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# Identification de marqueurs neuropsychologiques précoces dans la maladie d'Alzheimer : trajectoires des changements cognitifs et fonctionnels

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**Résumé**

L'objectif général de cette thèse était de caractériser les trajectoires de déclin cognitif et fonctionnel dans les phases précliniques et précoces de la maladie d'Alzheimer, faisant appel à deux grandes approches: l'étude du trouble cognitif léger dans la maladie d'Alzheimer sporadique et l'étude du phénotype cognitif d'individus porteurs de mutations autosomiques dominantes dans la maladie d'Alzheimer familiale. La thèse comprend 6 articles, dont 4 empiriques. Le premier article (Chapitre II) visait à faire une revue de littérature sur le trouble cognitif léger, son contexte historique, ses critères diagnostiques et les connaissances actuelles dans les domaines cognitif, génétique et de neuroimagerie. L'objectif de la deuxième étude (Chapitre III) visait à caractériser les différents domaines cognitifs (mémoire épisodique, fonctions exécutives, mémoire de travail, traitement visuospatial et langage) et leurs trajectoires dans le temps, chez des personnes avec un trouble cognitif léger, en distinguant celles qui ultérieurement progressent vers une démence, ou progresseurs, et celles qui ne progressent pas vers une démence, ou non-progresseurs. Les résultats indiquent que, chez les progresseurs, les trajectoires de déclin se distinguent selon le domaine cognitif : une fonction quadratique (fonction polynomiale de second degré, qui peut être interprétée comme représentant un plateau suivi d'un déclin accéléré) caractérise le rappel différé en mémoire épisodique et la mémoire de travail/vitesse de traitement de l'information et une fonction linéaire (plus graduelle et progressive) caractérise le rappel immédiat en mémoire, les fonctions exécutives et les habiletés visuospatiales. L'objectif de la troisième étude (Chapitre IV) était de caractériser les trajectoires de déclin des capacités à réaliser les activités de la vie quotidienne instrumentales chez ces mêmes individus ayant un trouble cognitif léger qui ont progressé vers une démence et de comparer ces trajectoires à celles que l'on retrouve chez les individus avec un trouble cognitif

léger n'ayant pas progressé. Les résultats montrent que les capacités autorapportées à réaliser les activités de la vie quotidienne suivent une trajectoire quadratique chez les progresseurs (ont rencontré les critères de démence au cours de l'étude), linéaire chez les déclineurs (ont présenté un déclin cognitif sans rencontrer les critères de démence au cours de l'étude) et n'ont pas changé à travers le temps chez les stables (sont demeurés cognitivement stables au cours de l'étude). Les résultats indiquent que ces patrons peuvent être surtout expliqués par une catégorie d'activités, les activités complexes (p.ex. gérer le budget), qui suivent les mêmes trajectoires. L'objectif du quatrième article (Chapitre V) était de présenter les différentes composantes (génétique, imagerie et cognition) d'un projet de collaboration initié en 2012 entre le Canada et la Chine, ayant pour but d'étudier les phrases précliniques de la maladie d'Alzheimer de type familial. L'objectif de la cinquième étude (Chapitre VI) était d'examiner l'apparition et l'évolution des atteintes cognitives dans la maladie d'Alzheimer de type familial, en distinguant les personnes porteuses de mutations PSEN1 menant à un diagnostic de démence de celles non-porteuses de ces mutations. Les résultats montrent que, chez les porteurs de mutation, le temps estimé au diagnostic suit une trajectoire quadratique pour le rappel différé et la reconnaissance en mémoire épisodique et une trajectoire linéaire pour le rappel immédiat en mémoire, la fluence verbale sémantique/catégorielle et les habiletés visuoconstructives. Enfin, l'objectif de la sixième étude (Chapitre VII) était de présenter les données d'imagerie préliminaires de la cohorte canadienne avec mutations PSEN1, avec une série de cas. Chez les porteurs de mutation, l'amyloïde est un marqueur précoce, significatif même chez les individus non symptomatiques. Le marqueur tau est significatif uniquement près de l'âge estimé du diagnostic chez les porteurs et semble être davantage associé aux déficits cognitifs.

**Abstract**

The main objective of this thesis was to characterize the trajectories of cognitive and functional decline in the preclinical and early stages of Alzheimer's disease, using two methodological approaches: the study of mild cognitive impairment in sporadic Alzheimer's disease and the study of the cognitive phenotype of individuals with autosomal dominant mutations in familial Alzheimer's disease. The thesis comprises 6 articles, 4 of which are empirical.

The first article (Chapter II) aimed to review the literature on mild cognitive impairment, its historical context, its diagnostic criteria and current knowledge in the cognitive, genetic and neuroimaging fields. The objective of the second study (Chapter III) was to characterize the different cognitive domains (episodic memory, executive functions, working memory, visuospatial processing and language) and their trajectories over time, in individuals with mild cognitive impairment, by distinguishing those who progressed to dementia, or progressors, and those that did not progress to dementia, or non-progressors. The results indicate that, in the case of progressors, the trajectories of decline are distinguished according to the cognitive domain: a quadratic function (a plateau followed by an accelerated decline) characterizes the delayed recall in episodic memory and working memory/processing speed and a linear function characterizes immediate recall, executive functions and visuospatial abilities. The objective of the third study (Chapter IV) was to characterize the trajectories of decline in the ability to perform instrumental activities of daily living in these same individuals with mild cognitive impairment who progressed to dementia and to compare these trajectories with those found in individuals with mild cognitive impairment who did not progress. The results show that the self-reported abilities to perform activities of daily living follow a quadratic trajectory in the

progressors (met the dementia criteria during the study), a linear trajectory in the declinors (presented a cognitive decline without meeting the dementia criteria during the course of the study) and did not change over time in the stable (remained cognitively stable during the study). The results indicate that these patterns can be mainly explained by a category of activities, the complex activities (e.g. managing the budget), which follow the same trajectories. The objective of the fourth article (Chapter V) was to present the different components (genetics, imaging and cognition) of a collaborative project initiated in 2012 between Canada and China, aimed at studying the preclinical phases of familial Alzheimer's disease. The objective of the fifth study (Chapter VI) was to examine the onset and course of cognitive impairment in familial Alzheimer's disease, by distinguishing individuals with PSEN1 mutations leading to a diagnosis of dementia from those not carrying these mutations. The results show that, in mutation carriers, the time to the estimated age of onset follows a quadratic trajectory for delayed recall and recognition in episodic memory and a linear trajectory for immediate recall, semantic/categorical verbal fluency and visuospatial abilities. Finally, the objective of the sixth study (Chapter VII) was to present preliminary imaging data for the Canadian cohort with PSEN1 mutations, using a case series. In mutation carriers, amyloid is an early marker, with a significant deposition, even in non-symptomatic individuals. The tau marker is significant only near the estimated age of onset in mutation carriers and appears to be more associated with cognitive deficits.

**Keywords :** Alzheimer's Disease, Mild Cognitive Impairment, Cognitive Trajectories, Activities of Daily Living, Early Markers, Biomarkers

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# Liste des sigles

Aβ : amyloïde-beta

APP : précurseurs à la protéine amyloïde

AVQ : Activités de la vie quotidienne

AVQi : Activités de la vie quotidienne instrumentales

CCFAD: Canada-China Familial Alzheimer's Disease

LCR: liquide céphalo-rachidien

MA : Maladie d'Alzheimer

MAf : Maladie d'Alzheimer de type familial

PSEN1: Presenilin-1

PSEN2: Presenilin-2

TCL: Trouble cognitif léger

*À mon père,*
*Serge.*

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# Chapitre 1 : Contexte théorique

# 1. Introduction Générale

Plus de 24 millions d'individus sont atteints de la maladie d'Alzheimer (MA) à travers le monde (Ballard et al., 2011) et certaines projections estiment que ce nombre augmentera à plus de 80 millions en 2040 (Ferri et al., 2005). L'incidence serait d'environ 30 nouveaux cas par 1000 personnes de 65 ans et plus, par année (Fiest et al., 2016; Kröger et al., 2014). La MA représente un problème de santé publique majeur. Elle est la 6$^e$ cause de décès chez les personnes âgées (Thies, Bleiler, & Alzheimer's, 2013) et elle est associée à des coûts économiques importants. En 2015, les coûts socioéconomiques de cette maladie dans le monde étaient en effet estimés à plus de 167 milliards de dollars (Jia et al., 2018). La MA débute plusieurs années avant le moment où le diagnostic est posé, ce qui limite la capacité à en identifier ses causes et à obtenir une fenêtre thérapeutique appropriée. Il est donc important de trouver un moyen robuste et valide d'identifier cette maladie le plus tôt possible, étant donné qu'un diagnostic précoce permettrait le développement et l'instauration d'interventions plus efficaces (Cavedo et al., 2014). Une façon d'atteindre cet objectif est d'étudier l'apparition et l'histoire naturelle de l'évolution des symptômes cognitifs chez des personnes qui ne satisfont pas encore les critères diagnostiques de la démence, en distinguant ceux qui développeront une MA de ceux qui ne la développeront pas.

L'objectif principal de la thèse est de caractériser la trajectoire du déclin cognitif et fonctionnel qui s'opère dans les années précédant un diagnostic de démence, particulièrement la démence de type Alzheimer. Deux stratégies méthodologiques sont proposées pour atteindre cet objectif. La première stratégie consiste à documenter la progression des symptômes pendant la phase du trouble cognitif léger (TCL), une période pendant laquelle les individus présentent des atteintes cognitives objectives, mais ne satisfont pas les critères de démence, en faisant appel

à un devis longitudinal. La seconde stratégie est de caractériser les atteintes cognitives dans les phases précédant un diagnostic de MA de type familial (MAf), une forme rare qui représente un modèle idéal pour l'étude des phases précoces. En effet, cette forme de la maladie est associée à certaines mutations génétiques: les individus porteurs de ces mutations évoluent invariablement vers un diagnostic de démence. Par conséquent, le génotypage permet d'identifier des personnes qui auront la MA, et ce, de nombreuses années avant l'apparition des premiers symptômes. Il est également possible d'estimer avec une précision relativement bonne le temps avant l'apparition de la maladie en utilisant comme paramètre l'âge de progression du parent porteur de la même mutation. L'application de cette seconde stratégie s'inscrit dans un projet de collaboration internationale entre le Canada et la Chine.

La combinaison de l'histoire naturelle du TCL dans la MA de type sporadique et de l'étude des phases précoces de la MAf nous permettra d'avoir une idée de la façon dont le déclin cognitif s'opère dans les années avant la démence, étant donné que, dans les deux cas, le temps du diagnostic est connu ou estimé.

L'introduction présentera la littérature relative aux principaux éléments qui ont motivé ce travail. La première partie de l'introduction porte sur la MA. Elle présentera les critères diagnostiques de la MA, certains biomarqueurs associés, la définition de la MAf et les critères pour le TCL. La deuxième partie traitera de la progression de la maladie et des études d'histoire naturelle. Enfin, la troisième partie présentera certaines critiques de ces études. Seront ensuite présentés les objectifs généraux de la thèse, ainsi que les objectifs et hypothèses rattachés à chacun des six articles que comprend la thèse (voir également un article relié au travail qui sera présenté en annexe). Dans un premier temps, nous présenterons un article de revue qui permettra d'établir le contexte historique et les connaissances actuelles du concept de TCL (Article 1).

Puis, nous caractériserons les trajectoires du déclin cognitif (Article 2) et fonctionnel (Article 3) dans les années précédant un diagnostic de MA chez une cohorte d'individus avec un TCL. Nous présenterons le projet de collaboration internationale Canada-Chine qui vise à étudier la MAf (Article 4) et les données neuropsychologiques en fonction du temps estimé au diagnostic (article 5), ainsi que des données préliminaires d'imagerie cérébrale (article 6) de la cohorte canadienne d'individus avec mutations causant la MAf.

## 2. Maladie d'Alzheimer

### 2.1 Critères diagnostiques de la maladie d'Alzheimer

La MA présente un début insidieux et est généralement caractérisée par des difficultés en mémoire, manifestées, entre autres, par des oublis fréquents, par des répétitions dans les questions et les conversations et par l'égarement d'objets (Goldman, 2015). Jusqu'à très récemment, les cliniciens se basaient sur les critères du Diagnostic and Statistical Manual of Mental Disorders IV (American Psychiatric Association. & American Psychiatric Association. Task Force on DSM-IV., 2000) pour établir le diagnostic. Ces critères renvoyaient à 1) une altération de la mémoire et d'au moins un autre domaine cognitif (aphasie, apraxie, agnosie ou perturbations des fonctions exécutives); 2) une altération significative du fonctionnement social ou professionnel; 3) un début progressif et un déclin cognitif continu 4) Les déficits cognitifs ne doivent pas être dus à d'autres affections; 5) et ne doivent pas survenir de façon exclusive au cours de l'évolution d'un syndrome confusionnel. 6) Enfin, la perturbation ne peut pas être expliquée par des troubles de l'Axe 1.

Les nouveaux critères du DSM-V (American Psychiatric Association. & American Psychiatric Association. DSM-5 Task Force., 2013) mettent une plus grande importance sur le déclin par rapport au déficit de la fonction. Ils mettent également un moins grand accent sur le

trouble de mémoire, ce qui permet d'inclure des cas plus atypiques qui commencent, par exemple, avec un trouble de langage.

Le National Institute on Aging-Alzheimer's Association, aux États-Unis (NIA-AA) a proposé des recommandations pour le diagnostic d'Alzheimer probable (McKhann et al., 2011). Outre les critères cliniques communs à toutes les démences, il est proposé qu'un diagnostic de MA probable ne peut être établi que sur la base des critères suivants: 1) un début insidieux; 2) un historique clair d'aggravation de la cognition, rapporté ou observé; 3) des déficits cognitifs évidents, selon différents types de présentations (amnésique, langage, habiletés visuospatiales ou fonctions exécutives). La présentation amnésique est la forme la plus commune et est caractérisée par des déficits importants d'apprentissage et de rappel d'informations récentes, accompagnés de déficits dans au moins un autre domaine cognitif. En plus des critères cliniques, le NIA-AA avait également proposé des critères pour la recherche qui incorporent des biomarqueurs et des évidences de pathologies amyloïde et tau.

## 2.2 Maladie d'Alzheimer, amyloïde, Tau et biomarqueurs

L'amyloïde-beta (Aβ) est un peptide (polymère d'acides aminés) produit par protéolyse à partir de la protéine précurseure de l'amyloïde (APP). La déposition et l'accumulation d'oligomères Aβ sous forme de plaques sont un marqueur précoce de la MA et l'hypothèse de la cascade amyloïde, qui propose qu'un déséquilibre entre la production d'Aβ et son élimination soit le mécanisme central de la pathogenèse de la MA, demeure l'hypothèse dominante dans le domaine (Blennow, Mattsson, Scholl, Hansson, & Zetterberg, 2015). Ce déséquilibre se produirait différemment, selon qu'il s'opère dans la MA de type sporadique ou familial. Les mutations génétiques associées à la forme familiale, autosomique-dominante et à début précoce, causeraient, par différents mécanismes, une surproduction d'Aβ tout au long de la vie des

porteurs des mutations (Bateman et al., 2011; Citron et al., 1992). Dans le type sporadique, il s'agirait davantage d'un déficit à éliminer l'Aβ de façon efficace (Hardy, 2009).

