14, 40	15, 13	12, 14	P = .031
Education (Mean, SD)	15.11 (3.14)	15.46 (3.70)	15.20 (3.27)	P = .900
MoCA (Mean, SD)	28.17 (1.40)	27.68 (1.33)	24.96 (2.25)	$P = 2.03^{-12}$
Logical Memory Delayed Recall (Mean, SD)	13.69 (4.99)	12.68 (3.69)	11.00 (4.51)	P = .028
APOE4 carriers (N, %)	0 (0)	10 (35.71)	11 (42.31)	-
WML (Mean, SD)	0.57 (0.79)	0.64 (1.04)	0.4 (0.47)	P = .52
Associative memory score (Mean, SD)	2.59 (1.63)	2.18 (1.46)	1.62 (1.56)	P = .014

MoCA = Montreal Cognitive Assessment; WML = White matter lesions expressed as a percentage of intracranial volume

Table 2.2. Results from significant linear and quadratic models between fMRI activation and measures of neurodegeneration, and between fMRI activation and memory performance in the at-risk for AD group controlling for scanning site, age, sex and white matter lesions

fMRI ROI	Independent variable	Model	F	P	Standardized β	CI Lower boundary	CI Upper boundary	Adjusted R^2	Sig. F change
Left hippocampus	Left hippocampal volume	Linear	6.201	.017	-0.101	-1.33	-0.027	.122	-
		Quadratic	1.634	.119	0.048	-0.007	0.061	-	.899
Right inferior temporal lobe	Left hippocampal volume	Linear	5.272	.028	-0.100	-0.174	-0.027	.094	-
		Quadratic	7.319	0.01	-0.091	-0.177	-0.006	-	.305
Left superior parietal lobule	Mean global cortical thickness	Linear	<1	.867	0.025	-0.181	0.232	-	-
		Quadratic	5.303	.028	-0.164	-0.311	-0.017	.128	.009
Left middle temporal gyrus	Associative memory score	Linear	9.898	.000				.331	-
		Quadratic	7.063	.001	-			-	.268
Left superior parietal lobule	Associative memory score	Linear	1.762	.192	0.052	-0.028	0.013	-	-
		Quadratic	3.773	.009	-0.053	-0.096	-0.009	.110	.019

fMRI = Functional magnetic resonance imaging; ROI = Region of interest; CI = Confidence interval (set at 95%). Adjusted R^2 are only reported for best fitting models. Significance of F change indicates if the quadratic model was a significantly better fit than the linear one.

Table 2.3. Results from between-group comparisons for fMRI brain activation during the associative memory contrast correcting for scanning site, age, sex and white matter lesions

Brain region	F	P-value	η^2	Post-hoc (P-value)
Left hemisphere				
Hippocampus	4.903	.009	.09	SCD^+ > HC (.008)
Medial temporal lobe	5.904	.004	.091	SCD^+ > HC (.009) & MCI (.013)
Inferior temporal lobe	<1	.480	-	-
Temporal pole	1.470	.236	-	-
Angular gyrus	1.274	.285	-	-
Superior frontal gyrus	<1	.715	-	-
Superior parietal lobule	7.524	.000	.151	SCD^+ > HC (.043) & MCI (.001); HC > MCI (.039)
Supramarginal	1.652	.198	-	-
Precuneus	2.491	.089	-	-
Inferior frontal gyrus	4.445	.014	.098	SCD^+ > MCI (.011)
Right hemisphere				
Hippocampus	6.535	.002	.110	SCD^+ > HC (.002)
Medial temporal lobe	5.807	.004	.086	SCD^+ > HC (.023) & MCI (.006)
Inferior temporal lobe	4.489	.014	.096	SCD^+ > HC (.026) & MCI (.006)
Temporal pole	1.873	.160	-	-
Angular gyrus	1.578	.212	-	-
Superior frontal gyrus	<1	.986	-	-
Superior parietal lobule	<1	.942	-	-
Supramarginal	<1	.937	-	-
Precuneus	3.424	.014	.081	SCD^+ > HC (.046) & MCI (.022)
Inferior frontal gyrus	4.676	.011	.102	SCD^+ > MCI (.009)

Figure 2.1. Functional MRI memory task. A. In the encoding phase, target items consisted of pictures of common objects positioned in one of four quadrants and interspersed with grey squares (control stimuli). B. In the retrieval phase, 78 previously studied pictures and 39 new items were presented. Participants indicated whether or not the items were previously seen in the encoding phase, and were asked to remember their location.

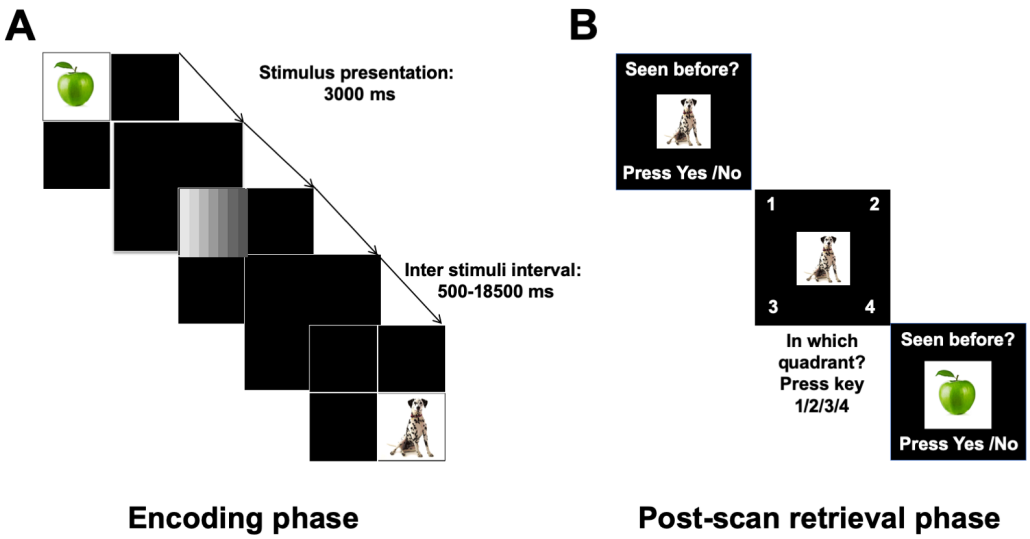


Figure 2.2. Within-group activation maps and group-wise comparisons in functional MRI activation. A. Within-group activation maps for the associative memory contrast (activation associated with grey squares subtracted from activation associated with the successfully encoded item with their position). The Family-Wise Error (FWE) correction was applied with a $P < 0.05$ threshold at the cluster and peak levels. B. Group-wise differences in fMRI activation in both hippocampi and regions from the cortical signature of AD for the associative memory contrast.

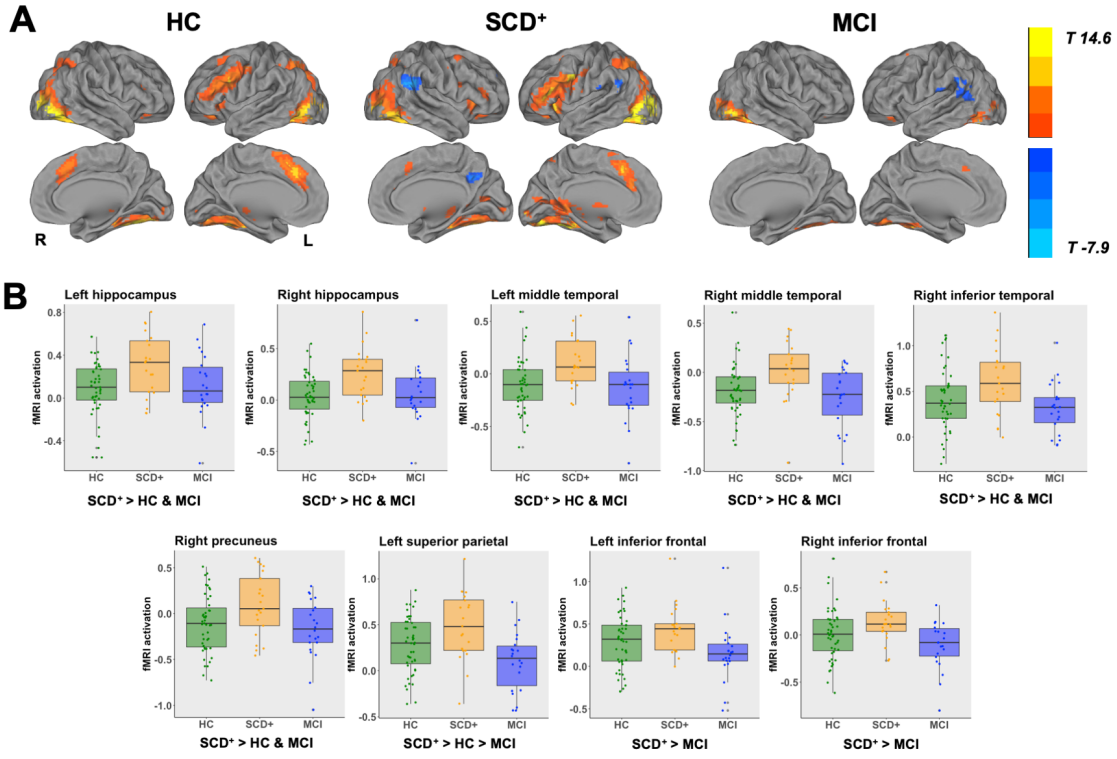
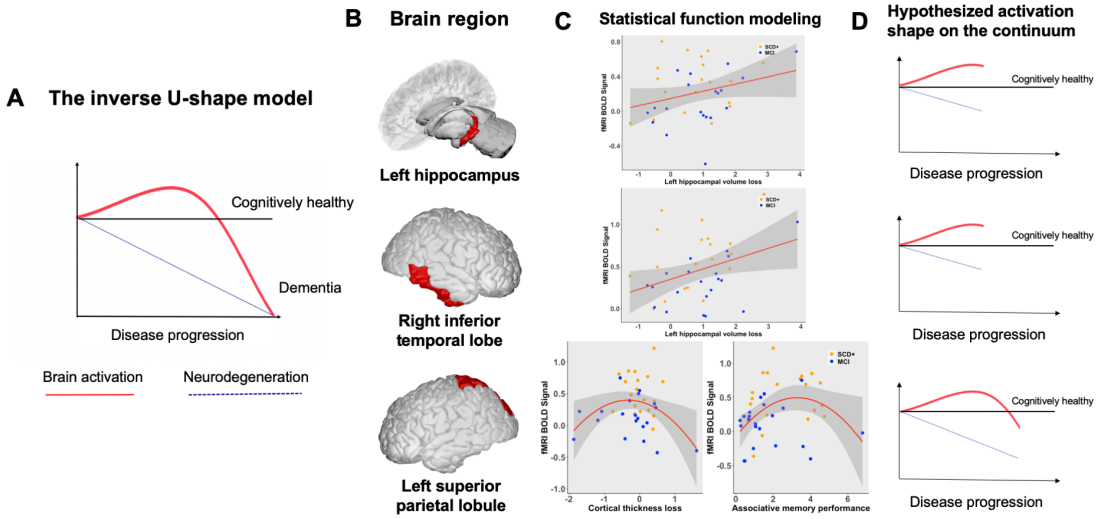


Figure 2.3. Graphical representation and statistical fitting of the "inverse U-shape" model. A. Graphical depiction of the "inverse U-shape" model of brain activation trajectory with AD progression. Increased activation (i.e. hyperactivation) is found in the early phase of the disease when neurodegeneration is mild, while decreased activation (i.e. hypoactivation) is observed in the later stages when structural damage becomes more prominent. B. Brain regions which showed a significant linear or quadratic relationship with measures of neurodegeneration or memory performance. BrainPainter was used to display brain images (Marinescu et al., 2019). C. Polynomial regressions (i.e linear or quadratic) between fMRI activation from brain regions depicted in B, and measures of neurodegeneration (hippocampal volume, cortical thickness) or associative memory performance controlling for scanning site, age, sex, and white matter lesions. D. The hypothesized shape of activation along the disease continuum for brain regions shown in B according to the mathematical model that best fitted the relationship between brain activation and proxies of disease severity shown in C.



Supplementary Materials

Sequence - T1w-3D				
Study	CDIP – PCID v3.7			
Vendor	GE	Philips	Philips	Siemens
Field Strength	3.0T	3.0T	3.0T	3.0T
Model	Discovery	Ingenia	Achieva	Trio
Version	23	R5	3.2.1	17
Sequence Name	3D FAST SPGR	3D TFE	3D TFE	3D MP-RAGE
Imaging Options	IrP - Asset	Fast (Sense)	Fast (Sense)	iPat
Pulse Timing				
TE (ms)	min full (2.932)	shortest (3.3)	shortest (3.3)	2.98
TR (ms)	min (6.66)	shortest (7.3)	shortest (7.3)	2300
Flip Angle (°)	11	9	9	9
TI (ms)	400	945	945	900
Scan Range				
FOV (in-plane) (mm)	256 x 256	256 x 248	256 x 248	256 x 256
Slice thickness (mm)	1	1	1	1
Gap between slices (mm)	0	0	0	0

No. Slices	180	180	180	192
Acquisition				
Orientation	Sagittal	Sagittal	Sagittal	Sagittal
Matrix size	256 x 256	256 x 248	256 x 248	256 x 256
Voxel size [L/R x A/P x I/S] (mm)	1 x 1 x 1	1 x 1 x 1	1 x 1 x 1	1 x 1 x 1
NEX	1	1	1	1
Acceleration factor (Parallel factor*)	2	2	2	2
Fold-Over direction	AP	AP	AP	AP
Reconstruction				
Matrix size	256	256	256	256
Voxel size [L/R x A/P x I/S] (mm)	1 x 1 x 1	1 x 1 x 1	1 x 1 x 1	1 x 1 x 1
Other				
Fat Suppression	None	None	None	None
Bandwidth	31.25kHz	228 Hz/px	228 Hz/px	240 Hz/px
Coil Type				
Head	x	x	x	x
Channel	8-12 (HNS)	15 (Head and Neck)	8	12

Timing				
Prescan Time+	00:30	00:30	00:30	00:30
Scan Time	04:52	06:20	06:17	05:21
Total Time (min)	05:22	06:50	06:47	05:51

Sequence - Task fMRI									
Study	CIMA-Q Add-on								
Vendor	Philips	Philips	Philips	Philips	Philips	Philips	Siemens	Siemens	Siemens
Field Strength	3.0T	3.0T	3.0T	3.0T	3.0T	3.0T	3.0T	3.0T	3.0T
Model	Ingenia	Ingenia	Ingenia	Achieva	Achieva	Achieva	Trio	Trio	Trio
Version	R5	R5	R5	3.2.3	3.2.3	3.2.3	17	17	17
Sequence Name	FFE EPI	FFE EPI	B0 Map	FFE EPI	FFE EPI	B0 Map	fMRI EPI	fMRI EPI	GRE field mapping
Imaging Options									
Pulse Timing									
TE (ms)	25	25	4.6	25	25	4.6	25	25	4.92 / 7.38
TR (ms)	2500	2500	475	2500	2500	475	2500	2500	476
Flip Angle (°)	90	90	60	90	90	60	90	90	60
TI (ms)	-	-	-	-	-	-	-	-	-
Scan Range									
FOV (in-	240 x 240	240 x 240	240 x	240 x 240	240 x 240	240 x 240	222 x 222	222 x 222	222 x 222

plane) (mm)			240						
Slice thickness (mm)	3	3	3	3	3	3	3	3	3
Gap between slices (mm)	0.3	0.3	0.3	0.3	0.3	0.3	0	0	0
No. Slices	41	41	41	41	41	41	41	41	45
Acquisition									
Orientation	AC-PA minus 20°	AC-PA minus 20°	AC-PA minus 20°	AC-PA minus 20°	AC-PA minus 20°	AC-PA minus 20°	AC-PA minus 20°	AC-PA minus 20°	AC-PA minus 20°
Matrix size	80 x 80	80 x 80	80 x 80	80x79	80x79	80 x 80	74	74	74
Voxel size [L/R x A/P x I/S] (mm)	3 x 3 x 3	3 x 3 x 3	3 x 3 x 3	3 x 3 x 3	3 x 3 x 3	3 x 3 x 3	3 x 3 x 3	3 x 3 x 3	3 x 3 x 3
NEX	1	1	1	1	1	1	1	1	1

Acceleration factor (Parallel factor*)	1.8	1.8	1	1.3	1.3	1	1	1	1
Fold-Over direction	AP	First AP / Second PA	AP	AP	First AP / Second PA	AP	AP	First AP / Second PA	AP
Reconstruction									
Matrix size	80	80	80	64	64	80	74	74	74
Voxel size [L/R x A/P x I/S] (mm)	3 x 3 x 3	3 x 3 x 3	3 x 3 x 3	3 x 3 x 3	3 x 3 x 3	3 x 3 x 3	3 x 3 x 3	3 x 3 x 3	3 x 3 x 3
Other									
Fat Suppression	Fat Sat. SPIR	Fat Sat. SPIR	None	Fat Sat. SPIR	Fat Sat. SPIR	None	Fat Sat.	Fat Sat.	None
Bandwidth	39.1	39.1	294.8	25.2	25.2	294.8	2502	2502	268

(Hz/Px)									
Number of acquisitions	300	4	-	300	4	-	310	4	-
Coil Type									
Head	x	x	x	x	x	x	x	x	x
Channel	15 (Head and Neck)	15 (Head and Neck)	15 (Head and Neck)	8	8	8	12	12	12
Timing									
Prescan Time+	00:30	00:30	00:30	00:30	00:30	00:30	00:30	00:30	00:30
Scan Time	12:35	00:17	01:17	12:35	00:17	01:17	13:03	00:17	01:17
Total Time (min)	13:05	00:47	01:47	13:05	00:47	01:47	13:33	00:47	01:47
Comments:	Tested 22-AVR-15	Tested 22-AVR-	Tested 22-AVR-	Tested 10-AVR-15	Tested 10-AVR-	-	Tested 10-MAR-15	Tested 10-MAR-	Tested 10-MAR-15

		15	15		15			15	

Sequence - 2D FLAIR				
Study	CDIP – PCID v3.7			
Vendor	GE	Philips	Philips	Siemens
Field Strength	3.0T	3.0T	3.0T	3.0T
Model	Discovery	Ingenia	Achieva	Trio
Version	22	R5	3.2.3	17
Sequence Name	2D FLAIR	2D FLAIR	2D FLAIR	2D TDF
Imaging Options	EDR, Asset, IR	Fast (Sense)	Fast (Sense)	iPat
Pulse Timing				
TE (ms)	140	125	125	123
TR (ms)	9000	9000	9000	9000
Flip Angle (°)	125	150	150	165
TI (ms)	2250	2500	2500	2500
Scan Range				
FOV (in-plane) (mm)	240 x 240	240 x 210	240 x 210	240 x 240
Slice thickness (mm)	3	3	3	3
Gap between slices (mm)	0	0	0	0
No. Slices	48	48	48	48
Acquisition				

Orientation	Oblique axial	Oblique axial	Oblique axial	Oblique axial
Matrix size	256 x 256	256x224	256x222	256 x 256
Voxel size [L/R x A/P x I/S] (mm)	0.94 x 0.94 x 3	0.94 x 0.95 x 3	0.94 x 0.95 x 3	0.94 x 0.94 x 3
NEX	1	1	1	1
Acceleration factor (Parallel factor*)	1	2	2	2
Fold-Over direction	RL	RL	RL	RL
Reconstruction				
Matrix size	256	256	256	256
Voxel size [L/R x A/P x I/S] (mm)	0.94 x 0.94 x 3	0.94 x 0.94 x 3	0.94 x 0.94 x 3	0.94 x 0.94 x 3
Other				
Fat Suppression	None	None	None	None
Bandwidth	27.78 kHz	164 Hz/px	242 Hz/px	222 Hz/px
Coil Type				
Head	x	x	x	x
Channel	8-12 (HNS)	15 (Head and Neck)	8	12
Timing				
Prescan Time+	00:30	00:30	00:30	00:30

Scan Time	04:32	04:48	04:12	04:05
Total Time (min)	05:02	05:18	04:42	04:35
Comments:	Flip angle should be set and not left to the scanner to decide	Set parameter "image filter" at Weak		

CHAPITRE 4 – Article 3

Latent patterns of task-related functional connectivity in relation to regions of hyperactivation in individuals at risk for Alzheimer's disease

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NeuroImage: Clinical (sous révisions)

Abstract

The goal of this study was to assess how task-related hyperactivation relates to brain network dysfunction and memory performance in individuals at risk for Alzheimer's disease (AD). 108 participants from the CIMA-Q cohort were included, of which 54 were healthy controls (HC) and APOE4 negative, 28 had subjective cognitive decline plus (SCD^+) as they presented with memory complaint in addition to smaller hippocampal volume and/or APOE4 allele, and 26 had mild cognitive impairment (MCI). Functional magnetic resonance imaging (fMRI) activation was measured during an object-location memory task. A seed-partial least square analysis (seed-PLS) was used to yield a set of orthogonal latent variables (LVs) which revealed that regions of hyperactivation related to multivariate brain network dysfunction in individuals at risk of AD. Interestingly, we found increasing hyperactivation-network dysfunction from SCD^+ to MCI stages, suggesting of a sequence in the early disease phase. Moreover, the interaction between these functional alterations related to the increasing symptomatology associated with the disease. Our data provides empirical evidence that early dysfunction in brain activation and connectivity is present in the very course of AD and may contribute to the phenotypical presentation of the disease.

Keywords: Functional connectivity, hyperactivation, mild cognitive impairment, subjective cognitive decline, task-related fMRI

Introduction

Early changes in brain function have been proposed to represent an early hallmark of Alzheimer's disease (AD) (Pasquini et al., 2019; Sperling et al., 2010; 2011). Interestingly, individuals in the early stages of AD show increased brain activation – a phenomenon known as hyperactivation – in regions vulnerable to AD. Increased task-related fMRI activation has been reported in patients with mild cognitive impairment (MCI) and subjective cognitive decline (SCD), compared to healthy controls (HC) (Celone et al., 2006; Clément & Belleville, 2010; 2012; Clément et al. 2010; 2013; Corriveau-Lecavalier & al., 2019; submitted; Erk et al., 2011; Rodda et al., 2009; 2011). Therefore, the presence of hyperactivation in specific brain regions could serve as an early signature of AD and may shed light on early brain dysfunction related to the disease.

Increasing knowledge about functional brain changes in AD shows that the disease not only targets specific brain regions but also impacts the functional integrity and connectivity of multiple brain networks (see Jacobs et al., 2013 for a meta-analysis). Hence it is plausible that hyperactivation found in brain regions vulnerable to the disease may be associated with altered patterns of functional connectivity in brain networks affected by AD. Preclinical studies and animal models suggest that early hyperactivation of specific brain regions could drive and/or be driven by dysfunction in neuronal networks (for a review, see Zott et al., 2018). This is consistent with the finding that hyperactivation occurs in brain areas that are part of large-scale networks vulnerable to the early pathophysiological processes of AD (Chhatwal et al., 2018; Jones et al., 2016; 2017; Franzmeier et al., 2020; Schutlz et al., 2017). For example, task-related hyperactivation has repeatedly been observed in the hippocampus (Berron et al., 2019; Celone et al., 2006; Corriveau-Lecavalier et al., 2019; submitted, Dickerson et al., 2004; 2005; Huijbers et al., 2015; 2019; Kircher et al., 2007; Putcha et al., 2011) and temporo-parietal areas (Clément &

Belleville, 2010; 2012; Clément, Belleville, & Mellah, 2010; Clément, Gauthier, & Belleville, 2013; Corriveau-Lecavalier et al., 2019; Elman et al., 2014; Marks et al., 2017). These regions are integrated in functional brain networks known to be affected in AD, such as the default mode and the fronto-parietal/task-positive and dorsal attention networks (Chhatwal et al., 2018; Franzmeier et al., 2019; 2020; Jones et al., 2011; 2016; 2017; Sepulcre et al., 2017; Schultz et al., 2017).

Thus, one important question is whether regional hyperactivation is associated with network dysfunction in individuals at risk of AD. This link would be plausible given that early neuronal hyperactivity is thought to originate in sites of early AD pathology accumulation (Bero et al., 2011; Busche et al., 2012; 2019; Wu et al., 2016). Abnormalities in brain activation might then propagate to functionally connected regions, orchestrating AD pathology through topological propagation in an activity-dependent manner (Bischof et al., 2019; Franzmeier et al., 2019; 2020; Kim et al., 2019). However, the presence of hyperactivation in localized regions vulnerable to AD and brain network dysfunction have only been assessed separately and their relationship remains unknown. This study aims to assess the link between hyperactivation and network dysfunction in individuals with MCI and SCD. Individuals with MCI show signs of cognitive impairment and while they do not meet criteria for dementia, they are at high risk of developing the disease. Participants with SCD complain about poor memory but do not show signs of cognitive impairment. However, a significant proportion of these individuals will progress to MCI. Hence the study of individuals with MCI and SCD allows the assessment of brain alterations occurring in the early stages of AD, prior to a dementia diagnosis. Given that SCD is a heterogenous construct and that other causes unrelated to neurodegenerative disease can result in memory complaint, SCD participants were only included in this study if they had smaller hippocampal volumes and/or were APOE4 carriers. This is in accordance with the most

recent criteria for SCD plus (SCD^+; Jessen et al., 2014; 2020), which suggest reliance on biomarkers that increase the likelihood of preclinical AD in individuals with SCD.

Another important objective of this study is to better understand functional brain alterations underlying cognitive impairment in patients with SCD^+ and MCI. Task-related designs are of particular relevance to assess patterns of dysfunction in brain activation and connectivity, which may underlie cognitive impairment associated with the early phases of AD. Associative memory is one of the first cognitive functions to decline in patients with AD (Atienza et al., 2011; Troyer et al., 2008). Thus, studying associative memory may help clarify the relationship between alterations in brain activation and connectivity, and cognitive impairment in individuals at risk of AD.

In summary, it is hypothesized that early hyperactivation is linked to altered patterns of functional connectivity in brain networks associated with higher-order cognitive functions, such as associative memory in people at risk of dementia. This altered hyperactivation-network interaction should be associated with differences in cognitive symptomatology of the disease. To test this hypothesis, a multivariate seed-based partial least square (seed-PLS; Krishnan et al., 2011; McIntosh and Lobaugh, 2004) analysis was used to assess between-group similarities and differences in the triple association between: i) seed activity in brain regions found to be hyperactive in individuals at risk of AD, ii) latent patterns of whole-brain task-related activation, and iii) associative memory performance in individuals with SCD^+, MCI or HC. Brain activation and connectivity were measured during an object-location associative memory task. Regions of interest (ROI) chosen for seed activation were the left hippocampus, the right inferior temporal gyrus and the left superior parietal lobule. These regions were selected because they were found to be either hyperactive or hypoactive in participants with SCD^+ and MCI used for this study

(Corriveau-Lecavalier et al., submitted). These regions were thus considered to represent potential candidates to reveal AD-related network dysfunction.

Materials and methods

Participants

The study included data from participants, who took part in the Consortium for the Early Identification of Alzheimer's disease-Quebec (CIMA-Q). CIMA-Q's main objective is to characterize a longitudinal observational cohort of more than 350 community-dwelling older men and women recruited from three Canadian cities (Montreal, Sherbrooke and Quebec City). Participants were either, 1) cognitively healthy with SCD, 2) suffering from MCI, or 3) were diagnosed with dementia due to probable AD. CIMA-Q collects clinical, cognitive, biological, radiological and pathological data from these participants in order to, 1) establish an early diagnosis of AD, 2) make a well-characterized cohort available to the scientific community, 3) identify therapeutic targets and interventions to prevent or slow cognitive decline and AD, and 4) support clinical studies (Belleville et al., 2019). Data for this study were obtained from 108 CIMAQ participants, who completed the fMRI memory examination at baseline. fMRI activation in this subgroup was reported in Corriveau-Lecavalier et al. (submitted). This study was approved by the CIMA-Q research committee as well as the Comité mixte d'éthique de la recherche vieillissement-neuroimagerie of the Centre intégré universitaire de santé et de services sociaux du Centre-Sud-de-l'Île-de-Montréal. All participants provided written informed consent prior to taking part in the study.

CIMA-Q clinical diagnoses were made by expert physicians based on widely accepted research criteria. The SCD diagnosis was based on the Subjective Cognitive Decline Initiative (Jessen et al., 2014; 2020) criteria, which include presence of a memory complaint and worry, performance within normal ranges on standardized clinical tests (scores of >26 on the Montreal

Cognitive Assessment or MoCA; Nasreddine et al., 2005; score of ≤3 for 0-7 years of education, ≤5 for 8-15 years, and ≤9 for 16 or more years on the Logical Memory subtest of the Wechsler Memory Scale, 1997) and a score of 0 on the Clinical Dementia Rating Scale or CDR (Morris et al., 1997). Participants meeting criteria for SCD^+ were selected based on the presence of at least one APOE4 allele and/or smaller hippocampal volume (>1 SD below mean of HC). The remaining SCD participants (n = 33) not meeting criteria for SCD^+ were integrated to the HC group. The MCI criteria were based on the NIA-AA workgroup (Albert et al., 2011) and include presence of a memory complaint and worry, objective cognitive decline based on standardized clinical tests (scores between 20-25 on the MoCA; score of ≤2 for 0-7 years of education, ≤4 for 8-15 years, and ≤8 for 16 or more years on the Logical Memory subtest of the Wechsler Memory Scale), and a score of 0.5 on the CDR. HC performed within normal range on standardized clinical tests (see criteria for SCD), had a score of 0 on the CDR and were APOE4 negative. All participants met safety criteria for inclusion in an MRI study and were right-handed.

Inclusion criteria included to be aged 65 and older, to live in the community or residence of an independent person, to have a score of 17 or higher on the telephone-Mini Mental State Examination (T-MMSE; Newkirk et al., 2004), to able to understand, read, and write in either French or English, to have sufficient auditory and visual acuity to participate to a neuropsychological assessment, and to have to be willing to answer to health-related questionnaires, to undergo physical and neuropsychological assessment, and to submit to a blood test. Exclusion criteria included planning to move outside of Quebec in the next three years, central nervous central system disease (e.g. subdural hematoma, subarachnoid hemorrhage, active epilepsy, primary or metastatic brain cancer), intracranial brain surgery, history of addiction to alcohol, drugs or narcotics, daily consumption of benzodiazepines equivalent or higher than 1 mg

of lorazepam taken orally, and/or illness or condition that could compromise participation in the study.

All participants underwent an extensive assessment to characterize them on clinical, physical and cognitive levels (see Belleville et al, 2019 for more details about the CIMA-Q assessments). Fasting blood sampling was conducted to determine participants' APOE genotype.

fMRI task and procedure

The memory task has been described in a separate publication (Belleville et al, 2019; Corriveau-Lecavalier et al., submitted). Brain activation was acquired during a 10-minute in-scan encoding phase of a memory task. Participants were exposed to 78 coloured pictures of common objects belonging to one of six semantic categories (musical instruments, animals, fruits and vegetables, kitchen tools, sports gear and food) and 39 grey squares (control condition). Participants were asked to memorize the stimuli, as well as their position on the screen, and pay attention to the grey squares without memorizing them. To ensure that participants kept their attention on the task, they were asked to press a button on a remote control with their right hand when the stimulus was presented (picture or grey square). Stimuli were displayed on a black background for three seconds in one of four quadrants on a computer screen (top left; top tight; bottom left; bottom right) with an inter-stimuli interval varying from 500 to 18500 milliseconds. The order of presentation of the stimuli was randomized across participants. Instructions were displayed prior to the encoding phase.

Retrieval was done in a separate room 10 minutes following the scanning session. Participants were presented with the 78 previously studied pictures and 39 new pictures, one at a time at the center of a computer screen. For each picture, participants were asked to indicate whether they had seen the picture during the encoding phase or not by pressing ''Yes'' or ''No'' on a keyboard. If a picture was identified as previously seen, the participant had to indicate in

which quadrant they had seen the stimulus using a keypad with buttons identified according to the locations on the four-position grid matching the visual display. There was an unlimited time to provide a response. The order of presentation of the stimuli differed from the encoding phase and was randomized across participants. To ensure participants understood the procedure, they performed a short practice of the task in a mock MRI with a reduced number of stimuli that differed from those used in the task.

Image acquisition

The CIMA-Q scanning protocol is referred to as the Canadian Dementia Imaging Protocol (Duchesne et al., 2018; www.cdip-pcid.ca). Image acquisition was performed using Siemens Healthcare (TrioTim and Prisma Fit) or Philips Medical Systems (Achieva and Ingenia) scanners with a magnetic field of 3 Tesla (see Supplemental details for more details about acquisition parameters). Sequences were harmonized between the sites of the MRI scan to optimize image quality between manufacturers/types of scan. Quality control procedures were performed monthly to ensure cross-scan comparability. Only the anatomical imaging (T1) and task-related functional acquisitions were of interest for this study.

fMRI preprocessing

Individual functional images were preprocessed using Statistical Parametric Mapping 12 (SPM12; Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, England) typical pipeline steps. The first four volumes of the run were discarded to exclude artefacts due to excessive movement. Functional images were unwrapped and realigned to median volume to create a mean image for every subject. The mean functional image was then coregistered to the corresponding anatomical T_1-weighted image, corrected for within-run movement and normalized to the Montreal Neurological Institute template with a voxel size of 3 X 3 X 3 mm. Images were smoothed by applying an 8 mm full width at half maximum (FWHM)

Gaussian kernel. A high-passed filter (128 seconds) was applied to remove low-frequency signal drifts. Subjects were excluded from analysis if their heads moved more than 3 mm during the functional run and/or failed quality control based on visual inspection of motion artefacts in the brain activations.

Anatomical MRI

Hippocampal volume segmentation was done using FreeSurfer 5.3 traditional pipeline steps (Dale et al., 1999). Raw hippocampal volumes were extracted and individually corrected for intracranial volume and used to assess whether the participants met the hippocampal volume criteria for SCD^{+} classification.

Statistical analyses

Between-group differences on sociodemographic measures were assessed with one-way ANOVAs and Tukey's tests for post-hoc comparisons for continuous variables, and chi square analysis for categorical variables.

To assess post-scan memory performance, an associative memory score was computed with the following = correct sources / (wrong sources + false alarms), where correct sources is the number of old items that were correctly recognized with their accurate position, wrong sources is the number of old items that were correctly recognized without their position, and false alarms is the number of new items that were falsely recognized. A positive asymmetric distribution was revealed for this variable using the Kolmogorov-Smirnov test and thus group differences on the associative memory score were assessed using a Kruskal-Wallis one-way ANOVA, with the Mann-Whitney U-test for post-hoc comparisons.

Task-related functional connectivity analyses were carried out using PLS software (Krishnan et al., 2011; McIntosh and Lobaugh, 2004) implemented in MATLAB 9.4. Analyses focused on activation associated with the encoding of items that were correctly recognized and

positioned during the post-scan recognition phase (associative memory encoding). Only participants with 12 events or more were considered for analyses. A between group multivariate seed-PLS analysis was used to determine how task-related activation within a seed ROI correlates with whole-brain activity and task performance between groups. Between group differences and similarities were assessed in three-way associations between: 1) seed activity of the left hippocampus (a region hyperactive in SCD^{+}; MNI coordinates X = -30, Y = -22, Z = -13) left superior parietal lobule (a region hyperactive in SCD^{+} and hypoactive in MCI; MNI coordinates X = -18, Y = -61, Z = 47), and right inferior temporal lobe (a region hyperactive in SCD^{+}; MNI coordinates X = 45, Y = -58, Z = -13); 2) whole-brain activity associated with associative memory encoding, and 3) associative memory scores.