L'accumulation de protéine tau anormalement phosphorylée dans les neurones est un autre marqueur de la MA (James, Doraiswamy, & Borges-Neto, 2015). Cette accumulation génère des amas neurofibrillaires avec filaments introduisant une dégénérescence neuronale (Scholl et al., 2016). Les hypothèses amyloïde et Tau ont été largement investiguées de façon indépendante et l'importance accordée à chacune par rapport à leur contribution dans le processus pathologique de la MA a varié selon les auteurs et selon les études (Ittner & Gotz, 2011). Le paradigme actuel semble accorder plus d'importance à l'interaction entre ces deux protéines caractéristiques de la MA. Ces modes d'interaction (Ittner & Gotz, 2011) incluent une augmentation de la pathologie tau par l'Aβ (Gotz, Chen, van Dorpe, & Nitsch, 2001), une médiation de la toxicité Aβ par la protéine tau (Rapoport, Dawson, Binder, Vitek, & Ferreira, 2002) ou encore des effets toxiques synergiques des deux pathologies (Querfurth & LaFerla, 2010).

Plusieurs essais cliniques dans les dernières années ciblant l'Aβ (Blennow, Hampel, & Zetterberg, 2014) ont échoué à montrer des effets significatifs pour ralentir ou arrêter la progression de la maladie (Doody, Farlow, Aisen, Alzheimer's Disease Cooperative Study Data, & Publication, 2014; Doody, Thomas, et al., 2014; Salloway et al., 2014). Une des raisons qui pourrait expliquer pourquoi les essais pharmaceutiques ciblant l'Aβ se sont montrés inefficaces est le fait que les participants recrutés ont souvent déjà un diagnostic de démence, ce qui pourrait être trop tardif dans le continuum de la MA (Blennow et al., 2015; Selkoe & Hardy, 2016). L'identification de biomarqueurs et de marqueurs neuropsychologiques précoces qui permettent de distinguer les individus qui progresseront vers un diagnostic de MA de ceux qui ne

progresseront pas est importante, puisqu'advenant un traitement éventuel, celui-ci devrait être administré plusieurs années avant que la maladie ait eu le temps de causer des dommages entraînant l'apparition des symptômes cliniques de la démence. Un biomarqueur est un indicateur objectivement mesuré permettant d'évaluer des processus biologiques normaux ou pathologiques ou encore des réponses pharmacologiques suivant des interventions thérapeutiques (Biomarkers Definitions Working, 2001).

Plus récemment, le NIA-AA a proposé un système de classification pour la MA, strictement basé sur les biomarqueurs associés à la maladie (Jack et al., 2018). Le système A/T/N proposé par le NIA-AA inclut 7 biomarqueurs divisés en 3 catégories : Amyloïde (amyloïde TEP, $A\beta_{42}$ du liquide céphalo-rachidien (LCR)), Tau (LCR phospho tau, TEP tau) et Neurodégénération ($[^{18}F]$-fluorodeoxyglucose-TEP, IRM structurelle et LCR tau total) (Jack et al., 2016). Ce système est descriptif et ne se veut pas un système de classification diagnostique.

Cette définition biologique de la MA est controversée. Certains auteurs avancent que plusieurs facteurs pathologiques ne sont pas inclus dans cette définition, mais contribuent pourtant de façon significative à la MA. Il s'agit notamment des changements vasculaires, de la pathologie à corps de Lewy et de la neuroinflammation (Gauthier, Zhang, Ng, Pascoal, & Rosa-Neto, 2018; Sweeney et al., 2019). De plus, étant une définition strictement biologique, la sphère clinique et les changements cognitifs ne sont pas considérés. Or, les tests cognitifs ont été démontrés comme étant de très bons prédicteurs de progression future dans le TCL (Belleville et al., 2017) et le tableau cognitif permet souvent d'établir un diagnostic différentiel entre la MA et les autres types de démence.

### 2.3. Tableau cognitif de la maladie d'Alzheimer

Du point de vue neuropathologique, les premiers changements dans la MA commenceraient dans les structures temporales médianes (hippocampes, cortex entorhinal), avant de toucher les aires associatives des lobes temporaux, frontaux et pariétaux. L'évaluation neuropsychologique reflète ce modèle de progression neuropathologique: la mémoire épisodique (associée aux structures médianes des lobes temporaux) est typiquement le premier domaine atteint dans la MA (D. Salmon, 2000), suivi par la mémoire sémantique (Chan, Salmon, Nordin, Murphy, & Razani, 1998) et les fonctions exécutives (Lefleche & Albert, 1995; Perry & Hodges, 1999; D. P. Salmon & Bondi, 2009). Le contrôle attentionnel serait également touché dans des phases très précoces comme le TCL (Belleville, Chertkow, & Gauthier, 2007). Avec la progression de la maladie, tous les domaines cognitifs finiraient pas être atteints (Braak & Braak, 1991; D. P. Salmon & Bondi, 2009).

### 2.4. Maladie d'Alzheimer de type familial

Sur le plan génétique, la plupart des cas de MA correspondent à la forme sporadique, c'est-à-dire qu'ils ne sont pas associés à des mutations génétiques identifiées comme facteurs causant la maladie. En revanche, la forme familiale de la MA, bien que très rare, est associée à des mutations génétiques sur les trois gènes suivants: presenilin 1 (PSEN1), presenilin 2 (PSEN2) et le précurseur à la protéine amyloïde (APP) (Lleo et al., 2002). Contrairement aux autres mutations génétiques ayant été identifiées comme augmentant le risque de développer une MA (Bettens, Sleegers, & Van Broeckhoven, 2013), tels que les porteurs de l'allèle e4 de l'Apolipoprotéine E (APOE ; (Mullan et al., 1996)), les mutations associées à la MAf présentent une transmission autosomique dominante, avec une pénétrance très élevée (de 95% pour PSEN2 à 100% à 65 ans pour PSEN1 ; (Bird, 2012)). La plus grande proportion des cas de MAf est

attribuée aux mutations associées à PSEN1, les formes causées par des mutations sur PSEN2 étant les plus rares (moins de 5 % des cas ; (Bird, 2012). Ces trois gènes sont d'ailleurs impliqués directement ou indirectement dans la production d'Aβ (Bettens et al., 2013) et supporte donc l'hypothèse amyloïde dans la MA (Beyreuther & Masters, 1991; Hardy & Allsop, 1991; Hardy & Selkoe, 2002; Jack et al., 2010).

L'Alzheimer de type familial représente moins de 1% de tous les cas de démence de type Alzheimer (Bekris, Yu, Bird, & Tsuang, 2010; Campion et al., 1999). Malgré cette faible prévalence, les familles avec cette forme familiale de la MA représentent une population idéale pour l'étude des phases précoces de la démence (Bateman et al., 2011; Dubois et al., 2016). Tout d'abord, la certitude du diagnostic permet d'étudier le tableau cognitif et d'intervenir bien avant l'apparition des premiers symptômes.

Ensuite, la connaissance de l'âge auquel le parent a reçu son diagnostic permet d'estimer l'âge auquel le participant convertira vers la MA. En effet, il existe une forte concordance entre l'âge prédit sur la base de l'âge du diagnostic du parent et l'âge effectif du diagnostic (Ryman et al., 2014). Par ailleurs, la MAf est connue comme étant d'apparition précoce, moins de 60 ans pour la plupart et aussi jeunes que dans la mi-vingtaine pour certains (Bateman et al., 2011; Snider et al., 2005). La présence de comorbidité avec d'autres conditions médicales est moindre qu'elle ne l'est chez les patients atteints de la forme sporadique. Or, la présence de comorbidité pourrait expliquer certains des déficits cognitifs, ce qui en complique leur interprétation (Doraiswamy, Leon, Cummings, Marin, & Neumann, 2002). Toutefois, une distinction doit être faite entre la MAf et la MA sporadique à début précoce. Cette dernière est généralement associée à une présentation atypique et non amnésique, avec des déficits attentionnels/exécutifs,

visuospatiaux ou langagiers (Joshi, Ringman, Lee, Juarez, & Mendez, 2012), ce qui n'est généralement pas le cas pour la MAf .

Finalement, les résultats obtenus dans l'étude de la forme familiale peuvent être transférés au type sporadique. La MA de type familial présente effectivement un décours semblable au type sporadique: au niveau des biomarqueurs, dans les deux cas sont retrouvés une atrophie hippocampique, une perte corticale temporo-pariétale, un hypométabolisme pariétal temporal, la présence de plaques amyloïde et d'enchevêtrements neurofibrillaires, une augmentation du marqueur $A\beta_{42}$ et une diminution du marqueur tau dans le LCR (Bateman et al., 2011; Shepherd, McCann, & Halliday, 2009).

**2.5. Trouble cognitif léger**

Le TCL a été initialement conceptualisé par un groupe de recherche de New York en 1991 à partir de l'échelle de détérioration globale (*Global Deterioration Scale;* GDS ; (Flicker, Ferris, & Reisberg, 1991; Gerstenecker & Mast, 2014), afin d'étudier les patrons cognitifs et le déclin présents dans les années précédant le début de la démence.

Le TCL est défini comme un déclin cognitif plus important que celui qui serait attendu chez un individu d'un certain âge et d'un certain niveau d'éducation, mais qui n'interfère pas avec les activités de la vie quotidienne (AVQ) (Gauthier et al., 2006). Il est conceptualisé comme la phase prodromique de la démence. Les critères cliniques de ce trouble sont les suivants (Winblad et al., 2004): (1) un début insidieux; (2) une plainte de mémoire; (3) une atteinte de la mémoire c'est-à-dire une performance dans des tâches objectives se trouvant en dessous d'1,5 écart-type de la moyenne par rapport à celle des sujets contrôle de mêmes âges et de mêmes niveaux d'éducation; (4) l'absence d'atteinte de la cognition globale; (5) l'absence d'interférence avec les AVQ; (6) et l'absence de diagnostic de démence.

Le TCL peut être classé en différents sous-types. D'abord, une classification selon la présentation clinique: amnésique (principalement un trouble de mémoire) ou non-amnésique (des difficultés plus saillantes dans un autre domaine cognitif, comme les fonctions exécutives) et ensuite, une classification selon l'étendue des symptômes cognitifs (simple domaine ou multiples domaines (Petersen, Doody, et al., 2001)). Le TCL amnésique serait davantage associé à la MA, ayant un taux de conversion vers ce type de démence plus élevé que le TCL non amnésique (Busse, Hensel, Guhne, Angermeyer, & Riedel-Heller, 2006). De plus, le TCL à multiples domaines apparaît comme étant plus prédictif d'un déclin ultérieur (Abner et al., 2012), ce qui est cohérent avec la conception de ce trouble comme étant un état transitoire entre la cognition normale et la démence, et d'une intensification et d'une diversification des symptômes à travers le temps.

La MA étant un phénomène neurodégénératif avec une augmentation graduelle de la sévérité des symptômes, un déclin significatif de la cognition globale est observé (Burns, Jacoby, & Levy, 1991; Yesavage, Poulsen, Sheikh, & Tanke, 1988), mais ce déclin ne suit pas nécessairement une trajectoire linéaire et homogène: il peut présenter un patron quadratique avec des phases plus lentes en début et en fin d'évolution (R. G. Stern et al., 1994), ou encore être modulé par un ensemble de facteurs, comme l'association avec des symptômes psychotiques (Wilkosz et al., 2010), ou avec l'éducation (Roe, Xiong, Miller, & Morris, 2007; Scarmeas, Albert, Manly, & Stern, 2006).

La grande majorité des études longitudinales sur le TCL sont des études de prédiction: elles cherchent à établir les facteurs/tests neuropsychologiques qui sont les plus prédictifs d'une future progression vers un diagnostic de démence (Ahmed, Mitchell, Arnold, Nestor, & Hodges, 2008; Belleville et al., 2017; Fellows, Bergman, Wolfson, & Chertkow, 2008; Mura et al., 2014;

Ritchie & Tuokko, 2010; Yaffe, Petersen, Lindquist, Kramer, & Miller, 2006). Les études d'histoire naturelle diffèrent de ces études de prédiction, car elles ont pour objectif de caractériser et de décrire en détail les symptômes d'une maladie, par le biais du suivi longitudinal d'une cohorte clinique où l'évaluation de la cognition est répétée.

## 3. Études d'histoire naturelle

### 3.1. Caractérisation et trajectoires des changements cognitifs dans le trouble cognitif léger

Le suivi d'une cohorte de participants avec TCL permet d'étudier la trajectoire des symptômes de leur apparition à leur évolution. Peu d'études ont évalué l'histoire naturelle des symptômes cognitifs dans le TCL. Ces études rapportent une certaine variabilité de déclin d'un domaine cognitif à un autre. Par exemple, Wilson et al. (2010) ont comparé les taux de déclin de personnes avec MA, TCL et cognition normale sur une période de 11 ans, en utilisant une mesure globale de la cognition. Ils ont trouvé que les patients MA déclinent plus rapidement que les individus TCL, et que ces derniers déclinent également plus rapidement que les personnes âgées en santé.

Dans une autre étude, Bennett et al. (2002) ont examiné le déclin cognitif en mesurant différents domaines cognitifs. Ils ont évalué le déclin sur une période de 7 ans dans un groupe de personnes âgées en santé et dans un groupe de personnes avec TCL. Leurs résultats mettent en évidence que les individus avec TCL avaient une performance significativement plus basse à l'entrée de l'étude et ont présenté un déclin cognitif accéléré par rapport aux personnes âgées en santé. De plus, ils ont noté que tous les domaines cognitifs ne présentaient pas un déclin similaire. Les individus avec TCL déclinaient plus rapidement que les personnes âgées en santé

au niveau de la mémoire épisodique, de la mémoire sémantique et de la vitesse perceptuelle alors que leur taux de déclin était similaire au niveau de la mémoire de travail et des habiletés visuospatiales.

Les études d'histoire naturelle ont généralement supposé que le déclin s'opère de manière linéaire. Toutefois, il est possible qu'il soit plutôt caractérisé par des trajectoires plus complexes, avec la présence de plateaux et d'accélération du déclin. Ces questions seront abordées dans l'article 2.