Event-related fMRI data was obtained during the encoding of successfully recognized and positioned items. Visual baseline events were stored in a data matrix, where the rows were organized so that event-types were nested within each participant, and participants were nested within group. Columns of the matrix contained the average signal per condition (collapsed across correct trials) for each voxel in the brain at each of the seven time lags after the event onset, where each lag represented one time of repetition (TR). Hence, this matrix contained fMRI data spanning 14 seconds after the event onset for each condition. This fMRI data matrix was then cross-correlated with a matrix containing event-related seed activity (left hippocampus, left superior parietal lobule, right inferior temporal lobe; activation averaged from lags 2 to 5 to capture the hemodynamic response peak) and associative memory performance, which was organized in the same order as the fMRI data matrix. The resulting cross-correlation matrix was submitted to singular value decomposition (SVD), which yields a set of Latent Variables (LVs) that is equal to the number of groups by condition, which is in this case 12 (3 groups X 4 (3 seeds + associative memory performance)). LVs can be broken down into three components: 1) a

singular value indicating the significance of the LV as well as the covariance accounted by this particular LV; 2) a correlation profile that depicts how whole-brain activation correlates with seed activity and memory performance for each group; 3) a singular image indicating the pattern of whole-brain connectivity accounted by the LV with positive and negative salience regions.

Significance of LVs was tested using 1000 permutation tests on singular values. Bootstrapping was used to yield a bootstrap ratio (BSR) reflecting the reliability of voxel activation contributing to a given LV (500 iterations; minimum of 20 mm^3 per cluster; significance threshold set at BSR of $\pm$ 3). An important aspect to keep in mind is that the pattern of whole-brain activation represented by a given LV is symmetrically reflected by the correlation profile, where positive salience regions positively relate to the correlation profile, and negative salience regions negatively relate to it. Hence in the event of a positive correlation profile, activity in positive salience regions would be positively related to the correlation profile, whereas activity in a negative correlation would be negatively correlated with it. The opposite would be true for a negative correlation profile: in this case, positive salience regions would negatively correlate with the correlation profile, and negative salience regions would positively correlate with it.

Results

Sociodemographic, clinical, and behavioral performance

Sociodemographic, clinical and neuropsychological data for this CIMAQ subsample are reported elsewhere (Corriveau-Lecavalier et al., submitted) and summarized in Table 1. Groups were comparable on education. HC comprised more females than the two other groups. Individuals with MCI were significantly older than HC but comparable to participants with SCD^+, who were not significantly older or younger than HC. By design, individuals with MCI had significantly lower scores on the MoCA than HC and SCD^+, and lower scores on Logical

Memory tests than HC. Individuals with SCD^+ performed as well as HC on the MoCA and Logical Memory tests. HC significantly outperformed individuals with MCI on the associative memory score, whereas individuals with SCD^+ performed as well as both the HC and MCI groups statistically. Of note, the SCD^+ and MCI groups had significantly smaller hippocampal volumes and had a higher proportion of APOE4 carriers than HC.

Multivariate functional connectivity analyses

Seed-PLS analysis revealed three significant LVs. Singular images (positive and negative salience regions) and correlation profiles are displayed in Figure 1 for the three LVs.

LV1

LV1 ($P < 0.001$, 32.11% variance explained) included a set of negative regions composed of a large bilateral set of regions included in the fronto-parietal/task-positive and default mode networks (see Table 2 for a summary of brain regions identified). Few positive regions were identified and involved only a small cluster of bilateral temporal areas. Examination of correlation profiles indicated negative correlations between this LV and activity in the left superior parietal and right inferior temporal seed activity in all groups. Left hippocampus activity correlated negatively with this LV in the HC and MCI groups only. This LV was not related to memory performance in any group.

LV2

The positive salience regions identified in LV2 ($P < 0.001$, 19.17% variance explained) included a fronto-temporal semantic network, the basal ganglia (left and right thalamus, and left caudate nucleus) and cerebellar regions (see Table 2). The negative salience regions involved a fronto-parietal network (including sensorimotor areas), in addition to the middle cingulate cortex, right caudate and cerebellar areas. LV2 was positively correlated with left hippocampal activity in all three groups. It was associated with better memory performance in HC but poorer memory

performance in SCD^+. Additionally, the HC group exhibited a positive correlation between LV2 and left superior parietal seed activity, and the SCD^+ group showed a negative correlation between this LV and right inferior temporal seed activity. In the MCI group, ROI activity did not correlate with any other ROI activity nor with subsequent memory performance.

LV3

The third LV (LV3, $P < 0.05$, 10.91% variance explained) identified positive salience regions which included the left and right hippocampus and prefrontal areas, in addition to the right caudate, left lingual gyrus, insula and cerebellar regions. Negative salience regions included a large network involving mostly fronto-parietal regions (including the anterior cingulate cortex and sensorimotor areas), as well as left and right insula cortices, temporal, occipital and cerebellar regions (see Table 3). LV3 was positively correlated with left superior parietal lobule activity in the SCD^+ group, but did not positively correlate with other ROI activity nor memory performance. In the MCI group, LV3 was positively correlated with left hippocampal activity and left superior parietal lobule activity, and negatively correlated with right inferior temporal activity and memory performance. There was no significant correlation between LV3 and ROI seed activity nor memory performance in the HC group.

Discussion

The primary objective of this study was to assess how regional hyperactivation in brain regions vulnerable to AD relates to multivariate patterns of functional connectivity in individuals with SCD^+ and MCI during an object-location associative memory task. The second objective was to examine how these relate to associative memory performance. To address these objectives, we used a multivariate seed-PLS analysis to yield a set of orthogonal LVs accounting for group similarities and differences in the triple association between, i) activity of two regions that were found to be hyperactive in SCD^+ — the left hippocampus and the right inferior

temporal region — and the left superior parietal lobule, which was hyperactive in participants with SCD^+ and hypoactive in participants with MCI, ii) latent patterns of whole-brain task-related activation, and iii) associative memory performance. Three LVs were found to be significant and, when combined together, explained 62.19% of variance in the relationship between seed activity, latent patterns of functional connectivity and subsequent associative memory performance across groups. Overall, these results show that hyperactivation appears to relate to network dysfunction in individuals at risk of AD, and that these hyperactivation-network interactions are associated with poorer memory performance across disease stages. The following paragraphs discuss each of these significant LVs in greater detail.

LV1 generally identified patterns of encoding-related activity that was similar across all groups and included areas from the default mode and fronto-parietal networks (negative salience regions). Since this network is found in all groups and comprises memory-related regions, it may represent a set of inter-connected brain regions that normally support associative memory (Benoit & Schacter, 2015). Moreover, activity in the brain regions identified by LV1 was positively correlated with activity in the right inferior temporal cortex and the right superior parietal cortex in all groups. However, there were group differences in how the left hippocampal seed activity correlated with LV1 brain regions. On the one hand, left hippocampal activity in HC and participants with MCI was positively correlated with activity in LV1 brain regions. On the other hand, the SCD^+ group's left hippocampal activity was not significantly correlated with encoding-related activity in LV1 brain regions. This should be interpreted in light of the fact that the left hippocampal region was characterized by hyperactivation in the SCD^+ group. Thus, early hippocampal hyperactivation in SCD^+ may indicate functional disconnection with healthy functional brain networks involved in associative memory encoding in this group. This disconnection could be due to pathological AD-related processes known to occur in the

hippocampus and interfere with synaptic connectivity, such as amyloid and tau accumulation (Berron et al., 2019; Busche et al., 2019; Hallinan et al., 2019; Huijbers et al., 2018; Mormino et al., 2012; Zott et al., 2019). The similar correlation profiles between LV1 and left hippocampal activity found in individuals with MCI and HC is paradoxical. It could reflect ‘’pseudo-normalization’’ of functional connectivity in individuals with MCI, which has often been observed with advancing pathology (Foster et al., 2018; Kennedy et al., 2018; Schultz et al., 2017; Sperling et al., 2010), although this phenomenon is not well understood and could also reflect inter-individual differences. The absence of correlation between LV1 and memory performance in all groups reflects similar expression of this network, and/or could be explained by the fact that this LV might also be associated with other cognitive processes in addition to associative memory (e.g. attentional capacities).

LV2 identified a set of brain regions where encoding activity was similarly correlated with hippocampal activity across groups. These regions included bilateral temporal/frontal areas (positive salience) and sub-cortical and parieto-occipital regions (negative salience). Intriguingly, activity in these brain regions was differentially correlated with seed activity in the right superior temporal region, the left superior parietal area and associative memory performance in participants with SCD^{+}, compared to HC. Positive correlations between left hippocampal and left superior parietal activity and positive salience regions predicted better memory performance in HC. In the SCD^{+} group however, the positive correlation between left hippocampal activity and positive salience regions predicted worse memory outcomes, whereas the negative correlation between right inferior temporal activity and negative salience regions was associated with better memory performance. Hence, a key finding is that differences in the relationship between left hippocampus activity and positive and negative salience regions predicts associative memory outcomes in HC and individuals with SCD^{+}. One explanation is that left hippocampal

hyperactivation in individuals with SCD$^+$ may result in altered connectivity involving the right inferior temporal gyrus, which in turn results in lower memory performance.

LV3 identified a network involving fronto-temporal areas (positive salience), as well as posterior parietal areas and regions from the default mode network (negative salience), that was differentially correlated with seed activity and subsequent memory performance in persons with SCD$^+$ and MCI. One possibility is that the patterns of memory-related brain activity identified in this LV reflects progressive pathology in functional connectivity between these groups. This interpretation is supported by the observation that ROI seed activity and memory performance are not related to this network in HC. In contrast, left superior parietal activity positively correlated with positive salience regions in individuals with SCD$^+$ but did not predict memory nor was connected to other regions. In MCI, left superior parietal activity and left hippocampal activity positively correlated with positive salience regions, which predicted poorer memory performance, whereas the positive correlation between right inferior temporal activity and negative salience regions was associated with better memory performance. This suggests a progression of abnormal connectivity from memory unimpaired SCD$^+$ to memory-impaired MCI. The negative correlation between left superior parietal activation and memory performance in MCI is intriguing given that parietal areas have often been associated with training-induced compensation mechanisms and/or better memory outcome in persons at risk AD (Belleville et al., 2011; Corriveau-Lecavalier et al., 2019; Elman et al., 2014). Additional research will be needed to elucidate the role of parietal hyperactivation in compensatory mechanisms.

Findings described above suggest a sequence in the interaction between localized task-related hyperactivation of AD-related regions and associated networks occurring from SCD$^+$ to MCI. Although the experimental design is cross-sectional and associative, results nonetheless suggest that early regional task-related hyperactivation of hippocampal and temporal areas in

SCD$^+$ could drive dysfunctional connectivity in healthy brain networks, as highlighted by LV1 and LV2. This is supported by animal models (Bero et al., 2011; Busche et al., 2012; 2019; Wu et al., 2016; Zott et al., 2019) and studies in humans targeting memory-related hippocampal hyperactivation reduction (Bakker et al., 2012; 2015), which provide evidence that these regions may represent early critical hubs where AD processes originate. Increased disease severity may be associated with hyperactivation-network interactions in pathognomonic networks in MCI, as highlighted by LV3. This is in line with the hypothesis that abnormalities in brain activation and connectivity may then propagate to other neocortical areas in the later stages of the disease, notably including the default mode network (Badhwar et al., 2017; Berron et al., 2020; Greicius et al., 2004; Jones et al., 2011; Sorg et al., 2007; Zhou et al., 2010). However, it remains unclear whether this sequence in patterns of functional connectivity between networks across the AD continuum represents solely pathological processes or an attempt of compensation, or both (Jones et al., 2016; 2017).

Our findings have several implications: First, they provide information regarding the link between localized hyperactivation, multivariate patterns of functional connectivity and memory performance in the different early stages of AD, which have never before been examined. A task-related design was chosen to facilitate the measurement of brain activation and connectivity that is directly elicited by associative memory, a process known to decline in the very early phase of AD (Atienza et al., 2011; Troyer et al., 2008) and be a sensitive marker of AD pathology (Rentz et al., 2011). This represents a strength compared to resting-state paradigms, which have limited cognitive relevance (Mill et al., 2019). Moreover, to our knowledge, this is the first study to find altered patterns of hyperactivation-network interactions in individuals with SCD$^+$, who were identified with criteria known to increase their likelihood of developing AD in the future. Hence, this reinforces the hypothesis that the hyperactivation-network interactions described here

contribute to identifying individuals in the early disease phase. Finally, we consistently observed that left hippocampal hyperactivation was associated with abnormalities in patterns of functional connectivity and/or poorer memory performance in participants with SCD^+ and MCI. This is in line with several other studies and provides empirical support for the notion that hyperactivation in this region represents a very early biomarker of AD-related processes and links hippocampal hyperactivation with abnormal pathology accumulation and poorer memory performance in the early disease phase (Bakker et al., 2012; 2015; Berron et al., 2019; Busche et al., 2018; Hallinan et al., 2019; Huijbers et al., 2018; Mormino et al., 2012; Zott et al., 2019).

Some limitations must be acknowledged: Given the cross-sectional nature of the study, it was not possible to measure intra-individual longitudinal change in patterns of functional connectivity. Even though genetic and neurodegeneration biomarkers were incorporated to increase the likelihood of future progression in the SCD^+ group, the classification probably still represents a group of heterogeneous individuals and it is likely that a portion of them will not progress to dementia. Finally, measures of amyloid or tau were not included, and therefore the sample could not be characterized according to the A/T/N framework (Jack et al., 2016; 2018) and it was not possible to study the relationship between functional connectivity and these AD biomarkers.

In conclusion, this study is the first to examine the relationship between hyperactivation, latent patterns of functional connectivity and memory performance in individuals at risk of AD. Our data suggests that hyperactivation, and particularly hippocampal hyperactivation, contributes to functional network dysfunction that might characterize the early stages of AD or AD-related diseases, and that hyperactivation-network dysfunction occurs in sequence from the SCD^+ to MCI stages. Finally, these functional alterations could contribute to the gradual deterioration of cognition. Longitudinal and multimodal imaging studies will be required for an in-depth

understanding of the changes in the functional architecture of the brain and their implication in the fundamental disease processes.

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Table 3.1. Sociodemographic, clinical and behavioural data

	HC	SCD^{+}	MCI	P-values
Participants (N)	54	28	26	-
Age (SD)	71.54 (4.56)	73.23 (5.21)	75.73 (5.01)	P = .002
Sex, M/F	14, 40	15, 13	12, 14	P = .031
Education (SD)	15.11 (3.14)	15.46 (3.70)	15.20 (3.27)	P = .900
MoCA (SD)	28.17 (1.40)	27.68 (1.33)	24.96 (2.25)	$P = 2.03^{-12}$
Logical Memory Delayed Recall (SD)	13.69 (4.99)	12.68 (3.69)	11.00 (4.51)	P = .028
APOE4 carriers (%)	0 (0)	10 (35.71)	11 (42.31)	-
Associative memory score	2.59 (1.63)	2.18 (1.46)	1.62 (1.56)	P = .014

MoCA = Montreal Cognitive Assessment

Table 3.2. Summary of brain regions identified by LV1

Salience	Lag	BSR	Cluster size	MNI Coordinates			HEM	Brain region	BA
				X	Y	Z			
Positive	1	5.0301	37	18	-18	-30	R	Parahippocampal	36
	2	4.2538	24	-51	-33	-18	L	Inferior Temporal	21
	3	3.9337	34	-48	-24	-15	L	Middle Temporal	21
	2	3.8002	21	45	-24	-18	R	Inferior Temporal	20
Negative	3	-9.9362	18163	39	-27	0	R	Superior Temporal	22
	7	-8.8344	9201	-18	-63	45	R	Superior Parietal	7
	4	-8.667	10219	-33	39	24	L	Medial Frontal	10
	4	-8.6241	2079	-12	-57	51	R	Precuneus	7
	5	-8.2991	4894	-18	-63	48	R	Superior Parietal	7
	5	-8.1976	6423	-33	-24	-12	R	Hippocampus	54
	6	-7.709	1604	36	42	18	L	Medial Frontal	10
	6	-7.6102	4359	57	-33	6	R	Middle Temporal	22
	1	-7.503	1124	48	-27	0	R	Superior Temporal	22
	1	-6.9576	3054	-9	-12	57	L	Supp Motor Area	6
	7	-6.4929	374	30	30	18	R	Medial Frontal	10
	2	-6.4525	388	36	42	15	L	Medial Frontal	10
	2	-6.4508	744	36	-3	-6	R	Insula	13
	6	-6.1531	1982	12	-9	63	R	Supp Motor_Area	6
	2	-6.1241	4103	12	-27	-6	L	Lingual	19
	6	-5.6531	247	42	-63	12	L	Middle Temporal	39
	2	-5.5521	79	-60	6	18	R	Pars Opercularis	44
	1	-5.4413	233	-63	6	21	R	Precentral	6
	2	-5.3941	32	60	-57	9	R	Middle Temporal	37
	6	-5.3808	226	-12	42	21	R	Superior/ Medial Frontal	9
	7	-5.2447	47	63	3	30	R	Precentral	6
	2	-5.2325	58	45	12	30	R	Pars opercularis	44
	3	-5.2113	73	18	-69	-42	L	Cerebellum 8	-
	2	-5.1671	118	48	15	0	L	Pars opercularis	44
	2	-5.1062	71	-36	-33	9	R	Superior Temporal	41
	2	-5.0678	151	-36	42	15	L	Pars Triangularis	46
	6	-5.0042	34	-27	-93	-6	R	Inferior Occipital	18
	6	-4.7492	98	15	-51	57	L	Superior Parietal	7
	3	-4.6891	23	60	0	-21	L	Middle Temporal	21
	1	-4.5831	143	-27	-30	-6	R	Hippocampus	54
	6	-4.5753	46	9	-93	18	L	Cuneus	18
	1	-4.5298	64	-48	-30	24	R	Supramarginal	40
	4	-4.5182	40	18	-78	-18	R	Cerebellum 6	-
	6	-4.5142	35	-33	-51	-45	R	Cerebellum 8	-
	5	-4.4978	54	9	-12	63	L	Supp Motor Area	6
	7	-4.4458	22	57	-54	18	R	Middle Temporal	39