**3.2. Caractérisation et trajectoires des changements fonctionnels dans le trouble cognitif léger**

Tel qu'indiqué dans les critères du TCL, il s'agit d'une classification pour caractériser les individus dont la performance lors de tests neuropsychologiques est considérée comme anormale selon l'âge et le niveau d'éducation, mais qui ne satisfont pas les critères diagnostiques pour une démence, étant donné que leurs déficits ne seraient pas assez sévères pour interférer de façon significative avec le fonctionnement au quotidien (Gauthier et al., 2006; Petersen, Stevens, et al., 2001; Sperling et al., 2011). Toutefois, la MA est une maladie progressive et, au fur et à mesure que les déficits cognitifs s'accumulent, les patients pourraient présenter de plus en plus de difficultés à réaliser les AVQ, particulièrement les activités instrumentales (AVQi), comme gérer les finances, utiliser un téléphone ou faire la cuisine, puisqu'il s'agit d'activités considérées plus complexes et requérant donc des compétences plus avancées (Pedretti, Pendleton, & Schultz-Krohn, 2006). L'étude des trajectoires des capacités fonctionnelles est donc importante, puisque ces difficultés sont susceptibles de s'accumuler avant le diagnostic de démence.

Certaines études semblent montrer que les individus avec un TCL sont significativement plus atteints dans leur capacité à compléter les AVQi que les personnes âgées saines (Gold, 2012). Comparativement aux contrôles, les individus avec un TCL pourraient avoir davantage de difficultés à compléter certaines AVQi reliées au fonctionnement frontal/exécutif, comme suivre leurs rendez-vous ou gérer leurs biens personnels (Ahn et al., 2009). Même lorsque le score de performance dans des échelles évaluant le fonctionnement au quotidien est similaire entre les sujets contrôle et les individus avec un TCL, des difficultés subtiles, mais significatives, sont observées chez les participants TCL, comme une vitesse d'exécution plus ralentie dans l'utilisation du téléphone ou dans la gestion des médicaments (Wadley, Okonkwo, Crowe, & Ross-Meadows, 2008). Des changements subtils dans les habiletés à réaliser des AVQi ont été relevés jusqu'à 10 ans avant le diagnostic de démence (Peres et al., 2008).

Des difficultés exécutives, qui renvoient notamment aux comportements orientés vers un but, sont associées aux difficultés à réaliser les AVQi dans les premiers stades de la démence (démence légère) (Cahn-Weiner, Boyle, & Malloy, 2002; Jefferson, Paul, Ozonoff, & Cohen, 2006; Marshall et al., 2011; Martyr & Clare, 2012). Des difficultés similaires pourraient survenir dans le TCL, étant donné que les fonctions exécutives sont souvent déjà touchées pendant cette phase (Clement, Gauthier, & Belleville, 2013; Johns et al., 2012; Rainville, Lepage, Gauthier, Kergoat, & Belleville, 2012).

Étant donné que les capacités à réaliser de façon efficace les AVQi semblent être atteintes tôt et indiquer un déclin futur, il serait important de connaître le moment où ces difficultés surviennent. Il serait aussi important de décrire leurs trajectoires à travers le temps, étant donné qu'un changement est souvent un marqueur de déclin futur plus sensible que des déficits évalués à un seul moment. Peu d'études longitudinales se sont intéressées aux

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trajectoires de changements pour les AVQi dans les années précédant le diagnostic de démence. Donc, on connait peu la façon dont ces atteintes évoluent et changent dans les phases prédémentielles comme le TCL. Comme pour les études d'histoire naturelle sur la cognition dans le TCL, des modèles plus complexes que le déclin linéaire n'ont pas été examinés. Aucune étude, à notre connaissance, n'a rapporté l'histoire naturelle du déclin au niveau des AVQi pour une cohorte clinique d'individus avec TCL, selon qu'ils progressent ou non vers un diagnostic de démence. Cette question sera abordée dans l'article 3.

### 3.3. Contribution des études de la maladie d'Alzheimer de type familial dans la caractérisation des phrases précoces

La MAf étant rare, très peu d'études ont caractérisé les atteintes cognitives de cette forme, et notamment celles présentes dans sa phase préclinique. L'étude de Newman, Warrington, Kennedy, and Rossor (1994) est l'une des premières à avoir évalué le profil cognitif d'un individu avec mutations causant la MAf, avant l'apparition des symptômes cliniques de démence. Ces auteurs ont suivi de façon longitudinale une femme avec mutation sur l'APP. Ils l'ont évaluée à trois reprises à 7 ou 8 mois d'intervalle, en utilisant une batterie comprenant des mesures verbales, de lecture, de reconnaissance, de dénomination, d'épellation, d'habiletés visuospatiales, d'arithmétique, de vitesse et d'abstraction. Lors de la 3ᵉ évaluation, la participante avait un score normal (29/30) au *Mini-Mental State Evaluation* (MMSE). Pourtant, dès la 1ʳᵉ évaluation, un déficit relatif en mémoire verbale était observé et le suivi a mis en évidence un déclin progressif en mémoire spatiale. Le langage et les habiletés de lectures sont demeurés stables.

De même, une autre étude d'histoire naturelle des symptômes cognitifs chez des personnes atteintes de la forme familiale a rapporté une préservation des habiletés de lecture et

d'orthographe, alors que la mémoire et l'intelligence générale étaient les domaines les plus précocement atteints, avant même le diagnostic de démence (Godbolt et al., 2004). Une étude prospective d'une durée de 6 ans comprenant 63 individus à risque de développer une MA par transmission autosomique dominante avait rapporté également des résultats similaires (Fox, Warrington, Seiffer, Agnew, & Rossor, 1998). Les participants qui avaient progressé vers la MA présentaient une performance initiale significativement plus faible en mémoire verbale et des tests de vitesse et d'habiletés perceptives. Par ailleurs, une autre étude suggère que les premiers signes de la MAf pourraient être une plainte subjective de mémoire (Ardila et al., 2000).

Swearer, O'Donnell, Drachman, and Woodward (1992) ont évalué les aspects neuropsychologiques de la MAf et ont voulu savoir si, malgré une étiologie différente, les deux formes de la MA (sporadique et familiale) présentent un profil neuropsychologique semblable. Pour cela, ils ont comparé un groupe de 7 patients issus de deux familles connues avec une MAf, un groupe de 23 patients avez une MA de type sporadique et deux groupes contrôles, appariés au niveau de l'âge et du niveau d'éducation (28 contrôles pour comparaison avec les patients de type familial et 59 pour comparaison avec les patients de type sporadique). Ils ont trouvé que les deux formes de la MA présentaient un profil similaire d'atteintes cognitives : des déficits importants en vitesse psychomotrice et en rappel différé pour du matériel verbal et des déficits légers à modérés en attention et en langage.

Malgré une grande similitude dans la présentation clinique des deux formes (Godbolt et al., 2004; Ringman et al., 2005), certaines études rapportent des différences par rapport aux atteintes cognitives entre la MAf et la MA de type sporadique. Par exemple, il a été rapporté que les patients avec MA de type sporadique sont significativement plus atteints en

dénomination et en reconnaissance d'objets alors que les patients avec la forme familiale présentent un déficit plus important en intelligence verbale (Warrington, Agnew, Kennedy, & Rossor, 2001). Les personnes avec MAf auraient une performance significativement plus faible au niveau des capacités visuospatiales, attentionnelles et exécutives que ceux avec une MA sporadique (Smits et al., 2012).

Des études plus récentes semblent indiquer que des déficits d'association en mémoire à court terme pourraient être un marqueur sensible de la MAf, et ce, même chez les porteurs de mutations asymptomatiques (Liang et al., 2016; Parra, Abrahams, Logie, & Della Sala, 2010; Parra et al., 2015).

Il est à noter toutefois que toutes ces études ont pour limite majeure un très petit échantillon de patients souffrant de la forme familiale. En effet, la MAf étant rare et les cas étant dispersés géographiquement, il est difficile pour une seule institution de recherche d'étudier la validité des marqueurs neuropsychologiques et des biomarqueurs de cette population en ayant un assez grand nombre de sujets. L'initiative du *Dominantly Inherited Alzheimer Network* (DIAN) a permis de répondre à ce problème de recrutement. DIAN est une étude longitudinale et multicentrique, de collaboration internationale, qui a comme objectif de développer une cohorte de patients avec une MA de type familial afin d'en étudier les biomarqueurs précoces (Morris et al., 2012). Le réseau comprend des groupes de recherche en Australie, en Europe et aux États-Unis.

Les groupes qui souhaitent contribuer à la cohorte doivent adopter une procédure standard développée par DIAN: 1) Une évaluation clinique pour établir le patron cognitif, 2) Une évaluation cognitive qui combine des tests papier-crayon obligatoires et des tests informatisés, facultatifs (Simon's Task, alternance et catégorisation) 3) une prise de sang pour

le génotypage et la collecte des biomarqueurs sanguins, 4) une ponction lombaire pour la collecte des biomarqueurs du LCR, 5) de l'imagerie, qui comprend de l'imagerie par résonance magnétique (IRM) structurelle et fonctionnelle, de la tomographie par émission de positrons avec traceurs FDG et PIB (FDG-PET et PET-PIB) et 6) une autopsie du cerveau suivant le décès des participants.

Cette initiative a permis d'établir une chronologie au niveau de l'apparition des biomarqueurs et des symptômes, qui vient appuyer le modèle de Jack et al. (2010). Environ 25 ans avant l'âge du diagnostic estimé, une diminution de la concentration de $A\beta_{42}$ dans le LCR est observée. Quinze ans avant le diagnostic estimé, il est possible de détecter une accumulation d'$A\beta$, ce qui serait suivi peu de temps après (10 ans avant le diagnostic prédit) par une baisse du métabolisme et une atteinte de la mémoire épisodique. Cette atteinte s'aggraverait avec le temps et des difficultés de cognition globale (MMSE, CDR) seraient détectées environ 5 ans avant l'âge prédit de conversion vers la maladie. Le diagnostic survient en moyenne 3 ans après l'âge prédit, ce qui témoigne que l'âge estimé est une mesure assez précise du moment où les patients convertiront vers la démence (Bateman et al., 2012). Cette étude a donc permis d'établir des patrons de déclin cognitif dans les phases précoces dans les domaines de la mémoire et de la cognition globale, mais d'autres domaines cognitifs plus subtils, comme les habiletés visuospatiales ou les fonctions exécutives, n'ont pas été rapportés.

De façon plus précise par rapport au déclin cognitif observé dans la cohorte de DIAN, les participants non porteurs des mutations, mais issus de familles avec une forme familiale de MA sont demeurés stables sur l'ensemble des fonctions cognitives de 30 ans avant à 20 après l'âge estimé du diagnostic (Bateman et al., 2012). Storandt, Balota, Aschenbrenner, and Morris (2014) ont décrit plus en détail les caractéristiques cliniques et cognitives de la cohorte DIAN

lors de l'entrée dans l'étude: 249 participants séparés en trois groupes selon qu'ils soient non-porteurs, porteurs sains et porteurs avec TCL. Une interaction significative groupe x temps dans des mesures de mémoire logique, de temps de réponse (Simon Task) et de mémoire de travail/vitesse perceptive (*Digit Symbol*) a été mise en évidence chez les porteurs de mutations: plus un individu est proche de son âge estimé de diagnostic, plus sa performance est altérée à ces mesures. De plus, en comparant les non-porteurs avec les porteurs sains (sans diagnostic de démence ou même de TCL), la performance des porteurs de mutations était significativement plus faible dans des tâches de catégorisation et de mémoire logique. Les porteurs de mutations seraient plus vulnérables que les non-porteurs, notamment en mémoire épisodique. Cependant, cette vulnérabilité pourrait refléter des faiblesses qui ont toujours été présentes ou encore pourrait être reliée à d'autres facteurs liés au style de vie par exemple.

## 4. Critique des études d'histoire naturelle dans les phases précoces de la maladie d'Alzheimer

Dans la MA sporadique, le peu d'études qui se sont intéressées aux trajectoires de changements cognitifs et fonctionnels dans le TCL montre que ce ne sont pas tous les individus avec TCL qui progressent vers une démence. Or, aucune étude n'a encore examiné l'histoire naturelle des symptômes cognitifs en prenant en compte la présence ou l'absence d'une future progression vers la démence. En distinguant le TCL en fonction du déclin futur, il serait possible de caractériser l'histoire naturelle des phases prédémentielles. De plus, la comparaison du déclin chez ces personnes (progresseurs) avec celui des personnes qui ne progressent pas vers la démence (non-progresseurs) pourrait permettre de recueillir des informations pertinentes et complémentaires. Les non-progresseurs pourraient présenter un déclin moins important que les

progresseurs, demeurer stables, ou présenter une amélioration de leur performance à certaines tâches cognitives.

Une autre limite de ces études est d'avoir utilisé des mesures globales ou des scores composites pour mesurer la cognition, ce qui empêche d'examiner des domaines cognitifs plus subtils. De ce fait, peu d'informations nous renseignent sur l'évolution des déficits mnésiques et sur l'apparition de déficits non mnésiques (par ex. fonctions exécutives, langage) sur le continuum qui s'étend du TCL à la démence. En étudiant l'apparition et la progression de ces différents déficits cognitifs, il devrait être possible de vérifier l'hypothèse de certains auteurs suggérant que le début de démence surviendrait principalement avec l'apparition de déficits exécutifs (Belleville, Fouquet, Duchesne, Collins, & Hudon, 2014; Saunders & Summers, 2010, 2011).

De plus, l'une des principales limites de ces études est l'impossibilité de sélectionner des patients au début de l'apparition de la maladie, car la MA demeure silencieuse par rapport aux symptômes cognitifs pendant une longue période de temps et aucun biomarqueur connu ne permet de la diagnostiquer à son début. Ainsi, dans ces études d'histoire naturelle, la date de recrutement des participants est généralement choisie comme le premier temps de l'étude. Ce premier temps où les participants consultent est extrêmement variable au cours de l'évolution de la maladie et peut dépendre d'un ensemble de facteurs qui ne sont pas nécessairement reliés aux facteurs intrinsèques de la maladie comme l'accès au service, le degré d'inquiétude face aux symptômes ou encore la présence ou non d'un support familial. Par conséquent, tous les participants ne se situent pas au même point dans la progression de la maladie au moment du recrutement. Une manière de contrer partiellement ce problème est de définir l'année où les participants reçoivent leur diagnostic comme le temps zéro plutôt que l'année d'entrée dans

l'étude afin de décrire les trajectoires de déclin précédant la démence. Une telle approche a été adoptée dans des études longitudinales de cohortes de personnes âgées. Dans une étude d'Amieva et al. (2005), la performance cognitive d'une de ces cohortes a été analysée sur une période de 9 ans précédent un diagnostic de démence. Les auteurs ont montré que les individus qui progressent vers une démence présentent déjà une performance cognitive basse à l'entrée dans l'étude et un déclin accéléré à certains tests cognitifs, 3 ans avant le diagnostic de MA.