6	-4.414	39	42	-45	-9	R	Fusiform	37
4	-4.3964	20	-33	-90	0	L	Middle Occipital	18
2	-4.3943	84	36	-63	45	R	Angular	39
1	-4.3885	98	-27	15	27	L	Pars opercularis	44
1	-4.3021	44	-45	48	12	L	Pars Triangularis	46
7	-4.2031	44	-51	-69	6	R	Middle Temporal	19
1	-4.1812	48	48	-78	0	R	Inferior Occipital	19
4	-4.1398	21	18	-54	-45	R	Cerebellum 8	-
6	-4.0709	29	-27	57	-6	L	Superior Orbitofrontal	10
1	-4.0611	93	36	27	9	R	Pars Triangularis	45
7	-4.0503	20	51	-9	18	R	Pars Opercularis	44
5	-3.9688	20	36	-27	33	R	Postcentral	1
1	-3.9241	33	-30	12	-6	R	Putamen	49
2	-3.8988	22	-45	-66	-27	L	Cerebellum Crus1	-
2	-3.8353	32	36	-63	-9	L	Inferior Occipital	37
1	-3.8223	30	57	6	30	R	Precentral	6
1	-3.8156	44	-39	27	6	L	Pars Triangularis	45
6	-3.8012	51	3	48	42	R	Superior/Medial Frontal	9
3	-3.7839	87	-21	-51	-42	R	Cerebellum_9	-
2	-3.7537	21	21	-66	27	L	Cuneus	19
3	-3.7252	23	39	-75	-30	L	Cerebellum Crus1	-
7	-3.6681	20	6	-12	6	L	Thalamus	50
7	-3.5964	23	-33	-57	-27	L	Cerebellum 6	-
6	-3.5896	27	6	-75	42	L	Precuneus	7
7	-3.4509	29	33	0	51	L	Precentral	6

Distance between clusters >20mm; Cluster size >20mm; Bootstrap ratio set to $\pm$ 3. BSR = Bootstrap ratio; HEM = Hemisphere; BA = Brodmann area

Table 3.3. Summary of brain regions identified by LV2

				MNI Coordinates					
Salience	Lag	BSR	Cluster size	X	Y	Z	HEM	Brain region	BA
Positive	4	7.1981	424	-18	-21	-15	L	Parahippocampal	36
	7	7.1033	919	-27	-57	-36	L	Cerebellum 6	-
								Inferior	47
	2	6.8735	1280	-30	24	-15	L	Orbitofrontal	
	7	6.8129	508	-39	-9	-21	L	Fusiform	37
	4	6.6042	686	-9	3	-12	L	Caudate	48
	2	6.4124	287	-57	-57	-6	L	Inferior Temporal	37
	1	6.3777	1150	-57	0	-15	L	Middle Temporal	21
	5	6.2052	1073	-39	-18	-18	L	Fusiform	37
	6	6.2014	95	-24	45	30	L	Medial Frontal	9
	6	6.194	994	-24	0	-18	L	Amygdala	53
	2	6.1444	893	27	6	-12	R	Amygdala	53
	7	6.1329	34	-15	-12	-6	L	Thalamus	50
	6	5.9876	41	12	30	-12	R	Rectus	11
	5	5.9795	142	36	-30	-15	R	Parahippocampal	36
	4	5.9717	322	39	6	-12	R	Insula	13
	3	5.967	192	-36	-24	-15	L	Hippocampus	54
	7	5.8799	117	-18	33	6	L	Caudate	48
								Superior/Medial	9
	1	5.7165	36	0	48	45	L	Frontal	
	7	5.6971	200	54	-33	-3	R	Middle Temporal	21
	1	5.6853	83	-48	-63	-15	L	Inferior Occipital	37
								Inferior	47
	3	5.354	113	-45	30	-12	L	Orbitofrontal	
	1	5.2935	167	36	-30	-12	R	Parahippocampal	36
								Superior/Medial	9
	4	5.2872	40	-3	42	48	L	Frontal	
	7	5.2778	91	57	-6	-15	R	Middle Temporal	21
								Superior	10
	7	5.2662	33	18	39	-9	R	Orbitofrontal	
	1	5.1257	158	-6	24	39	L	Middle Cingulate	8
	2	5.1175	81	60	-51	-9	R	Inferior Temporal	37
	2	5.0948	82	15	-45	-27	R	Cerebellum 4/5	-
	6	5.0816	131	-60	-57	-6	L	Inferior Temporal	37
	6	5.0614	217	42	-42	6	R	Superior Temporal	22
	5	5.0308	333	30	18	-15	R	Insula	13
	5	5.0154	111	-24	39	27	L	Middle Frontal	9
	6	4.9933	26	57	-33	18	R	Superior Temporal	22
	3	4.9805	42	27	-78	-30	R	Cerebellum Crus1	-
	6	4.978	176	42	-63	-27	R	Cerebellum Crus1	-
	2	4.9702	70	33	-81	-33	R	Cerebellum Crus1	-
	3	4.9625	45	0	6	-12	L	Olfactory	-
	3	4.8757	56	42	27	-15	R	Inferior	47

5	4.8367	62	12	33	-9	R	Orbitofrontal Anterior Cingulate	32
7	4.8126	60	-27	27	-15	L	Inferior Orbitofrontal	9
4	4.804	183	-12	36	-3	L	Anterior Cingulate	32
5	4.7959	78	18	27	30	R	Middle Cingulate	8
1	4.7698	57	30	18	-12	R	Insula	13
3	4.7618	30	6	33	-3	R	Anterior Cingulate	24
5	4.665	133	-21	-48	-30	L	Cerebellum 6	-
3	4.6047	50	48	-51	-18	R	Inferior Temporal	37
1	4.6014	59	57	12	0	R	Superior Temporal Pole	44
1	4.5889	23	27	60	0	R	Superior Orbitofrontal	10
7	4.5861	136	30	-57	-36	R	Cerebellum Crus1	-
6	4.5844	52	-3	51	18	L	Superior/Medial Frontal	10
3	4.5709	47	48	-12	-12	R	Middle Temporal	21
7	4.5475	23	18	18	18	R	Caudate	48
5	4.4412	52	0	-12	-9	L	Thalamus	50
5	4.4202	68	39	-66	-27	R	Cerebellum Crus1	-
4	4.3181	61	-27	45	24	L	Medial Frontal	10
1	4.2787	124	15	-48	-27	R	Cerebellum_4/5	-
5	4.2683	120	21	-54	-27	R	Cerebellum 6	-
5	4.2646	61	57	-36	3	R	Middle Temporal	21
1	4.2598	28	42	-63	-27	R	Cerebellum Crus1	-
6	4.2341	32	-48	-69	9	L	Middle Temporal	21
6	4.2205	51	33	-18	-15	R	Hippocampus	54
7	4.2175	44	-54	-66	-6	L	Inferior Temporal	37
3	4.1384	50	-51	-51	-21	L	Inferior Temporal	37
5	4.1372	81	30	-6	-9	R	Amygdala	53
2	4.1284	64	48	21	-24	R	Superior Temporal Pole	38
5	4.052	27	0	-48	-15		Vermis 4/5	-
4	4.0393	25	-48	24	12	L	Pars Triangularis	45
2	4.0027	20	45	-45	-21	R	Inferior Temporal	37
6	3.9677	34	-66	-18	0	L	Middle Temporal	21
2	3.9639	29	-27	-81	-36	L	Cerebellum Crus2	-
1	3.9628	22	-27	54	3	L	Medial Frontal	10
5	3.9184	79	-57	-60	-6	L	Inferior Temporal	37
7	3.8144	26	39	36	-9	R	Inferior Orbitofrontal	47
6	3.8092	26	18	15	15	R	Caudate	48
5	3.7681	38	-63	-39	0	L	Middle Temporal	21
6	3.691	33	51	15	-6	R	Superior Temporal Pole	22
1	3.4027	21	0	-18	-18	L	Parahippocampal	36

Negative	3	-5.7038	412	15	12	60	L	Superior Frontal	6
	2	-5.5035	49	9	-57	57	L	Precuneus	7
	3	-5.4588	435	-45	-9	45	L	Postcentral	6
	3	-5.2274	137	-42	-45	45	L	Inferior Parietal	40
	2	-5.0845	284	30	-39	15	L	Hippocampus	54
	3	-4.9819	66	36	-36	54	L	Postcentral	1
	4	-4.9374	98	-18	-66	51	L	Superior Parietal	7
	2	-4.8435	216	-12	-3	54	L	Supp Motor Area	6
	3	-4.7735	41	12	-69	48	L	Precuneus	7
	4	-4.5366	24	39	6	51	L	Precentral	8
	2	-4.496	96	21	0	48	R	Medial Frontal	6
	2	-4.4492	23	-57	-54	27	L	Angular	39
	3	-4.3987	97	36	15	12	R	Insula	13
	6	-4.3864	26	-15	-27	24	R	Caudate	48
	4	-4.3159	20	-39	-57	-45	R	Cerebellum 7b	-
	3	-4.3047	65	-12	-75	39	L	Cuneus	7
	5	-4.2709	54	-48	-42	45	L	Inferior Parietal	40
	3	-4.2577	82	-21	15	57	L	Superior Frontal	6
	2	-4.2383	45	-36	-24	18	R	Pars Opercularis	44
	2	-4.2332	46	-27	42	36	L	Medial Frontal	9
	4	-4.2224	71	-36	-9	45	L	Precentral	6
	3	-4.2061	93	-36	-27	60	R	Postcentral	1
	3	-4.1651	33	-27	33	36	L	Superior Frontal	9
	3	-4.1583	32	-24	-87	24	R	Superior Occipital	19
	5	-4.1273	34	12	-21	54	R	Supp Motor Area	6
	7	-4.1191	53	-51	-42	42	L	Inferior Parietal	40
	2	-4.0854	22	-45	-3	42	R	Precentral	6
	3	-4.0362	41	-21	-27	36	R	Middle Cingulate	23
	3	-4.0136	40	-36	6	12	L	Insula	13
	1	-3.916	34	12	-57	54	R	Precuneus	7
	3	-3.9097	21	-12	-36	-36	R	Cerebellum 10	-
	5	-3.8674	55	-21	-33	57	L	Postcentral	1
	2	-3.7393	21	45	-21	18	R	Pars Opercularis	40
	3	-3.6682	24	9	-30	27	R	Middle Cingulate	23

Distance between clusters >20mm; Cluster size >20mm; Bootstrap ratio set to $\pm$ 3. BSR = Bootstrap ratio; HEM = Hemisphere; BA = Brodmann area

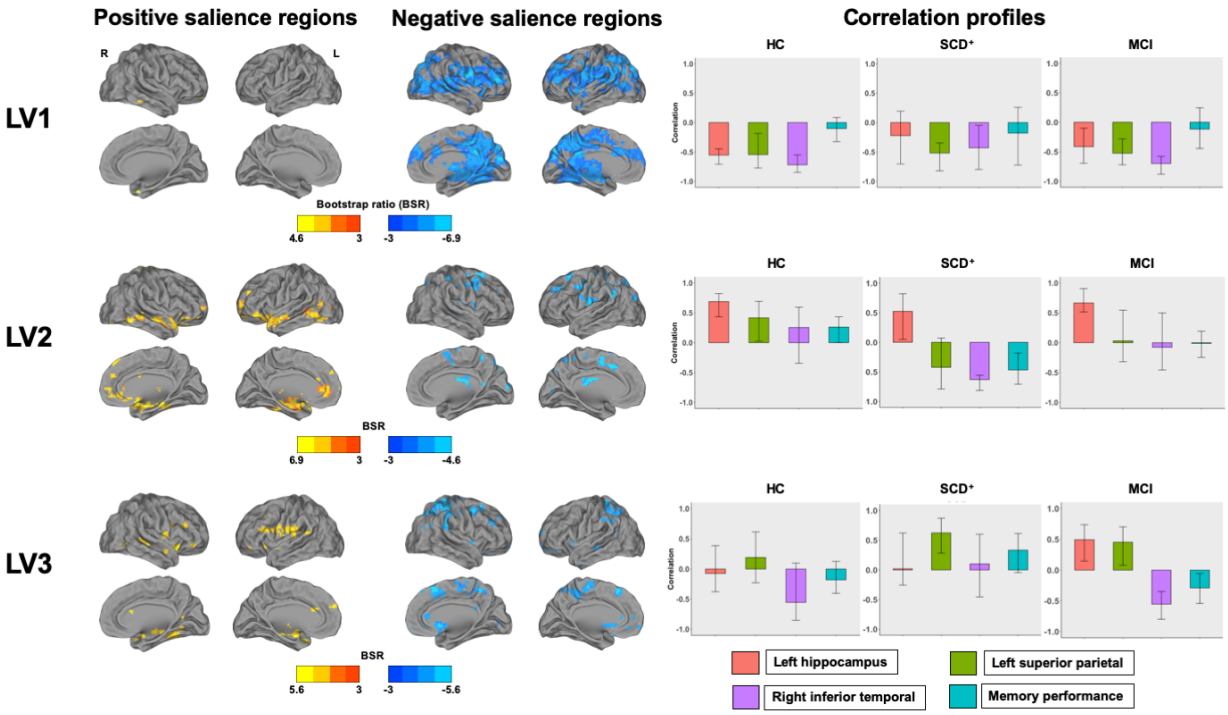
Table 3.4. Summary of brain regions identified by the LV3

				MNI Coordinates					
Salience	Lobe	BSR	Cluster size	X	Y	Z	HEM	Brain region	BA
Positive	2	6.9872	1016	39	-30	0	R	Superior Temporal	22
	4	6.5025	850	30	15	-9	R	Insula	13
	5	6.2915	802	-33	-6	-18	L	Hippocampus	54
	2	6.2226	42	60	3	-12	R	Superior Temporal	38
	7	6.1766	354	33	-24	-9	R	Hippocampus	54
	4	6.1241	189	39	-27	-3	R	Hippocampus	54
	1	5.9863	808	9	-60	-6	R	Lingual	18
	1	5.9608	47	3	-45	-27	R	Vermis 10	-
	4	5.6461	203	39	-24	-3	R	Hippocampus	54
	4	5.5534	185	-6	-18	-15	L	Hippocampus	54
	4	5.3816	54	-36	-42	-30	L	Cerebellum 6	-
	6	5.2761	102	-33	-12	-12	L	Hippocampus	54
	4	5.2702	90	39	-27	-6	R	Hippocampus	54
	1	4.9483	193	-12	-15	-15	L	Hippocampus	54
	6	4.8086	127	0	-30	-24		Vermis 1/2	-
	6	4.7772	31	54	-3	9	R	Pars Opercularis	44
	4	4.6912	137	-12	39	45	L	Superior Frontal	8
	4	4.3433	61	-33	-9	-18	L	Hippocampus	54
	5	4.2866	50	-36	-36	18	L	Pars Opercularis	40
	3	4.2162	22	42	39	-3	R	Inferior Orbitofrontal	47
	2	4.1807	29	45	27	27	R	Pars Triangularis	9
	3	4.1548	29	24	27	24	R	Medial Frontal	9
	6	4.1164	26	36	-51	-24	R	Cerebellum 6	-
	7	3.9988	45	-36	-12	-15	L	Hippocampus	54
	5	3.8346	32	3	-45	-24	R	Vermis 1/2	-
	1	3.7044	21	24	18	21	R	Caudate	48
	2	3.5049	22	-33	18	24	L	Pars Triangularis	44
Negative	4	-6.6248	293	15	15	-15	R	Rectus	11
	4	-6.5283	53	-51	-27	-15	R	Middle Temporal	21
	4	-6.4068	1005	24	-51	60	L	Superior Parietal	7
	7	-5.7768	24	18	15	-12	R	Rectus	11
	3	-5.7482	51	15	18	-15	R	Rectus	11
	6	-5.7261	30	-6	6	-15	R	Olfactory	-
	3	-5.6913	40	-60	-30	-6	R	Middle Temporal	21
	5	-5.6358	42	-18	15	-12	L	Rectus	11
	2	-5.5828	375	-6	21	51	R	Supp Motor Area	8
	2	-5.5345	1427	27	-48	57	L	Superior Parietal	7
	6	-5.4017	44	60	-42	27	L	Supramarginal	40
	3	-5.3754	37	-15	54	-9	L	Superior Orbitofrontal	11
	5	-5.299	309	-33	-51	57	R	Superior Parietal	7
	1	-5.2571	48	15	15	-15	L	Rectus	11

6	-5.235	81	-18	-45	63	L	Superior Parietal	7
3	-5.0393	251	27	-54	60	R	Superior Parietal	7
5	-5.0089	112	54	-45	48	L	Inferior Parietal	40
6	-4.9626	53	-42	-27	-21	L	Inferior Temporal	20
3	-4.8541	53	-36	-45	57	L	Superior Parietal	7
1	-4.8068	51	-18	27	-9	R	Superior Orbitofrontal	11
6	-4.768	56	24	-51	63	R	Superior Parietal	7
6	-4.6121	28	9	24	-12	R	Rectus	11
7	-4.5659	38	24	-30	-33	R	Cerebellum 4/5	-
7	-4.5086	168	12	-42	66	L	Precuneus	7
2	-4.4788	21	-18	54	-9	L	Superior Frontal	10
5	-4.4766	94	27	-54	60	R	Superior Parietal	7
7	-4.4163	217	-15	-63	57	L	Precuneus	7
1	-4.4063	23	-18	54	-9	L	Superior Orbitofrontal	10
3	-4.3929	31	3	27	12	R	Anterior Cingulate	24
7	-4.3396	41	-60	-30	-6	L	Middle Temporal	21
5	-4.2802	37	-51	-18	0	R	Middle Temporal	41
5	-4.2524	35	45	0	51	R	Precentral	6
2	-4.2364	20	36	51	24	L	Medial Frontal	10
2	-4.1849	97	33	27	33	L	Medial Frontal	9
5	-4.1	32	18	15	60	L	Superior Frontal	6
2	-4.0849	38	-54	-51	33	L	Angular	39
2	-4.0808	49	60	-39	27	R	Supramarginal	40
3	-3.9403	28	-15	33	-6	L	Anterior Cingulate	25
7	-3.9038	20	-45	-39	-18	R	Fusiform	37
3	-3.8714	35	-21	-66	30	R	Superior Occipital	7
7	-3.836	77	-36	9	0	R	Insula	13
5	-3.7534	24	12	-84	6	R	Calcarine	17
7	-3.6858	39	36	-12	48	L	Precentral	6
6	-3.6522	20	3	-66	-42	L	Vermis 8	-
7	-3.6402	39	57	-21	45	R	Postcentral	1
5	-3.5879	20	-39	12	3	L	Insula	13

Distance between clusters >20mm; Cluster size >20mm; Bootstrap ratio set to $\pm$ 3. BSR = Bootstrap ratio; HEM = Hemisphere; BA = Brodmann area

Figure 3.1. Singular images and correlation profiles for each latent variable (LV). Positive salience regions are illustrated in orange to yellow (left) and negative salience regions are illustrated in blue (middle) with a bootstrap ratio (BSR) threshold set at ± 3. Error bars in the correlation profiles graphics (right) express confidence intervals (95%).



CHAPITRE 5 – Discussion générale

5.1. Rappel des objectifs et des principaux résultats

Cette thèse avait pour buts généraux de déterminer la présence et la trajectoire de l'hyperactivation, et d'examiner le lien entre l'hyperactivation et la dysfonction de réseaux cérébraux fonctionnels supportant les capacités de mémoire chez des individus à risque de développer la MA. Afin de répondre à ces objectifs, nous avons utilisé l'IRMf en situation de réalisation de tâches d'encodage en mémoire épisodique pour examiner le changement longitudinal d'activation cérébrale chez des individus TCL ayant ultérieurement progressé vers le stade démentiel, et pour évaluer les patrons d'activation cérébrale et de connectivité fonctionnelle chez des participants présentant soit un TCL ou un DCS^{+}. Globalement, les résultats suggèrent que l'hyperactivation caractérise les individus TCL qui progresseront éventuellement vers une démence et le stade du DCS^{+}. De plus, l'hyperactivation serait impliquée dans la dysfonction de réseaux cérébraux fonctionnels supportant les capacités d'encodage en mémoire associative dans le TCL et le DCS^{+}. La présente section vise à rappeler brièvement les méthodes et les résultats des études composant cette thèse.

L'étude 1 avait pour but d'évaluer la présence, la localisation et la trajectoire longitudinale de l'hyperactivation chez des individus atteints d'un TCL ayant ultérieurement progressé vers le stade démentiel. Pour ce faire, un groupe d'individus présentant un TCL ainsi qu'un groupe de participants âgés cognitivement sains ont été évalués à l'aide de deux examens par IRMf effectués sur un intervalle de deux ans, lors desquels ils effectuaient une tâche d'encodage de paires de mots. Un suivi clinique longitudinal a permis d'identifier treize d'individus TCL ayant ultérieurement progressé vers le stade de démence, alors que six autres sont demeurés stables sur le plan cognitif. Les résultats ont révélé la présence d'hyperactivation, c'est-à-dire un niveau supérieur d'activation, dans la région du gyrus supramarginal droit chez les individus avec un TCL ayant progressé vers une démence comparativement aux participants

contrôles. Cette hyperactivation était accompagnée d'hypoactivations de l'hippocampe et de la région préfrontale du pars opercularis de l'hémisphère gauche. L'hyperactivation et les hypoactivations présentes dans ces régions sont demeurées stables lors du suivi longitudinal. Par ailleurs, l'hyperactivation du gyrus supramarginal droit n'était plus significative lorsque tous les participants TCL (progresseurs et stables) étaient inclus dans l'analyse. Cela suggère donc que ce patron d'hyperactivation serait spécifique aux participants TCL ayant bel et bien évolué vers le stade démentiel.

L'étude 2 avait pour objectif d'examiner la fonction mathématique qui caractérise la relation entre le degré de sévérité de la maladie et l'activation cérébrale dans un groupe d'individus à risque de progresser vers la MA. Elle visait également à déterminer si l'hyperactivation était présente dans un groupe d'individus avec un DCS^{+}, que l'on soupçonne d'être à un stade de la maladie en amont du TCL. À ces fins, des groupes d'individus DCS^{+} et TCL, ainsi qu'un groupe de participants âgés cognitivement sains ont été évalués lors d'un examen par IRMf. L'activation cérébrale était mesurée alors que les participants accomplissaient une tâche de mémoire associative où ils devaient encoder une série d'images et leur position spatiale. Les trouvailles de cette étude ont indiqué qu'une fonction quadratique caractérise la relation entre des marqueurs de sévérité de la maladie (épaisseur corticale, performances en mémoire) et l'activation cérébrale du lobule pariétale supérieur gauche, au sein du groupe d'individus à risque de développer la MA (DCS^{+} et TCL combinés). De plus, des modèles linéaires ont révélé qu'un plus faible volume hippocampique était associé à un plus haut degré d'activation hippocampique gauche et temporal inférieur droit. De l'hyperactivation a également été mise en évidence au niveau des hippocampes et de plusieurs régions temporo-pariétales dans le groupe d'individus DCS^{+}, comparativement aux participants TCL et contrôles. Les personnes avec un TCL montraient quant à elles de l'hypoactivation (c.-à-d. un plus faible niveau

d'activation) dans le lobule pariétal gauche comparativement aux participants DCS^+ et aux contrôles. En résumé, les résultats de cette étude supportent l'hypothèse d'une forme en « U inversé » de l'activation en fonction du degré de sévérité de la maladie, caractérisée par la présence d'hyperactivation dans le stade du DCS^+ et d'hypoactivation dans le TCL.

L'étude 3 avait pour but d'examiner la relation entre l'hyperactivation et les patrons de connectivité fonctionnelle chez des individus à risque de développer la MA. Elle avait également pour but d'étudier comment l'interaction entre l'hyperactivation et ces réseaux cérébraux fonctionnels est liée à la symptomatologie cognitive. L'échantillon et la tâche de mémoire utilisés pour répondre à ces objectifs étaient les mêmes que ceux utilisés lors de l'étude 2. Nous avons fait appel à une analyse multivariée pour identifier trois variables latentes qui, mises ensemble, pouvaient expliquer 62,17% de la covariance entre 1) le degré d'hyperactivation de trois régions (hippocampe gauche, lobe temporal inférieur droit, lobule pariétale supérieur gauche), 2) l'activation du cerveau entier, et 3) les performances de mémoire associative au sein des groupes DCS^+, TCL, et contrôle. La première variable latente a mis en évidence un réseau incluant des régions du réseau du mode par défaut et du réseau fronto-pariétal, dont le degré d'activation corrélait de façon généralement similaire avec l'activation des régions d'intérêt au sein des différents groupes. Toutefois, chez le groupe DCS^+, l'hyperactivation hippocampique gauche n'était pas significativement corrélée avec cette variable latente. La deuxième variable latente a identifié un réseau cérébral dont l'activation était positivement corrélée avec l'activation hippocampique gauche chez tous les groupes. La connectitvité entre l'hippocampique gauche, le lobule supérieur pariétal gauche et les régions à salience positive identifiées par cette variable latente permettait de prédire de meilleures performances de mémoire chez le groupe contrôle. De façon intéressante, la connectivité entre l'hyperactivation hippocampique gauche et ces mêmes régions prédisait de moins bonnes performances de mémoire dans le groupe DCS^+. Enfin, la

troisième et dernière variable latente a permis d'identifier des corrélations entre l'activation d'un réseau cérébral fonctionnel, le degré d'activation des régions d'intérêt et les performances en mémoire qui étaient presqu'exclusives au groupe TCL. En effet, dans ce groupe, la connectivité entre l'hippocampe gauche, le lobule pariétal supérieur gauche et les régions à salience positive prédisait de moins bonnes performances de mémoire. Dans le groupe DCS^{+}, l'activation des régions à salience positive était positivement corrélée avec l'activation pariétale supérieure gauche seulement. Il n'y avait aucune corrélation significative entre ce réseau, l'activation des régions d'intérêt et les performances de mémoire dans le groupe contrôle. Ces résultats indiquent ainsi que l'hyperactivation régionale serait associée à la dysfonction de réseaux cérébraux fonctionnels supportant les capacités de mémoire associative chez les individus à risque de développer la MA.

5.2. L'hyperactivation comme biomarqueur précoce de la maladie d'Alzheimer

Les résultats de cette thèse fournissent des évidences empiriques en faveur de l'hyperactivation comme biomarqueur précoce de la MA. En effet, des niveaux d'activation supérieurs à celui des contrôles ont été retrouvés chez des individus présentant un TCL ayant ultérieurement progressé vers le stade de démence (étude 1) et chez des individus présentant un DCS^{+} (étude 2).

Ces résultats sont particulièrement innovants. Nous démontrons que l'hyperactivation cérébrale est présente dans un groupe d'individus présentant un TCL qui sont réellement atteints d'un processus neurodégénératif. Ces résultats sont compatibles avec plusieurs études antérieures (Clément & Belleville, 2012 ; 2012; Clément, Belleville, & Mellah, 2010; Clément, Gauthier, & Belleville, 2013; Dickerson et al., 2004; 2005; Hämäläinen et al., 2007; Sperling et al., 2007; Putcha et al., 2011), bien que celles-ci portaient sur des personnes avec un TCL pour lesquelles aucune information n'était disponible quant à une progression ultérieure vers la démence. Ainsi,

l'hyperactivation pourrait potentiellement servir de marqueur pour identifier les individus présentant de légères atteintes cognitives et se situant dans la phase prodromale de la MA.

Bien que l'étude 1 ait permis de confirmer la présence de l'hyperactivation chez des individus TCL dans la phase pré-démentielle, plusieurs enjeux demeuraient à être examinés. En effet, le faible échantillon de cette première étude ne permettait pas l'utilisation de modèles statistiques plus complexes pour tester l'hypothèse d'un « U inversé » de l'activation en fonction du degré de sévérité de la maladie. De plus, cette étude ne permettait pas de déterminer si l'hyperactivation précède l'apparition des atteintes cognitives objectivables. Les résultats découlant de l'étude 2 ont permis de répondre à ces questions. En effet, nous démontrons qu'une fonction quadratique en « U inversé » caractérise la relation entre le degré de sévérité de la maladie et l'activation cérébrale du lobule supérieur pariétal gauche, ce qui concorde avec plusieurs études et modèles théoriques antérieurs (Clément & Belleville, 2010; 2012; Clément, Mellah, & Belleville, 2010; Clément, Belleville & Gauthier, 2013; Sperling et al., 2010; Gregory et al., 2017). Par ailleurs, la présence d'hyperactivation au sein du groupe DCS^{+} dans plusieurs régions vulnérables aux processus neurodégénératifs de la MA suggère que la présence d'hyperactivation serait observable avant même l'apparition des atteintes cognitives objectivables. Lorsque considérés ensemble, la mise en évidence d'une fonction en « U inversé » de l'activation et de la présence d'hyperactivation dans le DCS^{+} suggère que l'hyperactivation serait à son niveau maximal bien avant le diagnostic de démence, alors que les atteintes cognitives sont encore très légères, voire absentes. La fenêtre temporelle où l'hyperactivation pourrait servir à idenfier les individus à risque de futur déclin cognitif pourrait ainsi se situer en amont des déficits observables aux épreuves cliniques et neuropsychologiques standardisées.

5.3. L'apport de la connectivité fonctionnelle

L'étude 3 indique que l'hyperactivation pourrait contribuer à la dysfonction de réseaux cérébraux fonctionnels supportant les capacités de mémoire associative. Les régions identifiées par les trois variables latentes faisaient principalement partie des réseaux fronto-pariétal et du mode par défaut, qui sont connus pour interagir lors de l'accomplissement de tâches cognitives (Murphy et al., 2020; Palva et al., 2010; Ptak, 2012) et pour être atteints par les processus de la MA (Chhatwal et al., 2018; Elahi & Miller, 2017; Greicius et al., 2004; Jones et al., 2011; 2016; 2017; Sorg et al., 2007). Ces résultats concordent ainsi avec la proposition que l'hyperactivation retrouvée dans des régions vulnérables aux processus précoces de la MA serait impliquée dans la dysfonction de réseaux cérébraux fonctionnels supportant les capacités cognitives de haut niveau (Bero et al., 2011; Busche et al., 2012; 2019a; 2019b; Wu et al., 2016; Zott et al., 2018; 2019). Cette étude est toutefois la première à fournir des évidences en ce sens chez l'humain, et plus particulièrement au sein de groupes cliniques à risque de développer la MA.

Par ailleurs, les résultats de cette étude suggèrent qu'une séquence dans les interactions entre l'hyperactivation et les réseaux cérébraux fonctionnels se produirait entre les stades du DCS^+ et du TCL, et que ces interactions seraient associées à une symptomatologie cognitive croissante. Cette proposition est cohérente avec la « *Network degeneration hypothesis* », qui stipule que les différentes maladies neurodégénératives cibleraient des patrons de réseaux neuronaux fonctionnels distincts de façon séquentielle et stéréotypée (Brown et al., 2019; Brier et al., 2014; Greicius, 2013; Raj et al., 2012; Rohrer et al., 2010; Seeley et al., 2009; Tahmasian et al., 2016). En effet, les deux premières variables latentes ont mis en évidence des anomalies dans la connectivité cérébrale au sein du groupe DCS^+, et ce, dans des réseaux cérébraux fonctionnels typiquement impliqués dans la mémoire associative. La troisième variable latente a quant à elle mis en lumière des anomalies dans la connectivité fonctionnelle qui étaient spécifiques au groupe

d'individus présentant un TCL. Les différences observées entre le DCS^{+} et le TCL pourraient s'expliquer par le fait que différents réseaux seraient atteints à différents stades de la maladie. En effet, les anomalies dans l'activation et la connectivité fonctionnelle pourraient débuter dans les réseaux neuronaux typiquement associés aux processus mnésiques. Elles se propageraient ensuite vers des réseaux possiblement pathognomoniques lorsque l'atteinte clinique serait plus avancée. En somme, ces résultats suggèrent que l'hyperactivation observée au niveau régional pourrait jouer un rôle clé dans les mécanismes affectant les réseaux fonctionnels supportant les fonctions cognitives qui connaissent un déclin précoce dans le procesuss de la MA. De futurs efforts seront toutefois nécessaires pour élucider les mécanismes biologiques par lesquels ces anomalies pathologiques se propagent à travers les réseaux cérébraux fonctionnels.

5.4. Les hypothèses compensatoire et excitotoxique

Rappelons qu'il existe deux propositions principales pour expliquer la nature de l'hyperactivation dans le continuum de la MA. D'une part, l'hypothèse compensatoire propose que ce phénomène refléterait la mise en place de mécanismes compensatoires permettant de maintenir la cognition à un niveau optimal (Clément & Belleville, 2010; 2012; Clément, Belleville & Gauthier, 2013; Gregory et al., 2017; Prvulovic et al., 2005). D'autre part, l'hypothèse excitotoxique propose au contraire que l'hyperexcitabilité neuronale contribuerait au maintien de boucles neuropathophysiologiques rétroactives. Cela aurait pour effet de compromettre l'intégrité des réseaux cérébraux fonctionnels supportant les fonctions cognitives de haut niveau et de contribuer à la progression de la maladie (Bero et al., 2011; Busche et al., 2012; Busche & Konnerth, 2015; Busche et al., 2019a; 2019b; Jagust, 2009; Palop & Mucke, 2016; Rodriguez et al., 2019; Wu et al., 2016).

Bien que cette thèse ne fût pas conçue pour départager ces deux propositions, il est intéressant d'examiner comment nos résultats pourraient contribuer à cette question. Certains de

nos résultats apportent des évidences en faveur de l'hyperactivation en tant que phénomène compensatoire. Dans l'étude 1, l'hyperactivation du gyrus supramarginal était observée en présence d'hypoactivation de régions traditionnellement impliquées dans les tâches de mémoire, soit l'hippocampe gauche et lobe préfrontal gauche (Daselaar et al., 2003; Duverne et al., 2008; Miller et al., 2008). Il est ainsi possible que le recrutement de cette région pariétale droite soit survenue dans le but de compenser une incapacité à activer les régions normalement impliquées dans la tâche de mémoire. Notons également que la région pariétale contrôlatérale gauche était activée dans le groupe de participants contrôles, en absence d'un recrutement des aires pariétales droites. Ceci est compatible avec un important modèle de compensation dans le vieillissement, le modèle HAROLD (*Hemispheric Asymmetry Reduction in OLDer adults* en anglais; Cabeza, 2002). Celui-ci propose que le recrutement de régions contrôlatérales refléterait des mécanismes de compensation. Par ailleurs, lors de l'étude 2, le lobule supérieur pariétal gauche était la seule région où une relation quadratique était observée entre les performances en mémoire associative et le niveau d'activation au sein du groupe d'individus à risque de développer la MA (DCS^+ et TCL combinés). Cette relation pourrait s'expliquer par le fait qu'un niveau plus élevé d'activation serait nécessaire pour maintenir de bonnes performances chez les individus avec une atteinte mnésique très légère, alors qu'une diminution dans le niveau d'activation mènerait à des performances amoindries chez les individus plus atteints. Mis ensemble, les résultats de ces deux études suggèrent que les aires pariétales pourraient représenter des régions clés pour la mise en place de mécanismes compensatoires. Cette proposition concorde avec plusieurs études ayant attribué un rôle compensatoire aux aires pariétales chez des individus à risque de progresser vers le stade démentiel (Belleville et al., 2011; Elman et al., 2014). Notamment, Belleville et al. (2011) ont montré que le recrutement de l'aire pariétale droite était associée à de meilleures performances post-intervention chez un groupe d'individus avec un TCL ayant suivi un

entraînement cognitif de 6 semaines. Il est toutefois important de garder en tête que les observations décrites ci-dessus n'impliquent pas de lien causal. Des études futures seront nécessaires pour directement évaluer la possibilité que l'hyperactivation reflète des mécanismes compensatoires.