La majorité des études s'intéressant à l'histoire naturelle de la MA supposent que le déclin cognitif serait linéaire. Ici, au contraire, nous faisons l'hypothèse que certains domaines cognitifs seraient caractérisés par une période de stabilité suivie d'un déclin accéléré (un patron qui serait modélisé par une fonction quadratique). Ce type de fonction de déclin peut être mis en évidence en faisant appel à des modèles polynomiaux. Les régressions polynomiales permettent en effet de tester, outre la fonction linéaire, un ensemble de modèles complexes, comme les fonctions quadratique et cubique.

D'ailleurs, tout comme celles qui ont porté sur la MA sporadique, les études qui ont caractérisé les atteintes cognitives dans les phases précoces de la MA de type familial ont en commun de prendre pour acquis que le déclin cognitif est linéaire et n'ont pas investigué des modèles plus complexes pour représenter la façon dont les symptômes évoluent dans les années précédant le diagnostic de démence. Certains domaines cognitifs pourraient demeurer stables de nombreuses années avant de présenter un déclin rapide, alors que d'autres pourraient présenter des atteintes précoces et décliner de façon graduelle. De plus, DIAN inclut des centres de recherche en Australie, en Europe et aux États-Unis. Il y avait donc un besoin pour une approche similaire au Canada et en Chine. Le projet Canada-China Familial Alzheimer's Disease (CCFAD) est un programme de recherche de collaboration internationale entre le Canada et la

Chine, financé par les Instituts de Recherche en Santé du Canada et par la Fondation Nationale de Science Naturelle de Chine, depuis 2012. Il a pour but de constituer un registre de participants issus de familles avec mutations connues pour la MAf dans les 2 pays, afin de faciliter le recrutement. Une partie des travaux de cette thèse avait pour objectif d'élaborer une batterie d'évaluation cognitive pour ce projet (Article 4) et de procéder à l'évaluation neuropsychologique de la cohorte canadienne (Article 5).

## 5. Objectifs et hypothèses de recherche

En résumé, divers éléments majeurs ressortent de la revue de littérature qui précède et soutiennent le présent travail. D'abord, même si la MA commence plusieurs années avant le diagnostic, on connaît peu sur l'histoire naturelle de la phase prodromique de la maladie. Les études de prédiction ont permis d'identifier les domaines cognitifs qui sont atteints précocement telles que la mémoire épisodique, la mémoire de travail et les fonctions exécutives. Les études d'histoire naturelle en revanche sont rares et présentent certaines limites. Elles utilisent rarement des mesures fines de la cognition. Elles ne considèrent pas des modèles plus complexes que les modèles linéaires qui pourraient pourtant mieux décrire le déclin qui s'opère dans cette période prodromique. Ensuite, dans le type familial, l'identification de mutations génétiques comme facteurs menant à un diagnostic permet de distinguer avec précision les progresseurs des non-progresseurs, plusieurs années avant même la présence de symptômes cognitifs ou de biomarqueurs. Là encore, les études sont rares particulièrement celles qui portent sur l'histoire naturelle, les centres du Canada et plus précisément du Québec ne sont pas bien représentés dans les grandes études de cohortes comme DIAN, et des modèles plus complexes que les modèles linéaires pourraient rendre compte des processus de déclin qui s'opèrent dans les années qui précèdent le diagnostic de démence. Cette thèse se propose donc de contribuer à ces questions

à l'aide des six articles décrits ci-dessous dont quatre sont des articles empiriques. Nous présentons plus bas les objectifs des six articles présentés dans cette thèse, ainsi que les hypothèses pour les quatre articles empiriques.

### 5.1 Article 1: Mild Cognitive Impairment

*Objectifs.* L'objectif de ce premier article est de faire une revue de littérature sur le TCL, son contexte historique, ses critères diagnostiques et les connaissances actuelles dans les domaines cognitif, génétique et de neuroimagerie. Il s'agit également de présenter brièvement les études de prédiction, de prévention et d'intervention chez les individus avec un TCL.

### 5.2 Article 2: Patterns of Cognitive Decline Prior to Dementia in Persons with Mild Cognitive Impairment

*Objectifs.* L'objectif de cet article empirique est de caractériser différents domaines cognitifs (mémoire épisodique, fonctions exécutives, mémoire de travail, traitement visuospatial et langage) et leurs trajectoires dans le temps chez des personnes avec TCL, en distinguant celles qui ultérieurement progressent vers une démence ou progresseurs et celles qui ne progressent pas vers une démence ou non-progresseurs.

*Hypothèses.*

1) Pendant le stade prodromique de la MA, les progresseurs présenteront un déclin cognitif dans un ou plusieurs domaines cognitifs alors que les non-progresseurs devraient demeurer stables sur l'ensemble des domaines cognitifs.

2) Chez les progresseurs, les différents domaines cognitifs présenteront divers types de trajectoires de déclin pendant le stade prodromique de la MA : le déclin de certains domaines cognitifs sera modélisé par une fonction linéaire, mais d'autres domaines auront un patron de déclin de type quadratique et/ou cubique.

3) Il n'est pas possible sur la base de la littérature actuelle de prédire précisément le type de patron attendu pour chaque domaine cognitif. Toutefois, comme certains auteurs croient que l'entrée dans la démence pourrait résulter du déclin des fonctions exécutives accompagnant le déclin en mémoire, il est possible que ces domaines suivent une trajectoire quadratique, c'est-à-dire qu'ils se caractérisent par des années de performance stable, suivies par une chute importante peu de temps avant le diagnostic de MA. En revanche, les habiletés visuospatiales et le langage pourraient montrer un déclin linéaire, vu qu'une atteinte significative de ces domaines n'est notable que tardivement.

## 5.3. Article 3: Trajectories of Decline on Instrumental Activities of Daily Living Prior to Dementia in Persons with Mild Cognitive Impairment

*Objectifs.* L'objectif de cet article empirique est d'évaluer les trajectoires de déclin des capacités à réaliser AVQi chez des individus avec un TCL ayant progressé vers une démence et de comparer ces trajectoires à celles que l'on retrouve chez des individus avec un TCL n'ayant pas progressé. Un second objectif est de combiner ces informations par rapport aux trajectoires de changements fonctionnels aux changements cognitifs afin d'évaluer si ceci offre un modèle de prédiction sensible de progression vers une démence.

*Hypothèses.*

1) Pendant le stade prodromique de la MA, les progresseurs présenteront un déclin significatif par rapport à leurs capacités à réaliser les AVQi alors que les non-progresseurs devraient demeurer stables sur leurs habiletés à réaliser ces activités.

2) Chez les progresseurs, le déclin de certains sous-domaines sera modélisé par une fonction linéaire, mais d'autres domaines auront un patron de déclin de type quadratique et/ou cubique.

4) La combinaison des performances cognitives et des capacités à réaliser les AVQi devraient offrir un modèle de prédiction ayant une bonne précision diagnostique, particulièrement plus on s'approche du temps de conversion vers la démence chez les progresseurs.

**5.4 Article 4: Perspectives on a Collaborative Canada-China Research Program on Diagnostic Biomarkers for Pre-Dementia Stages of Alzheimer's Disease**

*Objectifs.* L'objectif de cet article méthodologique est de présenter les différentes composantes (génétique, imagerie et cognition) d'une étude multicentrique initiée en 2012 entre le Canada et la Chine, ayant pour but d'étudier les phrases précoces de la MAf.

**5.5 Article 5: Canada-China Familial Alzheimer's Disease (CCFAD): Cognitive Data from the Canadian Cohort with PSEN1 mutations**

*Objectifs.* L'objectif de cette étude empirique est de caractériser l'apparition et l'évolution des atteintes cognitives dans la MA de type familial en distinguant les personnes porteuses de mutations menant à un diagnostic de démence de celles non-porteuses de ces mutations. Les performances seront également évaluées en tenant compte de l'âge estimé de conversion vers la MA chez chacun des porteurs. L'âge estimé correspond à l'âge où le parent a reçu son diagnostic. La distance au diagnostic correspond au nombre d'années entre l'évaluation cognitive et l'âge estimé du diagnostic. Il est possible ainsi de mesurer indirectement l'effet de la distance au diagnostic sur le patron cognitif.

*Hypothèses.*

1) Les individus qui sont porteurs de mutations auront une performance plus faible dans les tests neuropsychologiques que les non-porteurs, et cet effet sera plus marqué pour les mesures de mémoire épisodique.

2) Il y aura un effet de distance au diagnostic chez les porteurs, mais pas chez les non-porteurs. Une performance plus faible sera associée à une plus faible distance au diagnostic chez les porteurs seulement.

3) Pour certains domaines cognitifs, l'effet du temps au diagnostic sera modélisé par un modèle linéaire, mais pour d'autres domaines, cet effet suivra un patron de type quadratique et/ou cubique.

4) Il n'est pas possible sur la base de la littérature actuelle de prédire précisément le type de patron attendu pour chaque domaine cognitif. Toutefois, on s'attend à ce que les décours par domaine soient similaires à ceux observés dans notre étude de la MA de type sporadique.

## 5.6. Article 6: Short Communication: Canada-China Familial Alzheimer's Disease (CCFAD): Preliminary Amyloid and Tau Data from the Canadian Cohort with PSEN1 mutations

*Objectifs.* L'objectif de cette étude empirique est d'observer le patron des pathologies amyloïde et tau, en fonction du temps estimé au diagnostic, sur la base d'une série de cas rapportant les données préliminaires d'imagerie cérébrale de la cohorte canadienne avec mutations PSEN1.

*Hypothèses.*

1) Les individus non porteurs de mutation ne devraient pas présenter une accumulation significative d'amyloïde ou de tau.

2) On devrait observer un effet du temps au diagnostic sur les marqueurs amyloïde et tau chez les porteurs de mutation. En d'autres termes, plus un individu porteur est près de l'âge estimé au diagnostic, plus la probabilité est élevée d'observer une accumulation significative d'amyloïde et de tau.

3) Chez les porteurs de mutation, le marqueur amyloïde devrait être présents plus précocement que le marqueur tau.

**Chapitre II**

**Article 1 :** *Mild Cognitive Impairment*

# Article 1 : Mild Cognitive Impairment

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**DEFINITION**

Alzheimer's disease (AD) is a neurodegenerative disorder and its symptoms progress on a continuum from very mild deficits to dementia. Thus, the transition from normal cognition to dementia is not sudden, but rather a gradual process during which the number and severity of symptoms increase over time. The term mild cognitive impairment (MCI) is used to identify older adults whose performance on neuropsychological tests is deemed abnormal for their age and educational level but is insufficient to interfere notably with activities of daily life and to justify a diagnosis of dementia. Many individuals who meet the criteria for MCI will progress to more severe symptoms. Hence, the condition might indicate a prodromal phase of Alzheimer's disease. Persons with MCI might also suffer from other age-related neurodegenerative disorders. It has been proposed that an MCI phase might also precede Parkinson's disease dementia, Lewy-body dementia, vascular dementia, and frontotemporal dementia.

**CURRENT KNOWLEDGE**

**The Concept of Mild Cognitive Impairment in the Continuum of Alzheimer′s Disease**

Dementia is a syndrome characterized by pervasive cognitive impairment and loss of autonomy. The number of individuals suffering from dementia worldwide was estimated to be 44 million in 2013 and is expected to rise considerably with the increase in population and life expectancy, especially in low- and middle-income countries. Though dementia can result from a range of brain illnesses, its most common cause is AD. AD is a progressive neurodegenerative disease characterized by two core pathological hallmarks: extracellular deposits of amyloid beta protein and intracellular neurofibrillary tangles. The disease has

devastating impacts on the social, economic, and psychological well-being of affected individuals, and it requires that substantial research efforts be devoted towards its understanding. Yet the cause of AD remains elusive. One major challenge is to identify patients as early as possible. Early diagnosis would facilitate identification of the causal mechanisms of the disease. It would also allow for the early implementation of prevention strategies or treatments, before the devastating effects of AD can take place.

Currently, AD is only confirmed by its histopathological hallmarks upon postmortem examination. The premortem diagnosis is provided on the basis of a set of inclusion criteria to confirm abnormal deterioration of cognitive functions and exclusion criteria to reject other etiologies as causative of the cognitive deficit. For many decades, the clinical diagnosis of AD was provided at the dementia phase, when cognitive impairment was pervasive and severe enough to significantly impact autonomy. Yet, it is now agreed that the clinical criteria for dementia identify patients many years after the onset of pathological events that lead up to AD and that the prodromal phase can span up to 15–20 years preceding dementia. This has generated considerable belief that AD could be diagnosed much earlier. A large number of terms have been proposed to identify this prodromal phase of AD; however, MCI is the one that prevails.

**Historical Background**

One of the earliest syndromic classifications of age-related cognitive decline was provided by Kral (Kral, 1962), who contrasted "benign senescent forgetfulness" with "malignant senescent forgetfulness." In this syndromic classification, "benign senescent forgetfulness" referred to a gradual decline of memory or cognition, which did not impact

significantly on daily functioning. This was contrasted with a "malignant" form that was associated with dementia. The use of the term "mild cognitive impairment," to describe patients who present significant cognitive decline but do not yet meet the criteria for dementia, may be originally attributed to a research team at New York University that used it in 1991 in the context of the stages proposed by the Global Deterioration Scale (GDS) (Flicker et al., 1991; Reisberg et al., 1982). The GDS comprises six stages of cognitive decline: Stage 1 – no cognitive decline, Stage 2 – very mild cognitive decline, Stage 3 – mild cognitive decline, Stage 4 – moderate cognitive decline, Stage 5 – moderately severe cognitive decline, and Stage 6 – severe cognitive decline. Stage 4 corresponds to early dementia. Patients in Stage 3 only experience mild deficits that would not interfere notably with activities of daily life. In 1991, Flicker and colleagues (Flicker et al., 1991) found that the mildly impaired subjects (classified in Stage 3) showed significantly poorer performance than healthy controls on tests of recent memory, remote memory, language function, concept formation, and visuospatial praxis. They used the term MCI to identify this condition.

Following this first conceptualization, Zaudig (Zaudig, 1992) proposed three types of MCI based on the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd Edition-Revised (DSM-III-R), and on the World Health Organization's *International Statistical Classification of Disorders and Health Related Problems*, 10th revision (ICD-10). Type 1 only involved memory impairment, Type 2 was characterized by impairment of memory and another cognitive domain, and Type 3 involved Type 1 or 2 with deterioration of emotional control, social behavior, or motivation. These early works laid the foundation for some of the more recent MCI classifications (Petersen et al., 2001; Winblad et al., 2004), NIA/AA (Albert et al., 2011).

## Recent Conceptualizations and Criteria

Based on follow-up studies of a large clinical cohort by the Mayo Clinic in the 1990s, Petersen and his colleagues posited that many persons with MCI were in the prodromal phase of dementia. They proposed a set of criteria to identify those individuals (Petersen et al., 1991) (see Table 1 for a summary of the main criteria for MCI based on recent conceptualizations): Persons with MCI complained about their memory, showed objective memory difficulties beyond what is expected considering their sociodemographic characteristics, did not show general cognitive impairment, still performed their daily activities independently, and failed to meet clinical criteria for dementia.