D'autres résultats mis en lumière par cette thèse penchent vers l'hypothèse excitotoxique. D'abord, les résultats de l'étude 2 montrent que le niveau d'hyperactivation hippocampique gauche et temporal inférieur droite était corrélé avec un indice de sévérité de la maladie (volume hippocampique). Toutefois, aucune association significative n'était retrouvée entre l'hyperactivation de ces régions et les performances en mémoire. Or, la littérature suggère que la présence d'hyperactivation dans ces régions pourrait être liée à l'accumulation précoce de protéine tau (Berron et al., 2019; Gordon et al., 2015; Huijbers et al., 2018; Maass et al., 2019). Il est toutefois important de considérer cette interprétation avec prudence puisque que nos résultats n'ont pas examiné le lien direct entre l'hyperactivation et l'excitotoxicité de ces régions.

Le patron observé pour l'hyperactivation hippocampique semble donc plutôt appuyer l'hypothèse excitotoxique. Les résultats de l'étude 3 vont également dans ce sens, où l'hyperactivation hippocampique était associée à la dysfonction de réseaux cérébraux fonctionnels et de moins bonnes performances en mémoire dans le DCS^{+} et le TCL. Le patron observé pour l'hyperactivation pariétale semble quant à lui davantage en faveur du modèle compensatoire. Cela est congruent avec l'hypothèse stipulant que la nature de l'hyperactivation varierait selon sa localisation (Leal et al., 2017; Marks et al., 2017).

5.5. Limites des études rapportées dans la thèse

Il existe plusieurs limitations en lien avec les études de cette thèse qui doivent être inévitablement considérées dans l'interprétation des résultats. Certaines limites concernent la composition, la taille et la caractérisation des échantillons. En effet, la taille des échantillons est

relativement modeste, particulièrement pour l'étude 1. C'est également le cas pour l'échantillon des études 2 et 3, bien que les investigations en IRMf s'étant penchées sur des questions de recherche similaires comportent des groupes de participants généralement plus faibles. Par ailleurs, la grande majorité des participants composant les deux échantillons étaient caucasiens et en moyenne hautement éduqués, et l'échantillon des études 2 et 3 comporte un nombre significativement plus élevé de femmes que d'hommes. Bien que certains de ces facteurs puissent être contrôlés de façon statistique, la capacité à généraliser nos résultats à des populations plus diversifiées demeure limitée. D'ailleurs, notons que l'incidence et la prévalence de la démence diffère selon le sexe (Mazure & Swendsen, 2016) et le groupe ethnique (Avila et al., 2019), et que le niveau d'éducation peut avoir un effet sur le décours temporel des symptômes de la MA (van Loenhoud et al., 2019; Wilson et al., 2019). Il est ainsi possible que ces caractéristiques démographiques aient un effet sur les processus neuropathophysiologiques menant à la manifestation phénotypique de la maladie.

Une limite additionnelle est l'absence de biomarqueurs (amyloïde, tau) pour caractériser nos participants selon la définition biologique de la MA (voir le schème A/T/N de Jack et al., 2016; 2018). L'indisponibilité de ces marqueurs ne permet pas d'assurer la présence de pathologie de type Alzheimer chez nos participants. Cela ne permet pas non plus de certifier l'absence de niveaux anormaux de ces biomarqueurs chez nos participants contrôles. Il demeure toutefois important de souligner que nous nous sommes assurés de caractériser nos échantillons pour identifier ceux étant réellement atteints d'un processus neurodégénératif (c.-à-d. sélection de participants avec TCL ayant progressé vers une démence dans l'étude 1) et ceux étant à plus haut risque de progresser vers une MA (c.-à-d. ; enrichissement du groupe DCS^{+} par la présence de marqueurs génétiques et/ou de neurodégénérescence de la MA dans les études 2 et 3).

D'autres limites sont inhérentes aux choix méthodologiques et statistiques de nos études. L'outil d'investigation qui a été préconisé pour examiner l'activation cérébrale et la connectivité fonctionnelle est l'IRMf. Bien qu'il s'agisse d'une méthode puissante, fiable et peu onéreuse pour investiguer les patrons d'activation et de connectivité fonctionnelle dans les stades précoces de la MA (Clément & Belleville, 2009), elle n'est pas sans contrainte. En effet, l'IRMf ne fournit qu'une mesure indirecte de l'activité neuronale via le niveau d'oxygénation dans le sang (signal BOLD). Il est ainsi plausible que certains éléments aient pu teinter le signal BOLD sans toutefois refléter de véritables changements dans l'activation neuronale (p.ex. pression sanguine, intégrité de la matière blanche; Bright et al., 2020; Esposito et al., 2003; Hussein et al., 2020). Rappelons également que l'IRMf est excessivement sensible aux mouvements de la tête, faisant en sorte que plusieurs corrections doivent être apportées dans les analyses statistiques pour éviter la présence d'artéfacts dus à ce facteur. Ces multiples correctifs peuvent avoir un effet sur les patrons d'IRMf observés.

Il est également important de souligner l'utilisation d'un protocole transversal pour les études 2 et 3. Ce type de protocole ne permet pas de mesurer les changements dans l'activation cérébrale ou dans la connectivité fonctionnelle à travers le temps. Il est également sous-optimal pour réduire l'influence de facteurs interindividuels sur les patrons d'activation ou de connectivité fonctionnelle comparativement aux devis longitudinaux. Par ailleurs, l'absence de suivi clinique dans ces études n'a pas permis d'identifier les participants ayant connu un déclin cognitif subséquent. Il est ainsi possible qu'une proportion des participants inclus dans ces études ne soient pas atteints de la MA et que leurs symptômes cognitifs demeurent stables ou reviennent à la normale avec le temps. Cette limite pourrait d'ailleurs être à l'origine de certaines divergences observées dans nos résultats. Par exemple, de l'hyperactivation était retrouvée chez le groupe de participants TCL dans l'étude 1, tandis qu'aucune région n'a été trouvée hyperactive

dans le groupe de participants TCL de l'étude 2. Cette différence pourrait effectivement être due à une plus grande hétérogénéité, soit clinique ou étiologique, du groupe TCL de l'étude 2 au sein duquel il n'a pas été possible d'identifier les participants ayant ultérieurement progressé vers une démence.

5.6. Implications cliniques

Les implications cliniques découlant de cette thèse sont multiples. D'abord, nous apportons des évidences en faveur de l'hyperactivation comme biomarqueur précoce de la MA, en amont des atteintes cognitives objectivables. L'hyperactivation pourrait ainsi potentiellement permettre d'optimiser l'identification d'individus dans la phase précoce de la maladie afin de les inclure dans des essais cliniques randomisés. Ce point relève d'une importance capitale, puisque approches préventives ou curatives de la MA devraient débuter avant l'apparition des symptômes cognitifs (Gauthier et al., 2016). L'hyperactivation en soit pourrait d'ailleurs être considérée comme une cible thérapeutique potentielle. En effet, au moment d'écrire ces lignes, un essai clinique randomisé en phase II est en cours pour tester l'utilisation du levetiracetam, un médicament qui a été montré efficace pour réduire l'activation hippocampique et améliorer les performances mnésiques dans le TCL (Bakker et al., 2012; 2015). Il demeure toutefois important de rester prudent quant au possible dépistage d'individus sur la base de l'activation cérébrale, puisque l'IRMf demeure à ce jour un outil de recherche et il n'existe présentement pas de seuil pour déterminer un niveau anormal d'activation.

L'hyperactivation pourrait jouer un rôle important dans le façonnage des interventions cognitives. Tel que soulevé plus haut, la nature de l'hyperactivation pourrait dépendre de plusieurs facteurs, dont la région cérébrale où elle est observée ou le stade de la maladie (Leal et al., 2017; Marks et al., 2015; Jones et al., 2016; 2017). Nous avançons l'hypothèse que les aires pariétales pourraient être impliquées dans la mise en place de mécanismes compensatoires. Il

pourrait ainsi être intéressant de développer des interventions cognitives qui ciblent l'activation de ces régions pour retarder l'apparition des symptômes cognitifs et/ou diminuer les conséquences de la maladie sur la qualité de vie. Inversement, il pourrait être pertinent de développer des interventions cognitives visant à diminuer ou éviter l'activation de certaines régions potentiellement liées à des processus pathologiques. Cela pourrait être notamment le cas pour l'hippocampe, une région hypothétiquement liée à des procesuss pathologiques selon nos résultats et la littérature scientifique actuelle (Bakker et al., 2012; 2015; Berron et al., 2019; Busche et al., 2012; 2019a; 2019b; Busche & Konnerth, 2015; Hallinan et al., 2019; Huijbers et al., 2019; Leal et al., 2017; Zott et al., 2019).

Une dernière implication clinique découlant de cette thèse est la consolidation du concept de DCS en tant que phase précoce de la MA. Nos données suggèrent que des changements dans l'activation cérébrale et la connectivité fonctionnelle surviendraient chez les individus présentant une plainte de mémoire avec un plus haut risque de développer une MA. La période où l'individu exprime une inquiétude envers ses capacités de mémoire pourrait ainsi représenter une période cruciale pour la prise en charge, avant que les symptômes cognitifs n'apparaissent ou ne s'accentuent. Cela devrait encourager les cliniciens et chercheurs à considérer le DCS comme une manifestation possiblement pré-TCL, et d'orienter une prise en charge conséquente.

5.7. Perspectives futures

Un nombre non-négligeable d'avenues demeurent à être explorées pour apprécier pleinement la nature et les implications de l'hyperactivation dans la MA et son continuum. En termes de diagnostic précoce, la présente thèse suggère que l'hyperactivation serait présente avant l'apparition des atteintes cognitives, au stade du DCS^{+}. Il n'est toutefois pas impossible qu'une augmentation anormale de l'activation cérébrale survienne avant l'apparition d'une plainte cognitive. En effet, les résultats provenant des modèles animaux suggèrent que

l'hyperactivité neuronale pourrait être induite par la présence d'amyloïde soluble, qui est présente avant la formation de plaques amyloïdes (Bero et al., 2011; Busche et al., 2012; Harris et al., 2020; Rodriguez et al., 2019; Zott et al., 2019). Sachant que des niveaux anormaux d'amyloïde peuvent être détectés dans le LCR plusieurs décénnies avant le diagnostic clinique (Insel et al., 2020b; Villemagne et al., 2013), il serait plausible que des changements dans l'activité neuronale seraient présents avant le stade du DCS. L'étude de la phase asymptomatique de la maladie est ainsi cruciale pour identifier les premiers changements dans l'activation neuronale et détecter la MA à ses tout débuts. En termes de diagnostic différentiel, il serait particulièrement intéressant de comparer des individus avec une pathologie Alzheimer à des individus souffrant d'autres types de pathologies (p.ex. a-synucléine, TDP-43, etc.) sur le plan de l'activation cérébrale. Cela permettrait de déterminer si l'hyperactivation est un phénomène spécifique à la MA.

Plusieurs efforts supplémentaires sont également essentiels pour mieux comprendre le rôle de l'hyperactivation dans la cascade pathologique de la maladie (Jack et al., 2010; 2013; Sperling et al., 2011). Pour ce faire, il sera nécessaire d'étudier en profondeur la relation entre l'hyperactivation et les autres biomarqueurs de la MA, comme l'accumulation de plaques amyloïde et de protéine tau. Plusieurs études récentes ont d'ailleurs été menées en ce sens, notamment pour éclaircir le lien entre l'activation cérébrale, la connectivité fonctionnelle et l'accumulation de ces protéines (Adams et al., 2019; Berron et al., 2019; Foster et al., 2018; Gordon et al., 2015; Franzmeier et al., 2019; 2020; Huijbers et al., 2018; Leal et al., 2017; Maass et al., 2019; Marks et al., 2017; Kennedy et al., 2018; Ossenkoppele et al., 2019; Quevenco et al., 2019; Vogel et al., 2020). Toutefois, il n'existe actuellement pas de modèle intégratif causal (plutôt que descriptif) qui soit en mesure de rendre compte de la complexité biologique de la MA, ni d'apporter un éclairage plus complet sur les mécanismes liant les changements neuropathophysiologiques de la maladie à sa présentation phénotypique. La conduction d'études

longitudinales et multimodales sera cruciale pour élucider la façon dont les changements cérébraux fonctionnels contribuent à cette cascade pathologique et au syndrome clinique de la maladie.

Sur le plan méthodologique et statistique, des études longitudinales prospectives comportant de larges échantillons seront nécessaires pour évaluer la sensibilité et la spécificité de l'hyperactivation en tant que prédicteur du déclin cognitif au niveau individuel. Les futurs modèles devront également prendre en compte la variabilité interindividuelle dans l'architecture fonctionnelle du cerveau (p.ex. Est-ce que la relation entre la fonction et la structure du cerveau est similaire d'un individu à l'autre? Quels sont les facteurs individuels influençant l'organisation cérébrale fonctionnelle?), ainsi que la variabilité au sein même du cerveau (p.ex. Est-ce que les propriétés cytoarchitecturales d'une région influencent le degré d'activation neuronale et son influence sur les réseaux fonctionnels associés?) pour effectuer des prédictions sur le plan individuel (Suarèz et al., 2020). Notons qu'à l'ère des neurosciences computationnelles, notamment des méthodes d'apprentissage automatique (ou *machine learning* en anglais), du « *big data* » et de la tendance grandissante en faveur de l'accès libre aux données, la possibilité de développer de tels modèles sera plus accessible que jamais auparavant.

Enfin, certaines pistes de recherche peuvent être envisagées pour départager les hypothèses compensatoires et excitotoxiques. Plusieurs propositions soulevées dans le paragraphe précédent (p.ex. modèles intégratifs, imagerie multimodale) contribueront certainement à mieux identifier la nature de l'hyperactivation dans le processus de la MA. Il pourrait également s'avérer particulièrement intéressant d'examiner les facteurs contribuant à l'émergence de l'hyperactivation. Il pourrait s'agir ici de facteurs de protection au niveau du style de vie (p.ex. niveau d'éducation, activités stimulantes, interventions cognitives), des caractéristiques morphologiques du cerveau (p.ex. réserve et maintenance neuronale, voir Barulli

et Stern, 2013; Cabeza et al., 2018) ou de la génétique (p.ex. génotype du BDNF). Inversement, on pourrait se pencher sur les liens entre l'hyperactivation et les facteurs de risque pour la MA (p.ex. neuroinflammation, diabète, hypertension, inactivité physique). Par ailleurs, l'utilisation de protocoles mesurant l'activation cérébrale et la connectivité fonctionnelle lors de l'accomplissement de tâches cognitives (en opposition à ceux évaluant l'activation cérébrale au repos) est primordiale pour contribuer à répondre à cette question de recherche. En effet, ce type de protocole est optimal pour examiner la façon dont le cerveau déploie des mécanismes potentiellement compensatoires en réponse aux demandes cognitives. Il demeure néanmoins important de souligner les défis qu'occasionnent l'opérationnalisation de la compensation et qui rendent cette question de recherche particulièrement complexe (voir Cabeza et al., 2018 pour une excellente revue sur le sujet). La mise en place de critères précis et opérationnels pour déterminer si l'hyperactivation est présente dans un contexte de compensation ou d'excitoxocité sera cruciale pour départager entre ces hypothèses, et conséquemment déterminer la nature de l'hyperactivation dans la MA.

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ANNEXE I – Article 4

Use of immersive virtual reality to assess episodic memory: A validation study in older adults

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Abstract

Virtual reality (VR) allows for the creation of ecological environments that could be used for cognitive assessment and intervention. This study comprises two parts which describe and assess an immersive VR task, the Virtual Shop, that can be used to measure episodic memory. Part 1 addresses its applicability in healthy older adults by measuring presence, motivation, and cybersickness symptoms. Part 2 addresses its construct validity by investigating correlations between performance in the VR task and on a traditional experimental memory task, and by measuring whether the VR task is sensitive to age-related memory differences. Fifty-seven older and 20 younger adults were assessed in the Virtual Shop where they memorized and fetched 12 familiar items. Part 1 showed high levels of presence, higher levels of motivation for the VR than for the traditional task, and negligible cybersickness symptoms. Part 2 indicates that memory performance in the VR task is positively correlated with performance on a traditional memory task for both age groups, and age-related differences were found on the VR and traditional memory tasks. Thus, the use of VR is feasible in older adults and the Virtual Shop is a valid task to assess and train episodic memory in this population.

Keywords: virtual reality, episodic memory, aging, validation study, neuropsychological assessment

Memory is a complex function which relies on a range of interacting processes and systems. A variety of experimental and clinical tasks has been devised to measure memory and to attempt to tease apart these different processes. For instance, different tasks and testing conditions have been developed to distinguish familiarity from recollection, item from associative memory, or memory for verbal, visual or spatial material. Memory tasks traditionally used in clinical practice or those used in experimental studies of aging are constructed to allow a fine control of the task parameters and testing conditions to reflect these fine-grained processes. However, these tasks generally lack ecological validity, as they fail to reflect the complexity and diversity of memory situations that older adults experience in their daily lives (Bowman, 1996; Chaytor & Schmitter-Edgecombe, 2003; Farias, Harrell, Neumann, & Houtz, 2003; Sbordonne & Long, 1996; Schultheis, Himelstein, & Rizzo, 2002; Shuchat, Ouellet, Moffat, & Belleville, 2012; Piolino, Desgranges, & Eustache, 2009). In real life, memorizing often occurs in noisy environments with multi-dimensional material and often happens while completing other tasks such as walking, talking, or problem solving. This is in marked contrast to the testing conditions that occur in experimental and clinical contexts where participants complete their tasks in quiet conditions, receive clear task instructions, encode unidimensional material most of the time and focus their attention on the task.