Follow-up studies of the group indicated that every year 10–15 % of persons meeting those criteria went on to develop AD, a far higher rate than that observed in the normal population (1–5 % per year) (see Gauthier et al., 2006). Later studies indicated that the progression rate of MCI varied as a function of their recruitment source, criteria, and follow-up length but was still much larger than that of non- MCI individuals. The work led by Petersen at the Mayo Clinic has had a considerable impact on the field, by providing well-defined criteria that stimulated an explosion of studies investigating prodromal AD and facilitated cross-study comparisons. Overall, these studies showed that the clinical and pathophysiological characteristics of MCI are close to those found with dementia of the Alzheimer type, supporting the notion that MCI captures a group of individuals in a transitional state between normal aging and dementia.

**Table 1**

Summary table of the main MCI criteria

| | MCI (Petersen et al.) | | MCI | MCI due to AD (NIA/AA, 2011) | MCI+ | Minor neurocognitive disorder |
|---|---|---|---|---|---|---|
| | 1999 | 2001 | (Winblad et al., 2004) | Clinical | Biomarkers | (DSM-5, 2013) |
| Concern reflecting a change in cognition | √ | √ | √ | √ | √ | √ |
| Demonstration of memory impairment by cognitive testing | √ | | | | | |
| Demonstration of cognitive impairment by cognitive testing | | √ | √(or) | √ | √ | √ |
| Evidence of cognitive decline over time | | | √ | √ | √ | |
| Intact ability to perform activities of daily living | √ | √ | | √ | √ | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Intact ability to perform basic activities of daily living | | | √ | √ | √ | |
| Minimal impairment in performing complex activities of daily living | | | √ | | | √ |
| Preserved overall cognitive functions | √ | √ | | | | |
| Absence of dementia | √ | √ | √ | √ | √ | |
| Cannot be explained by other causes or mental disorder | | | | √ | √ | √ |
| Indicate if etiology is consistent with AD | | | | √ | √ | √ |
| Biomarkers of amyloid deposition (CSF or PET) | | | | | √(or) | |
| Neuronal injury (Tau, FDG, SPECT, structural MRI) | | | | | √ | |

In spite of their heuristic value, the initial criteria were criticized on a number of grounds and other conceptualizations were proposed (Table 1; Petersen et al., 2001; Winblad et al., 2004). One major criticism was that MCI is a heterogeneous condition and that

cognitive symptoms are not restricted to the memory domain. As the initial criteria only included memory deficits, they failed to cover the entire range of symptoms that are found in prodromal AD. Thus, it was proposed that individuals with MCI and only memory deficits should be identified as having amnestic MCI, and the term "multidomain amnestic MCI" should be used to identify those with deficits in memory as well as in other cognitive domains. In turn, the authors suggest using the term nonamnestic single- or multidomain MCI for individuals presenting deficits in one or more domains other than memory (Petersen et al., 2001). There are also discussions regarding the heterogeneous etiology of MCI. It is now broadly agreed that different profiles might represent different etiologies, supporting the importance of qualifying the symptomatic profiles of MCI.

In 2011, the National Institute on Aging and the Alzheimer's Association workgroups (NIA/AA) on diagnostic guidelines for Alzheimer's disease proposed an updated set of criteria for MCI that distinguished clinical criteria from criteria to support research ( http://www.alz.org/research/ diagnostic_criteria and Table 1) (Albert et al., 2011). They proposed that the MCI clinical criteria be based on two processes. First, the clinician should establish the presence of clinical and cognitive criteria: (1) presence of a concern about a *change* in cognition, reported by the patient, an informant, or a clinician; (2) evidence of an impairment in one or more cognitive domains; (3) preservation of independence in functional abilities; (4) not demented. Second, the clinician should examine if the etiology is consistent with AD pathophysiology by: (1) ruling out vascular, traumatic, medical causes of decline; (2) providing evidence of cognitive decline over time, where possible; (3) reporting history consistent with AD genetic factors, where relevant. For research purposes, the workgroup proposed the use of biomarkers to document the likelihood of AD as the underlying etiology.

Hence, the presence of positive markers of amyloid deposition (Cerebrospinal fluid (CSF) or Positron emission tomography (PET)) and neuronal injury (Tau, Fludeoxyglucose-PET (FDG-PET), structural MRI) would indicate that there is a high likelihood that the MCI is due to AD.

The DSM-5 (American Psychiatric Association, 2013), published in 2013, also incorporated the notion of prodromal AD. However, the terminology is strikingly different from that used to describe MCI. The manual proposed three types of acquired neurocognitive disorders: delirium, minor neurocognitive disorders, and major neurocognitive disorder, with etiological subtypes for the latter two. Major neurocognitive disorder refers to dementia and, where applicable, can be attributed to Alzheimer's disease. The criteria for minor neurocognitive disorder are similar to those generally proposed for MCI (Table 1). They include: (1) a modest decline of at least one cognitive domain; (2) the decline has no significant impact on professional or social activities, though it is recognized that those activities might require more effort, adaptation, or compensation; (3) the decline does not occur during an episode of delirium; and (4) it is not explained by another mental disorder. When diagnosing a minor neurocognitive disorder, the clinician is expected to specify its etiology and whether it is accompanied by behavioral symptoms. The clinician will diagnose possible AD when there is objective decline in memory and at least one other cognitive domain, onset is insidious, decline is gradual, and when there is no evidence of a mixed etiology. To support a diagnosis of minor neurocognitive disorder with probable AD as an etiology, the clinician must have evidence of insidious onset, gradual decline, *and* presence of a genetic mutation related to AD.

## Cognitive Symptoms

Characterizing the cognitive deficits found in MCI is critical for neuropsychologists who contribute to diagnose AD and MCI and whose assessments are used to guide intervention strategies. For this reason, the study of cognitive impairment in MCI has been the subject of considerable research efforts. As a result, clinicians now have a fairly well-delineated picture of the impairments found in MCI. Episodic memory – the record of personal events encoded in their spatiotemporal context – is impaired early and quite extensively in persons with MCI. Episodic memory deficits were reported when tested with verbal or nonverbal material, with or without retrieval cues (Belleville et al., 2008). Among the different measures of episodic memory, delayed recall and associative memory, the ability to bind different items, are particularly sensitive in MCI (Belleville et al., 2008). This is unsurprising, given the hippocampal damage found early in prodromal AD. In addition, numerous studies reported evidence of impaired executive functions and attentional control in MCI. Impairments were found using tests that reflected different executive components: inhibition capacities, working memory, switching, and divided attention (Belleville et al., 2007, 2008; Dannhauser et al., 2005). Impaired executive functions might indicate a more severe stage of MCI. However, it has also been suggested to reflect comorbid conditions that are characterized by executive deficits, particularly vascular diseases and/or depression.

AD and MCI are both progressive; however, most studies have failed to reveal the patterns of changes as cognitive deficits unfold. Natural history studies can characterize these changes that occur as MCI progresses and provide the opportunity to study the trajectory of symptoms in different cognitive domains. Findings from natural history studies show that the decline occurs faster in MCI persons, compared to cognitively healthy controls (Wilson et

al., 2010). However, the trajectory of this decline varies greatly depending on the cognitive domain. Decline in a number of nonmemory cognitive domains (e.g., visuospatial abilities, inhibition) appears to be a gradual process, a continuous, linear trend (Cloutier et al., 2015). In contrast, episodic memory and working memory present a distinct pattern of decline: years of stable performance followed by a rapid decline, just prior to a dementia diagnosis. This decline pattern suggests that dementia may coincide with a failure of compensation in these memory domains (Twamley et al., 2006; Clement and Belleville, 2010).

**Noncognitive Symptoms**

Although MCI is typically defined as a cognitive syndrome, other noncognitive symptoms often occur. Many individuals report depressive symptoms, anxiety, signs of apathy, and sleep disturbances (For a review, see Apostolova and Cummings, 2008). It is not entirely clear whether those symptoms are psychological reactions to the cognitive changes of MCI or whether they are pathognomonic.

Notably, many studies indicate that those symptoms can predict progression from MCI to dementia (Apostolova and Cummings, 2008). This finding supports the notion that they are not due to the psychological distress caused by memory challenges, but rather result from biological changes associated with the disease. One possibility is that the symptoms reflect the presence of neuropathology in regions involved in emotional regulation.

**Neuroimaging Studies and Other Biomarkers**

Neuroimaging is a prominent field of MCI research, because it has tremendous potential to provide early in-vivo biomarkers of MCI pathophysiology. In addition, functional brain imaging can reveal the patterns of compensation and neuroplasticity that occur during

progression of MCI.

Pittsburgh Compound-B (PiB) is a tracer used in positron emission tomography (PET) to observe amyloid deposition in the brain. Persons with MCI who have significant amyloid burden are at a higher risk of converting to AD, and a higher PiB retention is correlated with poorer performance on episodic memory tasks (Forsberg et al., 2008). CSF can also provide sensitive markers of MCI pathophysiology. Compared to controls, MCI patients who will later progress to dementia have significantly lower CSF Aβ42 (marker of amyloid) levels and higher CSF Tau (marker of neuronal injury) and phosphorylated Tau (pTau; marker of tangles) levels (Andreasen et al., 2003), a pattern similar to that found in demented AD patients. These biochemical changes in CSF are the first detectable markers of the disease, and the combination of low CSF Aβ42 and high CSF Tau/pTau is a strong predictor of future cognitive decline in MCI.

Fludeoxyglucose (FDG)-PET is a marker of glucose uptake, which is an indirect measure of brain activity and metabolism, and reflects neuronal integrity. Hypometabolism, particularly in the temporoparietal regions, is a predictor of future progression in persons with MCI (Chetelat et al., 2003). Evidence of hypometabolism using FDG-PET, one of the earliest markers of the disease, was demonstrated in regions associated with episodic memory (hippocampus, entorhinal cortices), prior to showing cognitive symptoms or significant atrophy in presymptomatic carriers of familial type AD mutations (see section on genetics) (Mosconi et al., 2006).

Because the technique is widely available, noninvasive, reliable, and not costly images based on magnetic resonance imaging (MRI) have been well investigated. Structural

MRI studies have demonstrated that the atrophy rate of many regions of the brain follows a linear and distinct sequence as the individual progresses toward dementia (Risacher and Saykin, 2013). At the very beginning of the disease, atrophy is principally observed in the medio-temporal lobe, as the hippocampal volume reduces by 3 % annually. As the disease becomes more severe, atrophy tends to spread to other cortical regions like the lateral temporal, parietal, and frontal lobes (Risacher and Saykin, 2013).

Moreover, Apolipoprotein e4 (ApoE4) allele, a well-investigated gene in AD, has been shown to have a modest but significant effect on the annual atrophy rate (ApoE4 Risacher and Saykin, 2013). More precisely, ApoE4 carriers show a faster annual rate of atrophy of the hippocampal and entorhinal cortices.

Whereas neuronal integrity decreases gradually during the MCI phase, fMRI studies have shown a paradoxical inverted u-shape function to express task-related brain activation. Dickerson et al. (Dickerson et al., 2004) were the first to report such a selective relationship between fMRI activation, degree of impairment, and subsequent clinical decline among individuals with MCI. They found that greater activation in the parahippocampal gyrus (PHG) and hippocampal formation (HF) during encoding was associated with future clinical decline over an average of a 2.5-year follow-up period. They came to the conclusion that hyperactivation in these regions probably reflected compensatory mechanisms that are specific to predementia patients. Clément and Belleville (Clément and Belleville, 2012) elaborated a model of compensation-related activation in the brains of individuals with MCI, according to disease severity and task nature. They proposed that during the early phase of MCI, when there is only mild neuropathology in the region involved in a task, performance would be optimized by hyperactivating that region, as well as by recruiting additional regions

that were not implicated in the task. However, as the disease gets more severe and affects compensatory regions, the brain would no longer have the capacity to overrecruit and compensate. This compensation breakdown would result in less activation and fewer regions involved in a task, a pattern similar to that found in demented patients. Clément and Belleville (Clément and Belleville, 2012) proposed that the point at which compensation-related mechanisms would be observed during the progression of the disease is related to the nature of the task. They found that compensation occurs earlier for associative recognition, which relies on brain regions that are altered early in the disease, than for item recognition, which depends on brain regions impaired later in the disease. In this study, the brains of participants in a very early phase of MCI showed greater activation in regions known to be involved in episodic retrieval (e.g., dorsolateral and ventrolateral prefrontal cortices). Moreover, their brains recruited also additional regions: more posterior (i.e., precuneus, right temporal lobe, inferior and superior parietal lobules) and bilateral regions (i.e., prefrontal cortex) that are not usually involved in verbal episodic tasks or retrieval. Individuals with more severe MCI showed a shift in compensation mechanisms on tasks involving cognitive processes that are impaired later in the disease (an item recognition task). During the item recognition task, their brains showed hyperactivation in regions known to be involved in episodic retrieval and recruited additional bilateral regions (e.g., the prefrontal cortex). In contrast, the associative memory task resulted in lower activation, fewer regions involved in the task, and poorer performance. This suggests that these individuals' brains were not able to compensate for that task.

To summarize, the neuroimaging techniques and biomarkers available to clinicians and researchers help facilitate early diagnosis, identify the etiology, and understand the

pathophysiology of the disease, as well as the dynamic processes of compensation. Different markers have different uses and advantages. For instance, PiB-PET and FDG-PET show similar diagnostic accuracy for MCI, but PiB- PET may be better for identifying AD as an etiology of MCI. However, PiB retention is thought to rapidly reach a plateau during the prodromal phase, and hence, might not be the best indicator of disease severity.

**The Genetics of MCI**

One of the most well-known and researched genes in AD is the ApoE gene. The ε4 variant increases one's risk of developing MCI and converting to AD (Poirier et al., 1993). Genetics research has identified many other "risk genes" of AD, such as the clusterine (CLU) gene or the complement receptor 1 (CR1) gene (Bettens et al., 2013). Mutations on these genes augment one's risk of developing dementia but are not causative. A very rare type of AD, called autosomal-dominant familial AD, is caused by mutations on the amyloid precursor protein (APP), presenilin1 (PSEN1), and preseinilin2 (PSEN2) genes (Bird, 2012). This familial type is characterized by early onset, generally before the age of 60, and represents fewer than 1 % of all AD cases. This form of AD is preceded by a prodromal, or MCI, phase. Therefore, autosomal-dominant MCI and AD represent a unique resource to study: not only the cognitive profiles of the mutation carriers but also the imaging and biochemical markers of the disease in its early phases.

**Predicting Dementia in Persons with MCI**

A problematic issue regarding MCI is that its prognosis is uncertain. Whereas the majority of individuals with MCI will progress to dementia, a proportion varying between 13.5 % and 44 % will remain stable or revert back to normal (see Gauthier et al., 2006; Albert

et al., 2011). It is thus critical to identify those individuals who will develop AD. Many studies use longitudinal and prospective protocols to differentiate persons with MCI who will progress to dementia from those who will not. Cognitive measures have demonstrated very promising results for predicting dementia. Tests of episodic memory, especially associative memory, have been shown to be the most robust predictors; measures of working memory, executive functions, perception, and language have also been shown to be reliable predictors (Belleville et al., 2014a, b). However, prediction is optimal when neuropsychological assessments examine episodic memory along with multiple cognitive functions. For example, Belleville et al. (Belleville et al., 2014a) assessed a cohort of individuals with MCI using a battery of tests measuring episodic memory (macro elements of the MEMO-TEXT and free recall of words in the Free and Cued Recall Test), working memory, executive functions and attentional control (Alpha- Span), perception (orientation match and object decision of the BORB), and language (object-naming of the DO-80). Over an average of a 4.5-year follow-up period, their test battery predicted the individuals with MCI who would later develop AD and those who would remain stable, with an overall accuracy of 87.7 %.

In the field of neuroimaging, most studies have focused on medial temporal structure. Atrophy within these structures is observable many years prior to diagnosis, with the hippocampal volume being the strongest predictor (Trzepacz et al., 2014). For example, hippocampal and entorhinal cortex atrophy have been shown to predict AD in those with MCI, with an accuracy of 60 % over a 2.5-year follow- up period. When combined with clinical data, the accuracy reached 78.8 % (Belleville et al., 2014b). Other parts of the brain have also been shown to be reliable predictors of dementia. Peters et al. (Peters et al., 2014) assessed individuals with MCI over a 2-year follow-up period using neuropsychological and

MRI data. They demonstrated that atrophy of the right anterior cingulate and the right middle frontal gyri could predict progression toward dementia with an accuracy of 75 %. Furthermore, they elaborated a model combining atrophy of the right anterior cingulate gyrus with neuropsychological tests measuring episodic memory (immediate free recall and immediate recognition of the Memoria Battery). Their model showed prediction accuracy of up to 87.5 %. PiB-PET amyloid imaging has also been shown to be a reliable prediction technique, especially in combination with MRI measures. Trzepacz et al. (Trzepacz et al., 2014) assessed individuals with MCI using PET and MRI techniques over a 2-year follow-up period. The MRI scan of the temporal cortex showed 72 % accuracy, followed by a PiB-PET scan of the lateral temporal cortex and MRI scans of the entorhinal cortex and hippocampus, both with 68 % accuracy. Combined, the MRI and PiB-PET data had an accuracy of 76 %.

Overall, studies have shown that both cognitive and neuroimaging measures are useful in predicting progression to dementia. Predictive accuracy increases substantially when the different types of predictors are combined. As research begins to focus on earlier phases of the disease, an approach combining multiple cognitive measures with biomarkers will be required to support predictive accuracy and to understand the interaction between these predictors. This reflects the NIA/AA criteria for MCI of the Alzheimer type, where biomarkers take a prominent role in combination with clinical indicators to identify the underlying etiology of the disorder.

**Management, Prevention, Intervention**

In the absence of disease-modifying treatments, many scholars have recommended

using prevention or intervention strategies to delay the onset or progression of the cognitive symptoms of AD. To have the greatest effect, these strategies would likely have to be implemented early, specifically during the MCI phase, when the individual is still motivated and has the capacity to learn and apply new strategies and behaviors. Many studies have examined whether cognitive interventions techniques and programs designed to increase or optimize cognition – improve cognitive functioning in persons with MCI. Different types of training have been tested but most of them focused on episodic memory. Most of the programs that were used in MCI to improve their memory relied on compensatory techniques. Hence, participants were taught different mnemotechnics that make use of their intact visual imagery of semantic knowledge capacities to support memory encoding. A few programs have also relied on less demanding memory techniques, for instance, spaced retrieval techniques or vanishing cues. Most of the programs provided to MCI were multicomponential in that they not only targeted memory but also other cognitive domains, most often attention/executive functions. Results indicate that episodic memory, attention, and well-being can be improved by strategic attentional or memory training and that it can sustain over time (Simon et al., 2012). In addition, brain imaging indicates that those interventions can increase brain activation in alternative and specialized regions (Belleville et al., 2011; Hampstead et al., 2011). Those studies indicate that cognitive training programs can be a powerful tool and have beneficial effects during the MCI phase. Furthermore, cognitive training has a direct effect on the brain of those individuals, which indicates that it might increase brain reserve and brain plasticity.

Epidemiological studies have shown that lifestyle factors can increase the risk of cognitive decline, dementia, and AD and might account for up to 50 % of the AD cases

worldwide. Physical activity, diet, vascular risk factors, education, depression, and lifelong cognitive stimulation are among the modifiable risk factors that have the strongest relation with dementia. A successfully implemented prevention approach that targets these modifiable factors in persons at risk of AD has the potential to have a tremendous impact on the number of cases. Large-scale multimodal prevention trials are being carried out worldwide to determine whether improving some protective lifestyle factors in older age can reduce cognitive decline in persons at risk for the disease. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), a double-blind randomized control trial, enrolled 1260 older adults with a vascular risk of dementia. Participants received an intervention of healthy diet, physical exercise, vascular risk monitoring, and cognitive training versus general health advices. The authors recently reported that the intervention reduced the rate of cognitive decline over a two-year period when compared to the control group (Ngandu et al., 2015). The Multidomain Alzheimer Preventive Trial (MAPT) study (Vellas et al., 2014) examined whether a multidomain intervention including nutritional counseling, physical exercise, cognitive training, and social activities, in combination with omega-3 fatty acid supplementation, would reduce cognitive decline in older adults with a subjective complaint or risk of frailty.

**Future Directions**

The study of MCI has been influential and is growing quickly. Yet, there are still a number of unresolved issues related to the criteria, prognosis, early clinical manifestation, progression, and management of MCI. Given that new criteria have been proposed to identify those in the early stage of AD, studies will be required to test their validity and evaluate whether all items are necessary.

Another important challenge is to identify the source of interindividual variability among cognitive profiles and resistance to pathology and to identify the factors that contribute to different profiles. Studies on brain resilience and brain reserve will contribute to better understand why individuals vary in their resistance to neurodegenerative diseases.

Longitudinal studies of MCI and the use of complex methodology and statistical models will be critical to better understand how symptoms change during the early phase of the cognitive disease. For instance, it is generally assumed that decline occurs in a linear fashion; however, it is possible that more complex trajectories better explain the progression of cognitive symptoms during the MCI phase. Recent studies suggest that some domains are characterized by many years of stable performance, followed by a rapid decline just prior to AD diagnosis. Thus, future studies will have to assess complex patterns to provide an accurate picture of how the decline unfolds in the years preceding a dementia diagnosis. These should include persons with subjective cognitive decline. Some of these individuals might stand in a very early phase of the disease and their longitudinal assessment might be the key to reveal the earliest cognitive symptoms of AD.

The study of familial Alzheimer's disease (FAD) mutation carriers has been an important area of research. Carriers of mutations on the APP, PSEN1, and PSEN2 genes represent an ideal population for studying the early phases of dementia, due to the certainty that they will receive a future AD diagnosis. It is also possible to estimate their age of onset, based on the age at which their parent received his/her diagnosis. However, we need to know when and how symptoms unfold in mutation carriers and to assess whether individual or lifestyle characteristics affect the symptomatic expression of the disease in this population. We also need to improve our knowledge of how the preclinical phase of FAD compares with

that of sporadic AD.

There is still work to be done in the field of cognitive test development. As research moves towards studying earlier phases of the disease, neuropsychologists will need access to more sensitive measures and algorithms to identify the earlier cognitive changes. Technological advances in the fields of virtual reality, information and communication technologies, continuous performance monitoring, wearable or environmental sensors, and online testing might provide promising innovations. In addition, multimodal biomarker models that combine cognitive and clinical measures with innovative biomarkers will be necessary to optimize predictive models of dementia. Furthermore, future studies involving neuroimaging should examine the relationship between structural damage and activation patterns. Because compensation mechanisms are likely highly active during prodromal AD, functional brain imaging can contribute knowledge of these mechanisms taking place as brain damage progresses. Such knowledge will shed light on the way by which the brain expresses resilience during the early phase of the disease.

Finally, the MCI phase has been identified as one that might be a suitable target for intervention and secondary prevention strategies. Reducing the cognitive symptoms and delaying their impact on independence are potentially powerful approach to reduce the number of dementia cases worldwide. However, designing and implementing efficient intervention and prevention strategies is challenging and will require more research to identify responders, optimal temporal therapeutic windows, and ways to overcome barriers to behavioral changes.

Supporting such an ambitious research agenda will require large longitudinal studies

of well- characterized cohorts with clinical follow-up and, ideally, postmortem analysis of the brain to identify the etiology. The increasing efforts to develop national and multinational initiatives that use large cohorts and allow analyses of big data sets will enable these questions to be addressed. To be successful, those efforts will require at least some partial harmonization of clinical and data collection procedures. In addition, there will be a need to train clinicians to the notion of MCI in the context of slowly evolving neurodegenerative diseases so that the concept translate more rapidly from research to the clinical practice.

## References

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., Gamst, A., Holtzman, D. M., Jagust, W. J., Petersen, R. C., Snyder, P. J., Carrillo, M. C., Thies, B., & Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*, 270–279.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*. Washington, DC: American Psychiatric Association.

Andreasen, N., Vanmechelen, E., Vanderstichele, H., Davidsson, P., & Blennow, K. (2003). Cerebrospinal fluid levels of total-tau, phospho-tau and A beta 42 predicts development of Alzheimer's disease in patients with mild cognitive impairment. *Acta Neurologica Scandinavica. Supplementum, 179*, 47–51.

Apostolova, L. G., & Cummings, J. L. (2008). Neuropsychiatric manifestations in mild cognitive impairment: A systematic review of the literature. *Dementia and Geriatric Cognitive Disorders, 25*, 115–126.

Belleville, S., Chertkow, H., & Gauthier, S. (2007). Working memory and control of attention in persons with Alzheimer's disease and mild cognitive impairment. *Neuropsychology, 21*, 458–469.

Belleville, S., Sylvain-Roy, S., De Boysson, C., & Ménard, M.-C. (2008). Essence of memory. Characterizing the memory changes in persons with mild cognitive impairment. *Progress in Brain Research, 169*, 365–375.

Belleville, S., Clement, F., Mellah, S., Gilbert, B., Fontaine, F., & Gauthier, S.

(2011). Training- related brain plasticity in subjects at risk of developing Alzheimer's disease. *Brain, 134*, 1623–1634.

Belleville, S., Gauthier, S., Lepage, E., Kergoat, M. J., & Gilbert, B. (2014a). Predicting decline in mild cognitive impairment: A prospective cognitive study. *Neuropsychology, 28*, 643–652.

Belleville, S., Fouquet, C., Duchesne, S., Collins, D. L., & Hudon, C. (2014b). Detecting early preclinical Alzheimer's disease via cognition, neuropsychiatry, and neuroimaging: Qualitative review and recommendations for testing. *Journal of Alzheimer's Disease, 42*(Suppl 4), S375–S382.

Bettens, K., Sleegers, K., & Van Broeckhoven, C. (2013). Genetic insights in Alzheimer's disease. *Lancet Neurology, 12*, 92–104.

Bird, T. D. (2012). Early-onset familial Alzheimer disease. *GeneReviews(R)*. http://www.ncbi.nlm. nih.gov/books/NBK1236/

Chetelat, G., Desgranges, B., de la Sayette, V., Viader, F., Eustache, F., & Baron, J. C. (2003). Mild cognitive impairment: Can FDG-PET predict who is to rapidly convert to Alzheimer's disease? *Neurology, 60*,1374–1377.

Clement, F., & Belleville, S. (2010). Compensation and disease severity on the memory-related activations in mild cognitive impairment. *Biological Psychiatry, 68*, 894–902.

Clement, F., & Belleville, S. (2012). Effect of disease severity on neural compensation of item and associative recognition in mild cognitive impairment. *Journal of Alzheimer's Disease, 29*, 109–123.

Cloutier, S., Chertkow, H., Kergoat, M. J., Gauthier, S., & Belleville, S. (2015). Patterns of cognitive decline prior to dementia in persons with mild cognitive impairment. *Journal of Alzheimer's Disease, 47*, 901–913.

Dannhauser, T. M., Walker, Z., Stevens, T., Lee, L., Seal, M., & Shergill, S. S. (2005). The functional anatomy of divided attention in amnestic mild cognitive impairment. *Brain, 128*, 1418–1427.

Dickerson, B. C., Salat, D. H., Bates, J. F., Atiya, M., Killiany, R. J., Greve, D. N., Dale, A. M., Stern, C. E., Blacker, D., Albert, M. S., & Sperling, R. A. (2004). Medial temporal lobe function and structure in mild cognitive impairment. *Annals of Neurology, 56*, 27–35.

Flicker, C., Ferris, S. H., & Reisberg, B. (1991). Mild cognitive impairment in the elderly: Predictors of dementia. *Neurology, 41*, 1006–1009.

Forsberg, A., Engler, H., Almkvist, O., Blomquist, G., Hagman, G., Wall, A., Ringheim, A., Langstrom, B., & Nordberg, A. (2008). PET imaging of amyloid deposition in patients with mild cognitive impairment. *Neurobiology of Aging, 29*, 1456–1465.

Hampstead, B. M., Stringer, A. Y., Stilla, R. F., Deshpande, G., Hu, X., Moore, A. B., & Sathian, K. (2011). Activation and effective connectivity changes following explicit-memory training for face- name pairs in patients with mild cognitive impairment: A pilot study. *Neurorehabilitation and Neural Repair, 25*, 210–222.

Kral, V. A. (1962). Senescent forgetfulness: Benign and malignant. *Canadian Medical Association Journal, 86*, 257–260.

Mosconi, L., Sorbi, S., de Leon, M. J., Li, Y., Nacmias, B., Myoung, P. S., Tsui, W., Ginestroni, A., Bessi, V., Fayyazz, M., Caffarra, P., & Pupi, A. (2006). Hypometabolism exceeds atrophy in presymptomatic early-onset familial Alzheimer's disease. *Journal of Nuclear Medicine, 47*, 1778– 1786.

Ngandu, T., Lehtisalo, J., Solomon, A., Levalahti, E., Ahtiluoto, S., Antikainen, R., Backman, L., Hanninen, T., Jula, A., Laatikainen, T., Lindstrom, J., Mangialasche, F., Paajanen, T., Pajala, S., Peltonen, M., Rauramaa, R., Stigsdotter-Neely, A., Strandberg, T., Tuomilehto, J., Soininen, H., & Kivipelto, M. (2015). A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomised controlled trial. *Lancet, 385*, 2255–2263.