Virtual reality (VR) is a promising technology that could help increase the ecological validity of memory assessments and interventions. VR immerses the user in a dynamic virtual environment where he/she carries out cognitive and sensorimotor activities while interacting with virtual stimuli (Fuchs, Moreau, & Berthoz, 2006). One major asset of VR is that it offers environments that reproduce the sensorial characteristics of the real world (e.g., visual scenes, audible conversations) and

incorporate the cognitive and physical demands of situations that individuals face in their everyday lives. Thus, VR gives the opportunity to sample the integrity of cognitive functions in contexts that are more representative of everyday life.

These offer tremendous potential as measures of real-life cognition. Well-designed VR tasks might therefore better reflect real-life capacities than traditional neuropsychological tests (Rizzo, Schulteis, Kerns, & Mateer, 2004). Furthermore, VR has great potential to measure whether neuropsychological interventions transfer to daily life, which is a major challenge in rehabilitation studies (Adamovich et al., 2004; Lehmann et al., 2015; Ouellet, Boller, Corriveau-Lecavalier, Cloutier, & Belleville, submitted; Shuchat, Ouellet, Moffat, & Belleville, 2012; Sveistrup, 2004).

However, VR is a recent technology, and so is its application to cognitive measurement. Many reasons justify measuring the applicability of VR in older adults. Studies using VR protocols with older adults are rare and hence many crucial questions regarding the applicability and validity of VR tasks among older adults remain to be investigated. Designing and testing tasks that reflect memory in real life is particularly interesting in the context of aging. Episodic memory declines with age, is frequently impaired by brain disease and is one of the first signs of Alzheimer's disease. Thus, having access to a variety of sensitive and valid tools to assess and train episodic memory is crucial for clinical neuropsychologists. Furthermore, while there are many well-designed tasks to measure the fine processes involved in episodic memory, VR can provide tools that reproduce the complexity of memory in daily life. This is critical, as the impact of cognitive decline on autonomy is a major concern in the context of age-related cognitive decline, and VR could contribute to addressing these issues. Yet, the feasibility and applicability of VR in older adults is a potential problem because of differences in technological literacy. Since older adults are less prone to make use of

information and communications technologies than younger adults (Selwyn, 2004), it is critical to study factors that might contribute to their subjective experience when placed in a VR environment as well as potential barriers to the use of this technology.

This study will address the applicability of VR technology in a population of older adults and its potential application to memory assessment by measuring presence, motivation and cybersickness symptoms with a fully immersive episodic memory task (Part 1). It will also assess its construct validity (Part 2). The following section will briefly introduce these notions and how they have been addressed in the literature.

Presence is defined as the subjective experience of being in a place when one is in fact physically in another one (Witmer & Singer, 1998). Thus, in the context of VR, it refers to the subjective experience of actually being in the environment that is represented. It is measured with questionnaires measuring the quality of the interaction with the environment, whether the experience in the environment was consistent with the real-world experience and the quality and ease of the interface. In younger adults, larger scores on presence scales have been associated with better sustained attention (Witmer & Singer, 1998), psychomotor performance (Stevens & Kincaid, 2015; Witmer & Singer, 1994) and spatial memory (Bailey & Witmer, 1994). Because presence is positively related to cognition, it is important to know whether the VR environment elicits an appropriate sense of presence particularly in older adults. A number of factors might determine the magnitude of presence experienced by the participants. Some are related to the software and hardware characteristics of the VR environment, for instance the interface quality, the type of interaction (e.g., joystick vs. button response) or how participants navigate in the environment (e.g., active vs. passive navigation). Psychological factors related to the user can also contribute to presence and performance in VR. These include the participant's perception regarding the degree of

realism of the task, the level of control they have over the situation, the possibility they have to examine the elements of the environment, their subjective evaluation of their own performance, and their general motivation with respect to the task.

The degree of motivation towards the task might be particularly relevant when designing VR environments, as motivation optimizes performance and is related to resource allocation in older adults (Hess, 1994; Hess, Germain, Swaim, & Osowski, 2009; Hess, Popham, Emery, & Elliott, 2012). Because older adults are generally less technologically experienced, one might expect them to be less motivated by VR than by non-VR tasks. Interestingly, some results suggest that this may not be the case. In a study led by Benoit et al. (2015), participants were presented with a photograph or an image-based VR representation of familiar locations in their home city or new locations and were asked to indicate whether they recognized the location. The motivation level of older adults, which was measured with a homemade questionnaire, was found to be larger for the VR than for the non-VR version of the task, although the difference was non-significant. Using the same motivation questionnaire, Manera et al. (2016) reported that older adults with mild cognitive impairment or Alzheimer's disease actually experienced higher levels of satisfaction and security, and lower levels of anxiety, discomfort and fatigue during a highly realistic image-based VR cancellation task than during its paper-pencil version (Manera et al., 2015). Thus, both studies reported that older adults experience a higher level of motivation for the VR rather than the non-VR version of the same tasks. Though there is clearly a need for more empirical data, these preliminary findings are interesting and suggest that VR has the potential to elicit positive motivation in older adults.

Cybersickness is potentially a major limitation for the use of VR. Indeed, nausea, headaches and disorientation can occur while immersed in a virtual

environment (Jaeger & Mourant, 2001; Slater, 1999). Their occurrence could seriously hamper the applicability of VR technology in populations that are sensitive to these symptoms. A few studies have found more frequent cybersickness symptoms in older adults relative to younger ones, although the reported difference appears to be of a relatively small magnitude (Arns & Cerney, 2005; Liu, Watson, & Miyazaki, 1999). However, a more recent study reported no increase in cybersickness symptoms following immersion in older adults (Benoit et al., 2015).

Additionally, it is critical to know whether cognitive VR tasks reflect the construct that they are intended to measure. Construct validity refers to the capacity of a test to accurately reproduce the attributes and characteristics of a given construct (Cronbach & Meehl, 1955). Convergent validity is a type of construct validity and is determined by measuring whether performance on the VR task is related to performance on tasks that measure similar theoretical concepts. A few studies have addressed the convergent validity of VR tasks by comparing them with traditional tasks that assess the same cognitive processes. Studies in younger adults have generally reported significant correlations between VR and traditional tasks of inhibition (Armstrong et al., 2013; Henry, Joyal, & Nolin, 2012), and VR and traditional tasks of attention (Parsons & Courtney, 2014). Parsons & Rizzo (2008) reported positive correlations between a traditional word memory task and memory performance in a VR task where younger adults had to recall a list of 10 items (e.g., a blue car) encoded while navigating a virtual city. Plancher, Nicolas & Piolino (2008) and Jebara and colleagues (2014) found that older adults' performance on the recognition of items seen in a 2D VR car ride was positively correlated with performance on traditional recognition and executive tests, suggesting that the VR memory task may also reflect other cognitive capacities, such as executive processes.

Construct validity can also be assessed by examining whether a VR task is sensitive to the differences in episodic memory typically associated with aging. Previous studies have found age-related differences on the free recall of spatiotemporal characteristics of a list of items encoded during a virtual car ride (e.g., where and when the items were seen during the car ride; Plancher, Nicolas, & Piolino, 2008) and on the free recall of items presented in a virtual apartment (Sauzéon, N'Kaoua, Pala, Taillade, & Guitton, 2016). These results are broadly consistent with the literature, indicating that age is associated with a reduction of associative memory, defined as the capacity to bind pieces of information into a cohesive unit, and of episodic memory, defined as the memory for items encoded with their spatio-temporal context (Chalfonte, 1996; Johnson, 1996; Naveh-Benjamin, 1990; 2000).

In summary, VR has tremendous potential to measure memory in conditions that reflect cognition in everyday life. The use of VR might contribute greatly to how neuropsychologists assess cognition and provide interventions. Furthermore, the technology is becoming cheaper and more accessible, making its use with clinical populations likely to increase in the near future. However, there is a need for applicability and validation data to support VR as a useable technology in older adults and to ensure that VR variants of memory tasks reflect the constructs that they are meant to assess. The present study addresses these issues. The VR task developed here was meant to reflect a situation which is close to a real-life situation and which likely reflects memory in action. Participants encode visually presented items and are then asked to find them in a small convenience store. As is the case in real life, their performance is probably based on a combination of active retrieval (for instance "I need to go get the broom") and recognition because it is likely that some items are recognized as they walk in the virtual environment. Thus, the task is quite unique relative to

traditional memory tasks because the objects are present in the environment, yet the task involves active search and interference. The task requires a conscious mental representation of the items to fetch, which is to some extent close to the process of free recall: participants probably evoke their list while walking around in the store. Although the presented objects were present and could be used as cues, the subjective experience is clearly more complex than a typical recognition task because participants move in the environment to search for the memorized objects rather than being passively presented with lists of potential items. Another major innovative aspect of the study is to rely on a fully immersive 3D VR technology. Relying on 3D VR technology differs markedly from computerized flat screen VR tasks in that it provides a more immersive experience and more natural interaction with the surrounding environment. However, the technology might be more challenging to use by older adults or clinical populations than 2D technology. To our knowledge, no study has investigated the VR feasibility using a fully immersive technology.

Part 1 addresses the applicability of a fully immersive 3D VR episodic memory task where participants had to memorize and fetch a series of items in a virtual shop. This is addressed in younger and older adults by measuring presence, motivation and cybersickness symptoms. We hypothesize that the task will show strong feasibility in both younger and older adults. We also anticipate that older and younger adults will show a comparable level of presence and that presence will be related to performance in the VR task (Bailey & Witmer, 1994; Witmer & Singer, 1994). We also expected that the task would be motivating for participants, irrespective of their age. Finally, we did not expect cybersickness symptoms to interfere with the task completion, as a number of studies have reported that older adults have relatively few symptoms of cybersickness with tasks of short duration.

Part 2 measures construct validity of the immersive VR episodic memory task by comparing performance on the VR task with that obtained from traditional paper-pencil memory tasks and by measuring whether the VR task was sensitive to the age difference typically found in episodic memory. Given the results from prior work, we hypothesize that the task will be a valid representation of episodic memory capacities. We expect that the task will have appropriate construct validity. This will be supported by finding a positive correlation between memory performance on the VR task and performance on a traditional task measuring immediate and delayed free recall of a list of visually presented words. Construct validity will also be supported by findings of a lower VR memory performance in older adults compared to young adults.

General Method common to Part 1 and 2

Participants

The study included 57 cognitively healthy older adults and 20 younger adults. It includes a larger number of older than younger adults, as older adults were the main focus of our study. The goal was to assess the applicability and validity of VR in this population, and younger adults were included as a group of comparison. Furthermore, inter-individual variability increases with age and thus including a larger number of older adults increased the power to detect a group difference. The same participants were used for both parts to increase power and because this facilitates the comparison of the results obtained for feasibility and validity. Participants were recruited from the local community and were all native French speakers. Exclusion criteria included the following: presence or history of a neurodegenerative disease, life-threatening disease (e.g., cancer), stroke, uncontrolled sleep apnea, major psychiatric disorders (i.e.,

depression, schizophrenia, etc.), excessive drinking (> 25 drinks per week), substance abuse, general anesthesia during the past 6 months, balance difficulties, uncorrected visual impairment, and important hearing loss (corrected or not). We also used the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), a short cognitive assessment battery, to exclude older adults with impaired cognition (score ≤26). The Victoria Stroop Test (Troyer, Leach, & Strauss, 2006) and the free and cued recall test (Grober & Buschke, 1987) were included to characterize the sample of older adults and facilitate comparison between this sample and other samples that will be used in future studies.

The participants' demographic and clinical characteristics are presented in Table 1. Older and younger adults were equivalent on demographic characteristics. Furthermore, the scores of the older adults on the neuropsychological tests were within the normal range when considering their age and education level. This was expected given that cognitively impaired participants were excluded.

VR task

The virtual environment of the Virtual Shop (La boutique virtuelle) was developed and rendered using the 3DVIA Virtools 5 3D engine and was run on a Dell Precision T3600 PC with a Inter(R) Xeon (R) CPU ES-1620 0 (3.60 Ghz, 10 Gbytes in RAM) processor and a NVIDIA GeForce GTX 600 Ti graphic card. It was designed in collaboration with Cliniques et développement in virtuo (www.invirtuo.com). The virtual environment was in 3D and the immersion was produced by an Nvisor ST50 audio-visual headgear and by a Worldviz PPT-X studio tracking system that allowed the participant to rotate his/her head in a 360-degree view around the room, as well as look up and down, and interact and walk freely in the virtual environment. The participant was asked to stand in the empty assessment room while the assistant installed the

headgear and hand device. He/she was then presented with the virtual environment. The environment was a small convenience store built using the same dimensions as the assessment room (3.5m X 6.5m). Participants were told that they were free to move around the environment, explore and fetch items. Participants used a hand remote control to select and retrieve items. The remote control allowed them to display a target sign that they could move in the virtual environment in order to point to the items they wanted to select.

Participants began the task in front of a cashier working behind a countertop and were presented with a list of 12 familiar virtual images of common items (e.g., belt, milk) that they were asked to memorize and then fetch in the store. Each item was visually presented for 5s on a notepad situated on the countertop with the name of the item written below the image to ensure that the item was properly encoded. During encoding, irrelevant conversations were presented via the headgear in order to mimic a noisy environment. Following the presentation of the last item, the program initiated a 20s conversation between the cashier and the participant (e.g., Could you tell me the time, which is displayed on your right?) as a filled interference delay. At the end of the delay period, the cashier instructed the participant to fetch the items in the store he/she had previously seen. The participant could then walk freely in the room to find and select the items that were shown on the learning list. There were 24 items displayed in the shop: 12 target items and 12 distractors. We chose distractors that matched the targets by taxonomic category. This is relevant when designing episodic memory tasks, as memory errors most often preserve the category in free recall conditions and more errors are made when distractors share the same semantic category as the target in recognition conditions. Furthermore, this feature reduces the likelihood of simply guessing the correct item based on having encoded its semantic category. It therefore

makes the task more sensitive to memory failures. An ancillary benefit to using semantic distractors is that it enhances the ecological value of the test, as real-life shopping often requires selecting items among other ones from the same category. For instance, if one has to buy a particular vegetable to make a soup, it will be found in the "fruit and vegetable section" of the supermarket and the person will therefore be faced with distractors from the same category. The items were located on the shelves, on the floor or hung on the walls.

Participants used a hand remote control to select and retrieve the items and were given unlimited time to find them. Prior to the testing, they were familiarized with the virtual devices using a different version of the convenience store in a condition where they were simply asked to walk in the virtual environment and select an item that was not used in the memory test. During this familiarization phase, additional information and practice trials were given to participants who were unsure about the procedure of the task or with the operation of the remote control. Familiarization was continued until the participant was comfortable with the manipulation of the material in order to reduce the likelihood that problems would occur during the VR task.

Correct performance was measured as the number of targets that were correctly retrieved. A false recognition error response was recorded when the participant selected an incorrect item, that is, one that was not part of the encoded list. Note that all foils are related to one of the presented items and therefore, false recognition errors are semantic errors by design. There were other built-in parameters that were measured by the VR task, for instance, time before the first item was selected, and total time to complete the task. Although they were not used in the present study, they could be useful for researchers interested in a more extensive characterization of the participant's behavior in the task (see for instance Ouellet, Boller, Corriveau-Lecavalier, Cloutier, &

Belleville, submitted).

Traditional episodic memory task measures

A traditional experimental memory task was used to test convergent validity and compare motivation in a virtual vs. non-virtual variant of a memory task. The task was adapted from a validated free recall word list test (Belleville et al., 2002). Two lists of 12 concrete words were visually presented on a laptop using e-prime. The two lists were matched for word length (1 to 4 syllables), word frequency and concreteness. Participants were presented with the words at a rate of one item every 5s (4s of presentation and 1s of cross fixation). The lists were encoded and recalled with irrelevant verbal noise similar to the noise used in the VR task, and were presented through a Plantronix Audio 550 headset. Participants were instructed to remember as many words as possible. Immediately after the presentation of the list, participants were asked to write down the words they remembered in the order in which they came to mind. Free recall was repeated 4 minutes after participants had completed a short-term memory task (a digit span task).

The use of an experimental measure was preferred over that of a clinical measure as a test of convergent validity. This was done to allow for more flexibility and control over testing modalities. For instance, using a computerized presentation facilitated strict control over presentation modalities (e.g., presentation rate, recall delay). Designing the task allowed us to control the frequency and concreteness of the items using data collected from the French-Canadian population. It also allowed to construct a task that shared some of its characteristics with the VR task. For instance, it enables the use of similar encoding rate, interfering noise during encoding, and a visual presentation of the stimuli. We did not consider pairing the modalities for the retrieval phase, as retrieving items in the VR environment involved walking around and

searching for the items and could therefore not be matched with the type of task conditions traditionally used to measure verbal memory. Thus, retrieval in the VR environment involves active search and is carried out under very challenging conditions contrary to the typical recognition procedure. Finally, free recall is unlikely to be at ceiling contrary to typical recognition tasks.

Design

Health and demographic questionnaires were completed during a 30-min telephone interview. Eligible participants were tested with the cognitive and VR measures, and administered the presence, motivation and cybersickness questionnaires at the CRIUGM during a single 2-hour session. Participants first received the traditional memory task, followed by the motivation questionnaire related to the traditional memory task and the cybersickness questionnaire. They then completed the VR task followed by the cybersickness questionnaire for a second time, the motivation questionnaire related to the VR task, and the presence questionnaire. This study was approved by the Regroupement Neuroimagerie/Québec (RNQ) Comité mixte d'éthique de la recherche.

PART I: APPLICABILITY OF THE VIRTUAL SHOP

Presence, motivation and cybersickness questionnaires

The French version of the Presence Questionnaire (Witmer & Singer, 1994), which was adapted by the Cyberpsychology Laboratory of the Université du Québec en Outaouais (UQO) (Robillard, Bouchard, Renaud, & Cournoyer, 2002), included 19 items (e.g., to what degree did your interactions with the environment seem natural?) divided into five subscales: realism, possibility to act, interface quality, possibility to

examine, and self-evaluation of the performance. In this questionnaire, participants were asked to rate their VR experience on a Likert scale ranging from 1 (not at all) to 7 (completely). The questionnaire is constructed so that responses in the low range of the scale (1 to 3) indicate a negative experience, whereas responses in the high range of the scale (5 to 7) indicate a positive experience. This questionnaire was shown to have good internal consistency (Cronbach's alpha of 0.88), as well as content and construct validity (Witmer & Singer, 1994).