Peters, F., Villeneuve, S., & Belleville, S. (2014). Predicting progression to dementia in elderly subjects with mild cognitive impairment using both cognitive and neuroimaging predictors. *Journal of Alzheimer's Disease, 38*, 307–318.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: Clinical characterization and outcome. *Archives of Neurology, 56*, 303–308.

Petersen, R. C., Doody, R., Kurz, A., Mohs, R. C., Morris, J. C., Rabins, P. V., Ritchie, K., Rossor, M., Thal, L., & Winblad, B. (2001). Current concepts in mild cognitive impairment. *Archives of Neurology, 58*, 1985–1992.

Poirier, J., Davignon, J., Bouthillier, D., Kogan, S., Bertrand, P., & Gauthier, S. (1993). Apolipoprotein E polymorphism and Alzheimer's disease. *Lancet, 342*, 697–699.

Reisberg, B., Ferris, S. H., de Leon, M. J., & Crook, T. (1982). The global deterioration scale for assessment of primary degenerative dementia. *The American Journal of Psychiatry, 139*, 1136–1139.

Risacher, S. L., & Saykin, A. J. (2013). Neuroimaging and other biomarkers for Alzheimer's disease: The changing landscape of early detection. *Annual Review of Clinical Psychology, 9*, 621–648.

Simon, S. S., Yokomizo, J. E., & Bottino, C. M. (2012). Cognitive intervention in amnestic mild cognitive impairment: A systematic review. *Neuroscience and Biobehavioral Reviews, 36*, 1163– 1178.

Trzepacz, P. T., Yu, P., Sun, J., Schuh, K., Case, M., Witte, M. M., Hochstetler, H., Hake, A., & Alzheimer's Disease Neuroimaging Initiative. (2014). Comparison of neuroimaging modalities for the prediction of conversion from mild cognitive impairment to Alzheimer's dementia. *Neurobiology of Aging, 35*, 143–151.

Twamley, E. W., Ropacki, S. A., & Bondi, M. W. (2006). Neuropsychological and neuroimaging changes in preclinical Alzheimer's disease. *Journal of the International Neuropsychological Society, 12*, 707–735.

Vellas, B., Gillett-Gyuonnet, S., Touchon, J., Dantoine, T., Dartigues, J. F., & Andrieu, S. (2014). MAPT study: A multidomain approach for preventing Alzheimer's disease: Design and baseline data. *The Journal of Prevention of Alzheimer's Disease, 1*, 13–22.

Wilson, R. S., Aggarwal, N. T., Barnes, L. L., Mendes de Leon, C. F., Hebert, L. E., & Evans, D. A. (2010). Cognitive decline in incident Alzheimer disease in a community population. *Neurology, 74*, 951–955.

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L. O., Nordberg, A., Backman, L., Albert, M., Almkvist, O., Arai, H., Basun, H., Blennow, K., de Leon, M., DeCarli, C., Erkinjuntti, T., Giacobini, E., Graff, C., Hardy, J., Jack, C., Jorm, A., Ritchie, K., van Duijn, C., Visser, P., & Petersen, R. C. (2004). Mild cognitive impairment – Beyond controversies, towards a consensus: Report of the international working group on mild cognitive impairment. *Journal of Internal Medicine, 256*, 240–246.

Zaudig, M. (1992). A new systematic method of measurement and diagnosis of "mild cognitive impairment" and dementia according to ICD-10 and DSM-III-R criteria. *International Psychogeriatrics, 4*(Suppl 2), 203–219.

**See Also**

Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R. C., Ritchie, K., Broich, K., Belleville, S., Brodaty, H., Bennett, D., Chertkow, H., Cummings, J. L., de Leon, M., Feldman, H., Ganguli, M., Hampel, H., Scheltens, P., Tierney, M. C., Whitehouse, P., Winblad, B., & International Psychogeriatric Association Expert Conference on mild cognitive impairment. (2006). Mild cognitive impairment. *Lancet, 367*, 1262–1270.

Gerstenecker, A., & Mast, B. (2015). Mild cognitive impairment: a history and the state of current diagnostic criteria. International Psychogeriatrics, 27(02), 199–211.

# Chapitre III
**Article 2:** *Patterns of Cognitive Decline Prior to Dementia in Persons with Mild Cognitive Impairment*

**Article 2: Patterns of Cognitive Decline Prior to Dementia in Persons with Mild Cognitive Impairment**

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**Abstract**

Only a limited number of studies have investigated the decline of discrete cognitive domains as individuals progress from mild cognitive impairment (MCI) to dementia. Thus, the goal of this longitudinal study was to evaluate the cognitive changes underway during the years preceding a diagnosis of probable Alzheimer's disease (AD), and to compare these changes to those found in MCI participants who do not progress to dementia. Participants were compared as a function of whether they later converted to AD ($n = 47$) or not ($n = 74$). Cognitive change was assessed prior to the conversion year, using that year as a starting point. A combination of polynomial regression analyses and mixed ANOVAs assessed 1) the trajectory of cognitive decline for each domain and 2) the differences between non-progressors and those who had converted to AD. The different cognitive domains demonstrated very different patterns of decline in the group of MCI progressors. A quadratic function, i.e., many years of stable performance followed by a rapid decline just prior to diagnosis, was observed for delayed recall, working memory, and spatial memory. In contrast, a gradual linear decline was observed for immediate recall, executive function, and visuo-spatial abilities. Finally, language in progressors was impaired on all time periods relative to non-progressors, but there was no further change between the first assessments and conversion to AD. Individuals with MCI who progress to AD show abnormal cognition at least two years prior to their dementia diagnosis. The pattern of symptom change observed appears to depend upon the cognitive domain and thus, clinical studies should not assume similar rate of decline across domains. In contrast and, apart from verbal memory, the non-progressors present a performance similar to that of healthy older adults.

**INTRODUCTION**

Worldwide, it is estimated that more than 24 million people have Alzheimer's disease (AD), and this years as life expectancy rises (Ballard et al., 2011). Though most patients receive their AD diagnosis during the dementia phase (when symptoms are severe enough to limit independence), the disease undergoes a phase of mild cognitive impairment (MCI) during which the patient experiences cognitive deficits that are deemed abnormal when considering the individual's age and education level, but that tend to not interfere notably with activities of daily life (Gauthier et al., 2006; Petersen, Stevens, et al., 2001; Sperling et al., 2011). AD is progressive and shows a gradual increase in the number and severity of symptoms, which certainly also reflects the course of the MCI phase. However, little is known regarding the way by which the different cognitive symptoms lead to dementia. For instance, MCI was once considered an amnestic phase of the disease (Small, Fratiglioni, Viitanen, Winblad, & Backman, 2000). However, cumulating evidence indicates that other cognitive domains are also affected. Characterizing the pattern of change during the MCI phase may be critical to improve diagnosis and help develop measures that are sensitive to early interventions or treatment. For instance, many authors have suggested using cognitive decline rather than cognitive performance as a marker of future progression and to develop techniques that are sensitive to cognitive changes (Chen et al., 2001; Lindeboom & Weinstein, 2004; McKhann et al., 2011; Villeneuve, Belleville, Massoud, Bocti, & Gauthier, 2009). For all these reasons, it is critical to better understand how the decline unfolds during this phase of the disease.

*Natural history*

The majority of the studies assessing the cognitive profile in MCI are predictive studies aiming to identify the factors/neuropsychological tests that are predictive of future progression to

dementia (Ahmed, Mitchell, Arnold, Nestor, & Hodges, 2008; Belleville, Gauthier, Lepage, Kergoat, & Gilbert, 2014; Fellows, Bergman, Wolfson, & Chertkow, 2008) (for a review, see (Gainotti, Quaranta, Vita, & Marra, 2014)). In turn, natural history studies aim to characterize the changes that occur in different cognitive domains as individuals progress during the early phase of MCI, and to provide the opportunity to study the trajectory of the symptoms, per cognitive domain. Only a few studies have investigated the natural history of cognitive symptoms in MCI patients. Those studies have indicated that different cognitive domains may manifest different rates of decline. For instance, Wilson and colleagues (Wilson et al., 2010) compared the decline rate of persons with AD, MCI, and normal cognition over an 11-year period. They found that persons with AD decline more rapidly than those with MCI, and that MCI persons experience a faster decline rate than normal individuals. In another study, Bennett et al. (Bennett et al., 2002) examined cognitive decline for discrete cognitive domains. They evaluated decline over a seven-year period in a group of healthy older adults (HOA) and a group of MCI persons on composite measures of episodic memory, semantic memory, working memory, perceptual speed, and visuo-spatial abilities. Their findings revealed that individuals with MCI had significantly lower scores at baseline and displayed accelerated cognitive decline compared to HOA. However, they noted that not all cognitive domains exhibited a similar decline. Individuals with MCI experienced a faster decline rate in terms of episodic memory, semantic memory, and perceptual speed compared to HOA. The decline rate regarding working memory and visuo-spatial abilities, however, did not appear to be significantly faster in MCI persons compared to HOA.

The majority of the natural history studies have assumed that cognitive decline occurs in a linear fashion, although this may not be the case. There may be periods of stable performance followed by accelerated decline, or decline followed by a period of stability, and the cognitive

trajectories may differ from one cognitive domain to the other. For instance, a nonlinear pattern with an initial decline followed by a period of stability might be particularly characteristic of episodic memory, as this is a domain that is impaired very early in the disease process (Salmon & Bondi, 2009). This pattern could also occur due to the presence of early compensatory mechanisms followed by a rapid decline as compensatory mechanisms become compromised (Clement & Belleville, 2010). Interestingly, there are studies that have confirmed such a plateau model for episodic and short-term/working memory (Backman, Small, & Fratiglioni, 2001; Smith et al., 2007), but not for other cognitive domains (Smith et al., 2007). Thus, the decline in the years preceding conversion to dementia may vary as a function of the cognitive domain and trajectories may be characterized by periods of stability and accelerated decline, which might be better described by non-linear rather than linear models. It should be noted, however, that the study of Backman et al. (Backman et al., 2001) compared mean performances across different assessments and did not assess the cognitive trajectories with statistical modeling.

The few studies that have investigated the pattern of cognitive change during the MCI phase also contain certain limitations. First, not all MCI persons will progress to dementia and to the best of our knowledge, no study has yet examined the natural history of cognitive symptoms in MCI by considering the presence or absence of future progression to dementia. Since the goal is to characterize the natural history of pre-dementia AD, it is important to distinguish MCI as a function of future decline. It is also informative to describe what happens in patients that do not progress to dementia. This group of MCI individuals, also referred to as non-progressors, may remain stable, show improvement in their performance on certain tasks, or may show a decline to a lesser degree than that of progressors (persons that eventually develop dementia).

Second, studies have generally relied on overall cognitive measures, few of them having examined specific cognitive domains. As a result, it is unclear how memory deficits increase over time, and how and when non-memory deficits (e.g., executive functions, language) emerge in the MCI-to-dementia continuum. It is critical to understand the progression of deficits in these different domains, as some authors have suggested that dementia occurs predominantly as a result of the occurrence of executive deficits (Belleville, Gauthier, et al., 2014; N. L. Saunders & Summers, 2010; N. L. J. Saunders & Summers, 2011).

Third, the definition of the time frame may have considerable impact on the pattern of results. An ideal study of the natural history of AD would select patients at the onset of the disease or would analyze their data as a function of when the disease arose. In the case of AD, the absence of biomarkers for the disease and the fact that it remains symptomatically silent for a long period of time prevents researchers from determining the true onset of the disease. In the studies reported above, the date of recruitment as an MCI served as Time 1 and subsequent time points were determined as a function of study entry. This may be problematic. The moment at which participants present themselves for consultation in the course of the disease is extremely variable and may depend on a number of factors that are not necessarily related to intrinsic factors of the disease such as service access, tolerability to the cognitive symptoms, whether patients receive support from their family, and financial capability. As a result, it is likely that not all participants are at the same time point in their disease progression at the time of recruitment. One way to partially account for this is to align the time series on the year when participants received their diagnosis of AD, rather than on their recruitment as an MCI. In our view, this is a logical approach, as the goal is to describe the trajectories of the decline prior to dementia. This has been done on cohort studies following healthy older adults. In a study by Amieva et al. (Amieva et

al., 2005), the cognitive performance of a cohort of elderly adults was analyzed over a 9-year period. They found that individuals who will progress to dementia already had lower performance at baseline and that some cognitive tests presented an accelerated decline 3 years prior to AD diagnosis.

Hence, the present study is a longitudinal follow-up of a clinical cohort of people meeting the criteria for amnestic MCI (aMCI) and comprises the three following goals: 1) characterize the evolution of cognitive deficits as a function of whether the MCI persons later progress to dementia or not; 2) determine whether different cognitive domains have distinctive trajectories and sensitivity to change; 3) assess whether decline is linear or follows a more complex trajectory with periods of stability and acceleration, as the plateau model of Twamley et al. (Twamley, Ropacki, & Bondi, 2006) would suggest. These functions can be assessed by polynomial models, which are sophisticated extensions of the traditional linear regression. Polynomial regressions allow the testing of a range of complex models in addition to the linear model including second-order polynomial (quadratic function, i.e., years of stable performance followed by a rapid decline prior to conversion) and third-order polynomial (cubic function, i.e., two periods of significant decline with a period of stability between them).

**MATERIALS AND METHODS**

*Participants*

One-hundred and fifty one participants were recruited from memory clinics and met the following criteria (Petersen, Doody, et al., 2001; Winblad et al., 2004) for single-domain aMCI: 1) memory complaint confirmed by an informant; 2) performance of at least 1.5 SD below age- and education-normed values on a minimum of one memory test (RL/RI, text memory or recall of Rey Figure); 3) no global cognitive impairment on the basis of the Mini-Mental State

Examination using a cut-off score for age and education; and 4) absence of dementia based on *DSM–IV* clinical criteria for dementia of the Alzheimer type (American Psychiatric Association. & American Psychiatric Association. Task Force on DSM-IV., 2000). Finally, their cognitive difficulties had no significant impact on their functional independence, as assessed through clinical interviews with the participants. All participants were Francophone, with normal or corrected vision and audition, and made no use    of AD-related medication (donepezil, rivastigmine, galantamine, or memantine). Participants who made use of anxiolytics and antidepressants were included only if it was not a recent prescription, if the time they started taking the medication differed from the time they started having memory impairment (as assessed by clinical evaluation of referring physicians), and if they had no severe diagnosis of any severe psychiatric disorders, such as major depression. We also excluded participants who reported major current medical conditions, a presence or history of alcoholism, substance abuse, significant cerebrovascular, neurological, or neurodegenerative disorders (e.g., Parkinson's disease, multiple sclerosis, epilepsy, or Huntington's disease), stroke (including transient ischemic attacks) or large-vessel disease, or that had undergone general anesthesia within the last six months. In order to characterize the cognitive profile of our participants, they were administered the Mattis Dementia Rating Scale, a global scale of tests evaluating a range of cognitive domains (language, praxis, perception, memory, orientation, executive functions, reasoning) and the Geriatric Depression Scale, which assesses their anxiety and depressive symptoms. Given that patients met the criteria for amnestic MCI and showed no vascular or neurological co-morbidities, AD was expected to be the underlying etiology.