For the purpose of this study, we also constructed an experimental questionnaire to assess motivation evoked by the tasks. The questionnaire was constructed based on a literature review regarding the different components of motivation according to the concept of flow (Csikszentmihalyi, 2000) in relation to video games (Klasen, Weber, Kircher, Mathiak, & Mathiak, 2012), and media enjoyment (Weber, Tamborini, Westcott-Baker, & Kantor, 2009). One version was used for the VR task and another for the traditional memory task. Each version comprised 7 items where participants rated their level of motivation and interest regarding the task they completed (e.g., I felt engaged during the task on the computer/Virtual environment) on a Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). Lower scores indicated a low level of motivation. The questionnaire showed an appropriate internal consistency when tested in this sample (Cronbach's alpha = 0.79).

The French version of the Simulator Sickness Questionnaire (Kennedy, Lane, Berbaum, & Lilienthal, 1993), which was adapted by the UQO Cyberpsychology Laboratory (Bouchard, Robillard, & Renaud, 2007), was used to assess the occurrence, nature and severity of cybersickness symptoms when immersed in a virtual environment. Two subscales (nausea and oculomotor difficulties) included 16 items (e.g., headaches) where participants had to rate their symptoms on a scale of 0 (not at

all) to 3 (severely). Here, lower ratings correspond to low levels of symptoms. This questionnaire was found to have good internal consistency (Cronbach's alpha of 0.81), and to be a valid measure of motion-induced sickness symptoms (Kennedy, Lane, Berbaum, & Lilienthal, 1993).

Statistical analyses and results

The data was analyzed using Statistical Package for Social Sciences (SPSS) version 21.0. Three older adults did not complete the entire protocol: two of them reported severe cybersickness symptoms and thus could not complete the VR task, and one participant withdrew from the study before the VR task. Participants who withdrew for cybersickness symptoms completed the Sickness Simulator Questionnaire after the VR task and were thus included in the analysis of cybersickness symptoms. Since there were no significant differences in terms of education and gender distribution between the younger and older adults, it was not necessary to use them as nuisance covariates (Miller & Chapman, 2001).

In order to compare younger and older adults on different Presence Questionnaire subscales, independent t-tests (two-tailed) with significance levels set to $p < .01$ according to the Bonferonni correction for multiple comparisons were conducted, and Pearson bivariate correlations (two-tailed) were performed to investigate the relationship between the different Presence Questionnaire subscales and memory performance on the VR task. Comparisons were adjusted according to Levene's tests for homogeneity of variance when needed. A 2 (Type of task) x 2 (Group) ANOVA was used to assess the degree of motivation evoked by the different memory tasks in younger and older adults. To assess the magnitude of cybersickness symptoms, a 2 (Immersion) x 2 (Group) ANOVA was conducted in order to compare younger and older adults before and after the immersion.

Presence

Results (means and standards deviations) for the Presence Questionnaire subscales, the motivation questionnaires for the VR and the traditional memory tasks, the Sickness Simulator Questionnaire, and performance on the VR and traditional memory task measures are listed in Table 2. Overall, participants rated the aspects related to the different Presence Questionnaire subscales in the positive range. No group effect was found on any of the subscales (realism, $t(1, 72) = 0.59$, $p = 0.60$; possibility to act, $t(1, 72) = 0.31$, $p = 0.76$; interface quality, $t(1, 72) = 0.40$, $p = 0.69$, possibility to examine, $t(1, 72) = 0.06$, $p = 0.95$; self-evaluation of performance, $t(1, 72) = 2.32$, $p = 0.29$).

In older adults, there were significant positive correlations between VR performance and all subscales of the Presence Questionnaire (realism, $r = .36$, $p < .01$, possibility to act, $r = .41$, $p < .01$, interface quality, $r = .42$, $p < .001$, possibility to examine, $r = .28$, $p < .05$, self-evaluation of performance, $r = .37$, $p < .01$). In younger adults, VR performance only correlated positively with the interface quality subscale, $r = .53$, $p < .05$, but there were no significant correlations with the other subscales (realism, $r = -.27$, $p = 0.25$, possibility to act, $r = -.01$, $p = 0.98$, possibility to examine, $r = -.21$, $p = 0.37$, self-evaluation of performance, $r = -.31$, $p = 0.18$).

Motivation

The ANOVA indicated a significant effect for the Type of task, as the motivation scores for the Virtual Shop were higher than for the traditional memory task for both groups, $F(1, 72) = 23.65$, $p < .001$, $\eta^2 = 0.25$. Results also revealed a Group effect, as older adults had higher motivation scores than younger adults overall, $F(1, 72) = 1132.37$, $p < .001$, $\eta^2 = 0.40$. There was no Group x Type of task interaction, $F(1, 72) = <1$, $p = 0.54$.

Cybersickness symptoms

There were slightly more cybersickness symptoms following than prior to immersion but the effect just missed significance, $F(1, 74) = 3.71$, $p = 0.06$. There was neither a Group, nor an interaction effect, $F<1$ in both cases. Scores on the Sickness Simulator Questionnaire indicated that both groups experienced a low level of cybersickness symptoms, even after immersion.

PART II: VALIDATION OF THE VIRTUAL SHOP

Method and results

The second part of this study assesses construct validity by computing Pearson bivariate correlations (two-tailed) to assess the relationship between performance on the VR task and on free immediate and delayed recall measured with traditional word recall tasks in both younger and older adults (convergent validity). It also assesses construct validity by measuring whether the VR task was sensitive to the age-related effect typically observed on episodic memory tasks. Groups were compared on their performance on the Virtual Shop with independent t-tests (two-tailed) using the number of accuracies (correctly retrieved items) and the number of false recognitions as dependent variables. Their performance on the traditional memory task was compared with a 2 (Group) x 2 (Delay) ANOVA using correct word recall as the dependent variable.

Convergent validity

Performance on the VR task correlated with the immediate and delayed free recall scores of the traditional verbal memory task in both younger ($r = .57$, $p < .01$ and

r = .46, p < .05 respectively) and older adults (r = .28, p < .05 and r = .30, p < .05 respectively).

Construct validity

As expected, results on the traditional memory task showed a Group effect, $F(1, 75) = 41.28$, $p < .001$, $\eta^2 = 0.36$, a Delay effect, $F(1, 75) = 62.52$, $p < .001$, $\eta^2 = 0.60$, and a Group x Delay interaction, $F(1, 75) = 13.37$, $p < .001$, $\eta^2 = 0.15$. Tukey post-hoc analysis revealed a stronger effect of delay in older than in younger adults, $p < .001$. The VR task was sensitive to age, as younger adults performed significantly better than older adults when using the number of correct answers as a dependent variable, $t(1, 73) = 2.38$, $p < .05$, $d = 0.30$. However, there was no group effect on the number of false recognitions, $t(1, 75) = 0.79$, $p = .937$.

Discussion

To our knowledge, this study is the first to address the applicability and validity of a fully immersive episodic memory VR task in younger and older individuals. Overall, results indicate that the VR technology is a useable tool in aging and that the Virtual Shop has adequate validity properties to reflect episodic memory in a virtual context. This indicates that the technology is suitable to assess, and eventually train, episodic memory in older adults. These aspects of the study are discussed below.

The first goal of the study was to assess the feasibility of the VR task. Our hypothesis was that the Virtual Shop would show strong feasibility in younger as well as in older adults. All three indicators suggest good feasibility. The five subscales of the Presence questionnaire were positively rated by both age groups, and younger and older adults were comparable on all subscales. We found higher levels of motivation for the Virtual Shop than for the traditional memory task in both age groups. Finally, negligible

cybersickness symptoms were found following immersion for both younger and older adults.

Hence, the fact that older adults might have been less exposed to technology and electronic devices does not seem to impact their capacity to feel comfortable in virtual environments, to experience similar feelings and reactions as in real-life situations, and to enjoy realizing cognitive tasks in that sort of setting. Our environment was fully immersive, and the high degree of interaction could account for the high sense of presence (Slobounov et al., 2015) and to making it a more inviting and interesting experience than the traditional task. Furthermore, the resemblance of the Virtual Shop with everyday situations may have provided a more meaningful environment to older adults and contributed to our finding that younger and older adults experienced an equivalent level of presence and motivation. Also, it is interesting to note that we obtained very good indications of feasibility in older adults, in spite of the fact that the task remained sensitive to age as mentioned below. This indicates that being impaired on the task is not necessarily accompanied by a reduction in the level of motivation or sense of presence.

One frequently reported drawback regarding the use of VR in older adults is the fact that it elicits cybersickness and that these effects might be more frequent and/or severe in older adults. However, this study did not find more cybersickness symptoms following immersion or more symptoms in older than in younger adults. This might be due to our use of a relatively short duration. Thus, whether older adults can experience more cybersickness symptoms with longer durations remains to be determined. In spite of the fact that younger and older adults did not differ at the group level, it is of note that two older participants dropped out of the study, as they experienced severe cybersickness symptoms. The scores of these participants were kept in the analysis of

the cybersickness symptoms and therefore, the fact that they dropped out did not influence our findings.

It is of note that memory performance on the Virtual Shop was positively correlated with all subscales of the Presence questionnaire in older adults, its realism, the possibility to act upon and examine the environment, and self-evaluation of performance, whereas it was only related with the quality of the interface in younger ones. Thus, younger and older adults might be sensitive to different characteristics of VR. The performance of younger adults appears to be influenced by the technical quality of the task, whereas that of older adults appears to be influenced by the technical quality and content of the task as well as his/her personal appraisal and confidence with respect to the task. Thus, many dimensions appear to influence cognition measurement when using VR with older adults, and these should be taken into account when designing tasks adapted to this population. Importantly, this may not be particular to VR, as many of these characteristics have been shown to influence performance when testing older adults with traditional tools as well.

The second part of the study measured the construct validity of the Virtual Shop. Our hypotheses regarding construct validity were that the memory performance in the Virtual Shop would be correlated to that obtained from a traditional episodic memory task and that the task would be sensitive to age-related differences. Both hypotheses were confirmed. Performance in the VR task was positively correlated with performance in a traditional word-recall test. Thus, the Virtual Shop and the traditional memory task seem to reflect similar cognitive processes. This concurs with previous studies indicating that VR can measure similar constructs as those measured by clinical or experimental measures (Armstrong et al., 2013; Henry et al., 2012; Parsons & Courtney, 2014; Parsons & Rizzo, 2008; Plancher, Nicolas & Piolino, 2008). This is an

important finding. VR measures performance in complex conditions in the presence of auditory and visual distractions, and while the participant navigates the environment and manipulates new devices. Furthermore, older adults showed the typical age-related memory decrement when examining the number of correctly retrieved items as a dependent variable. This indicates that the VR task is sensitive to typical memory impairment. Interestingly, the two age groups showed an equivalent number of false recognition errors. Thus, older adults omit more items than younger ones but do not select erroneous semantic foils. This may be indicative of a prudent approach in older adults who would not tend to guess on the basis of semantic features when they forgot an item. It also highlights how the virtual shop can be used to distinguish omission from semantic errors.

Of note, our data show that the correlations between the VR and non-VR memory tasks were of a somewhat smaller magnitude in older adults than in younger ones. There might be many factors that account for differences, and we should remain cautious considering the small sample size. Nevertheless, one possibility is that other executive functions or attentional processes contributed more to performance in older adults than in younger ones, hence reducing the unique contribution of memory (Anderson, Craik, & Naveh-Benjamin, 1998; Li & Lindenberger, 2002; Li, Lindenberger, Freund, & Baltes, 2001). The attentional demand of the task may have made it particularly sensitive to an age effect. Hence, the Virtual Shop has the potential to unravel cognitive difficulties encountered by older adults in real life when conditions are more distracting or more demanding. Future studies will be needed to include measures of divergent criterion validity to investigate which cognitive and/or sensorimotor function are not engaged by a given VR task.

Results must be interpreted within the context of some limitations. The assessment of validity focused on measures of episodic memory even though other processes might have been involved in the task. Thus, it remains unclear whether other cognitive processes are implicated in the VR task, aside from episodic memory. Furthermore, the same sample was used for the two parts of the study. Hence, the possibility remains that performance in the VR task might have influenced the participants' responses on the motivation and/or presence questionnaire. However, since older adults showed lower performance than younger ones but higher motivation and an equivalent sense of presence, it does not seem to be the case. We did not include measures of exposition to video games and technology, cognitive training, or use of cognitive games and we did not measure test-retest reliability and comparability of parallel version. Also, the sample size for the group of younger adults was small, which might have reduced statistical power, particularly for correlations. The VR and traditional memory tasks were not entirely equivalent, particularly regarding the retrieval condition. Finally, the VR task does not perfectly match real-life shopping in terms of time duration and encoding conditions. Our goal was to design a task that would be feasible within a clinical context where time is a critical issue and because we were concerned that using longer exposures would elicit cybersickness symptoms. Note that we made sure to include other components to increase the similarity between the VR task and real-world situations, for instance including background conversations, providing complete immersion and having individuals physically walk in the VR environment to retrieve their items. These characteristics helped increase the similarity with real-world contexts and represent assets compared to other less elaborated protocols which rely on flat screens, joystick navigation or passive exploration.

In conclusion, our results indicate that the use of a fully immersive Virtual Shop task is feasible in older adults: it elicits presence, is engaging, and provokes limited symptoms of cybersickness within the conditions that were used here. Furthermore, it has appropriate construct validity to measure episodic memory: performance in the VR task is positively related with performance on a traditional memory task and is sensitive to age-related differences. The finding that the VR task is a feasible, valid and sensitive measure of memory makes it a promising tool to contribute to the clinicians' knowledge regarding an individual's daily functioning and the impact that memory impairment may have on his/her daily life. Thus, VR memory tasks could become useful instruments to reflect real-life memory and provide complementary information relative to more traditional measures. VR tasks might also contribute to enriching cognitive interventions with environments that are realistic and engaging, thus addressing some of the challenges encountered in geriatric rehabilitation such as lack of motivation and engagement, for instance (Choi & Twamley, 2013). Finally, given that VR is feasible and that VR-based tasks are valid measures, relying on VR technology to devise real-life tasks represents an interesting avenue to assess whether interventions or rehabilitation strategies provided in clinical contexts generalize to more complex environments of daily life (Bier et al., under press; Zelinski, 2009).

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Disclosure statement

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Table 4.1. Demographic and clinical characteristic of participants

	Younger (n = 20)	Older (n = 57)
Age (years)	21.65 (2.46)	67.77 (7.03)
Education (years)	13.90 (2.05)	14.86 (3.23)
Gender (f, m)	13, 7	47, 10
Montreal Cognitive Assessment (MoCA) (/30)	-	27.58 (1.74)
RL/RI-16 word recall test (3rd free recall)		11.46 (2.31)
RL/RI-16 word recall test (delayed free recall) (/16)	-	12.11 (2.08)
Geriatric Depression Scale (GDS)	-	1.77 (2.73)

Table 4.2. Mean scores for the questionnaires and time to complete the VR task

	Younger (n = 20)	Older (n = 57)
Presence Questionnaire		
Realism (/49)	34.40 (6.18)	33.77 (7.50)
Possibility to act (/28)	19.40 (3.42)	19.32 (5.34)
Interface quality (/28)	14.50 (2.82)	15.17 (3.43)
Possibility to examine (/14)	13.85 (2.52)	14.17 (3.72)
Self-evaluation of performance (/14)	11.55 (2.06)	10.06 (2.82)
Motivation questionnaires		
Virtual Reality (/35)	20.35 (7.50)	29.36 (5.16)
Traditional task (/35)	16.45 (7.97)	26.46 (5.14)
Sickness Simulator Questionnaire		
Pre-immersion		
Nauseas (/27)	1.35 (3.76)	0.93 (1.33)
Oculo-motor difficulties (/21)	2.55 (2.46)	3.57 (2.39)
Total score (/48)	3.90 (5.42)	4.46 (3.24)
Post-immersion		
Nauseas (/27)	2.75 (5.32)	2.73 (3.94)
Oculo-motor difficulties (/21)	3.05 (2.72)	2.95 (3.27)
Total score (/48)	5.80 (7.37)	5.67 (6.44)
Time to complete Task (seconds)	312.65 (99.17)	482 (153.30)

Table 4.3. Mean scores for the memory tasks

	Younger (n = 20)	Older (n = 57)
Memory tasks		
The Virtual Shop		
Items correctly identified	9.10 (2.13)	7.66 (2.37)
False recognitions	1.14 (0.25)	0.66 (0.09)
Episodic immediate recall (/12)	7.68 (2.08)	5.28 (1.42)
Episodic delayed recall (/12)	6.73 (2.59)	3.32 (1.75)

Figure 4.1a. The Virtual Shop. Image A shows the notepad on the countertop on which items appeared during the encoding phase, after which the cashier would talk to the participant as a filled interference delay. The image B shows a version of the Virtual Shop with the items placed on the shelves and hung to the walls. Finally, the image C shows an item that has been selected by the participant with the remote control.

Figure 4.2b. The Virtual Shop. Image A shows the notepad on the countertop on which items appeared during the encoding phase, after which the cashier would talk to the participant as a filled interference delay. The image B shows a version of the Virtual Shop with the items placed on the shelves and hung to the walls. Finally, the image C shows an item that has been selected by the participant with the remote control.

Figure 4.3c. The Virtual Shop. Image A shows the notepad on the countertop on which items appeared during the encoding phase, after which the cashier would talk to the participant as a filled interference delay. The image B shows a version of the Virtual Shop with the items placed on the shelves and hung to the walls. Finally, the image C shows an item that has been selected by the participant with the remote control.