Following study entry, participants received a yearly clinical follow-up that allowed us to identify those who had progressed (i.e., progressors) and those who had not progressed (i.e.,

non-progressors) to dementia. Progressors met the clinical *DSM–IV* criteria for dementia of the Alzheimer type, whereas non-progressors were individuals who did not fulfill the criteria for dementia over the course of the follow-up. Thus, progression was determined from clinical criteria based on the entire clinical data including functional autonomy. It is possible that some of the non-progressors were in the earlier stages of the disease process and had not yet reached the point at which they would meet criteria for dementia. For instance, some of the individuals included in the non-progressors group showed a significant cognitive decline on the neuropsychological tests over the course of the follow-up in spite of not reaching criteria for dementia. Those were nevertheless retained in the group of non-progressors to avoid generating an artificial increase in group differences. Note that excluding those participants from the non-progressors group did not substantially modify the models.

*Cognitive measures*

Six neuropsychological tests were used to measure cognition longitudinally to cover the domains of memory, executive functions, working memory, language, and visual perception.

*Memory*

The RL/RI (Van der Linden et al., 2004) (Rappel libre/Rappel indicé; a French adaptation of Buschke's Free-Recall and Cued Recall) is a measure of verbal memory where participants are asked to encode and then retrieve a list of 16 words with and without categorical cues. As a verbal memory variable, we used the total number of words recalled correctly without cues. Memory was also measured using the 3-minute recall of the Rey complex geometrical figure test (Rey, 1959) in which participants are first asked to copy the figure and then to draw

it from memory 3 minutes following the copy phase. This represents an incidental memory test, as the participants are not informed during the copy trial that they will have to recall the figure at a later time. The RL/RI has two alternative versions, which allowed us to alternate versions on consecutive years. Similarly, for spatial memory, the Taylor Figure was used alternatively with the Rey Figure.

*Working memory and executive functions*

Executive functions were measured using the Stroop-Victoria test (Regard, 1981) in which participants are first asked to read aloud the names of colors written with black ink. Then, participants are asked to name the color of dots. Finally, participants are asked to read aloud the color of the ink in which color names are printed. The names of the written colors are not coherent with the ink in which they are printed, leading participants to have to inhibit the automatic response which would be to read the written name of the color. As an inhibition variable, we used the additional time it took participants to name the color of the ink when the words were incoherent with the ink, compared to the other two conditions. In other words, we subtracted the average time for color names in black ink and dots in colors from the time of colored words. This represents a purer measure of inhibition, as it controls for the base reading time for each individual. We also used the Coding-subtest of the WAIS-R (Wechsler, 1997) as a measure of working memory and processing speed. In this test, participants are asked to reproduce symbols that are matched to a series of numbers.

*Visuo-spatial processing and language*

Visuo-spatial processing was measured with the Benton Judgment of line orientation (Benton, Hamsher, Varney, & Spreen, 1983) in which participants are asked to match lines that

are in the same position and orientation. Finally, language was measured using the 15-item version of the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983), for which the score was established by adding the total number of correctly identified pictures, without phonetic or semantic cues.

*Design*

Patients were recruited and classified by clinicians (HC, MJK, SG) in memory clinics. They were then referred to participate in the present study. At study entry, participants completed the clinical tests/questionnaires and neuropsychological battery. They were then invited for a yearly assessment using the same clinical and neuropsychological battery of tests. Measures were taken in a single testing session. The referring clinicians determined the dementia diagnosis and follow-up assessments ceased the year a patient received a diagnosis of dementia. Thus, the last assessment corresponds to the year of diagnosis. Data was assessed as a function of time from diagnosis. T0 represents the time of conversion, i.e., the year of the diagnosis of dementia for those who declined to AD, and the last evaluation for the non-progressors. T-1, T-2, T-3, and T-4 represent the testing data for one, two, three, and four years prior to diagnosis respectively. The approach is similar to that used by Amieva et al. (Amieva et al., 2005).

*Analysis*

For each of the cognitive tests, we first ran a polynomial regression analysis. This was done separately for progressors and non-progressors. Polynomial regression has many advantages over the classical linear regression analysis. An important asset, particularly in the context of clinical studies, is that it is fairly flexible and does not require that all participants have the same number of assessments. Also, polynomial regressions are more resistant to missing data

than traditional repeated measures analysis (Dupéré, Lacourse, Vitaro, & Tremblay, 2007). Finally, the analysis is well suited for natural history studies, as it is a non-parametric regression technique that considers less abrupt changes and assumes a more continuous, gradual, and natural change over time (Eubank, 1999). The data we entered in these analyses included all scores obtained from the testing years prior to diagnosis, ranging from Time 0 (year of diagnosis) to Time minus 4. To ascertain which model best fits the data, we first verified whether a linear model was significant and if it was, we proceeded to test more sophisticated models: the quadratic function, a second-order polynomial characterized by one fracture in the curve and the cubic function, a third-order polynomial. We also included age, gender, and education as controlled variables in the model. The polynomial regression requires the selection of a covariance matrix structure on which to base the analysis. We opted for the heterogeneous first-order autoregressive structure, as it is advisable for longitudinal studies. Moreover, it is consistent with our clinical expectation as it assumes that two points close in time should be more correlated than two points apart. Also, because it is a more complex structure, it reduces the risk of type 1 error (Field, 2013). However, given that the distribution of the group of non-progressor MCI was stable, the Hessian matrix was not defined as positive with this covariance structure, which led us to use a diagonal or an undefined structure.

For each cognitive measure, we used separate 2 (Group: progressors versus non-progressors) x 3 (Time: T0, T-1, T-2) mixed analyses of variance (ANOVA). Here, only three years were used in order to maximize the number of participants, as ANOVA is not resistant to missing data. This provided information about the extent of the patients' decline relative to non-progressors in the few years prior to the onset of AD. The number of participants retained for the ANOVA differs as a function of the task due to differences in missing data. Thus, the

N on which the analyses are performed are presented separately in the result section below. This analysis provides complimentary information to the polynomial regression analysis. Because it includes the two groups, it provided information regarding the time at which progressors and non-progressors significantly differed. It can also be used to better identify the time at which the onset of the decline occurs in domains for which the polynomial regression analysis has identified sudden changes. The adjusted F was used to correct sphericity by removing the part of the effect that is explained by the systematic error. Greenhouse-Geiser's estimates were used to correct for error of the first kind. Because it is a repeated design, homogeneity of variance was assumed.

**RESULTS**

*Socio-demographic and clinical characteristics*

The STAndards for the Reporting of Diagnostic (STARD) flow diagram (Bossuyt et al., 2003) is shown in Fig. 1. Thirty participants were excluded from the analyses because they only received one evaluation, and the polynomial regression analysis requires at least two points in time to establish a model to fit the data. The data from 121 participants (74 women) were analyzed for this study. Of this number, 47 progressed to clinical dementia (progressors) and 74 did not meet the criteria for dementia over the follow-up period (non-progressors). Demographic and clinical data are shown in Table 1. The non-progressors group did not significantly differ from the progressor group on age at entry ($t = 1$, $p = 0.32$; bimodal) nor at T0 ($t = 0.49$, $p = 0.63$; bimodal). The groups showed no differences regarding their completed years of education ($t = 0.48$, $p = 0.63$; bimodal), gender distribution ($x^2 = 0.23$, $p = 0.63$), or Geriatric Depression Scale score ($t = -0.26$, $p = 0.79$; bimodal). Unsurprisingly, the progressors presented significantly

lower scores on the Mini-Mental State Examination ($t = 4.24$, $p < 0.01$; bimodal) and on the Mattis Dementia Rating Scale ($t = 6.06$, $p < 0.01$; bimodal).

A summary of the polynomial regression analyses for all cognitive variables concerning the non-progressors group is presented in Table 2, while that for the progressor group is presented in Table 3. Fitted models for both groups can be seen in Figs. 2 to 8. When examining cognitive change with polynomial regression analyses in the group of non-progressor MCIs, none of the models were found to be significant, except for Coding in which a positive linear model was found to be significant. This denotes that performance in all measured domains remains stable over time with no significant deterioration or improvement except for the coding test, which shows a small practice effect. On most of the domains evaluated in the progressors, we observed a significant decline that varied considerably in terms of form and rate as a function of the cognitive domain. Because of the large variation across cognitive domains, results are presented by domain in the remainder of this section.
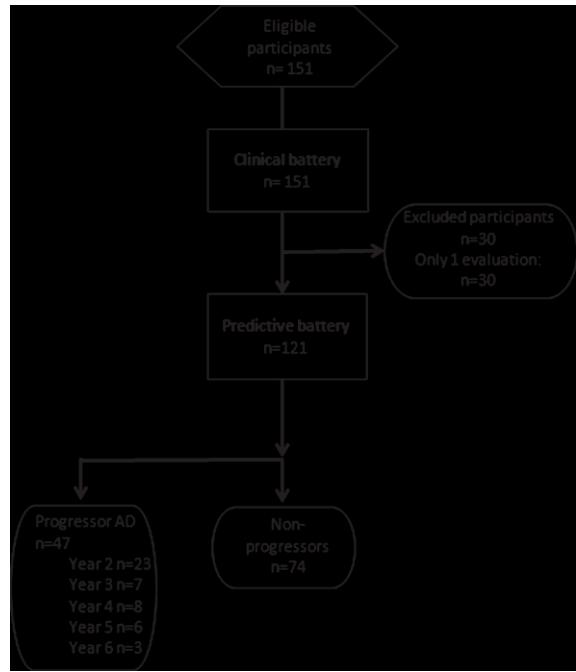
**Fig. 1.** STAndards for the Reporting of Diagnostic (STARD) flow diagram.

## Table 1
### Clinical and demographic characteristics (Mean, SD in parentheses)

|  | Non-progressors | Progressors | $t/\chi^2$ | $p$ |
|---|---|---|---|---|
| Age |  |  |  |  |
|   At entry | 69.95 (8.68) | 71.47 (7.3) | −1 | 0.32 |
|   On T0 | 73.38 (8.61) | 74.11 (7.27) | −0.49 | 0.63 |
| Years of education (mean and SD) | 14.61 (4.18) | 14.23 (4.09) | 0.48 | 0.63 |
| N (Men/Women) | 74 (30/44) | 47 (17/30) | 0.23 | 0.63 |
| Length of follow-up (months) | 35.85 (18.41) | 30.77 (19.57) | 1.45 | 0.15 |
| Geriatric Depression Scale | 14.93 (4.1) | 15.12 (2.78) | −0.26 | 0.79 |
| Mini-Mental State Examination | 27.96 (1.92) | 26.07 (2.6) | 4.24 | <0.01 |
| Mattis Dementia Rating Scale | 136.07 (5.79) | 126.17 (10.07) | 6.06 | <0.01 |

## Table 2
### Summary table for the polynomial regression analyses of performance in the non-progressors group

| Cognitive Test | Significant model | F value | $p$ value |
|---|---|---|---|
| Episodic Memory |  |  |  |
|   Immediate word recall | None | 2.65 | 0.11 |
|   Delayed word recall | None | 0.30 | 0.59 |
|   3-minute delayed Figure recall | None | 0.82 | 0.37 |
| Executive functions |  |  |  |
|   Stroop | None | 0.05 | 0.82 |
| Working Memory |  |  |  |
|   Coding | Linear (positive) | 8.13 | 0.006 |
| Language/visuo-spatial |  |  |  |
|   Boston Naming | None | 0.001 | 0.97 |
|   Benton line orientation | None | 1.08 | 0.31 |

## Table 3
### Summary table for the polynomial regression analyses of performance in the progressor group

| Cognitive Test | Significant model | F value | $p$ value | Beta |
|---|---|---|---|---|
| Episodic Memory |  |  |  |  |
|   Immediate word recall | Linear | 17.64 | <0.01 | −0.78 |
|   Delayed word recall | Quadratic | 4.84 | 0.03 | −2.1 |
|   3-minute delayed Figure recall | Quadratic | 5.57 | 0.020 | −3.55 |
| Executive Functions |  |  |  |  |
|   Stroop | Linear | 4.53 | 0.035 | 2.45 |
| Working Memory |  |  |  |  |
|   Coding | Quadratic | 8.68 | 0.004 | −0.9 |
| Language/visuo-spatial |  |  |  |  |
|   Boston Naming | None | 2.67 | 0.11 | −0.44 |
|   Benton line orientation | Linear | 6.7 | 0.02 | −1 |

Immediate Words Recall (RL/RI)

| | -4 | -3 | -2 | -1 | 0 |
|---|---|---|---|---|---|
| Non-Progressors: | 25 | 38 | 49 | 74 | 72 |
| Progressors: | 9 | 17 | 23 | 47 | 45 |
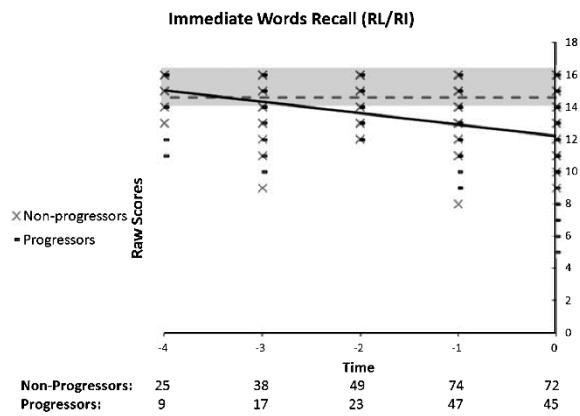
**Fig. 2.** Performance on the RL/RI's Immediate Words Recall as a function of time to diagnosis (for progressors) or on the last 5 cognitive assessments (for non-progressors). A linear function best describes the distribution for the progressors: black line. No significant model is found in the non-progressors: dotted grey line. The number of participants by group on each time point is presented. The shading area represents -1.5 and +1.5 SD of the mean performance of cognitively healthy older adults (derived from normative data for the mean age of the whole group).
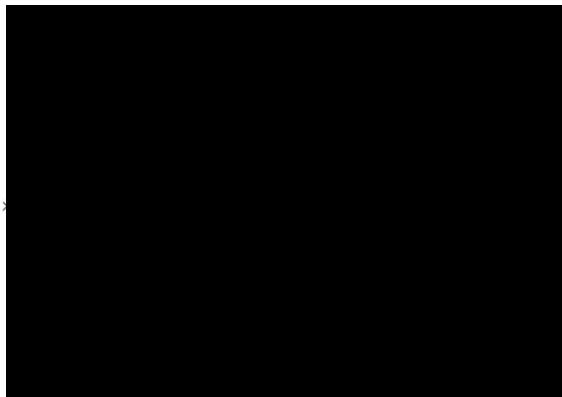


**Fig. 3.** Performance on the RL/RI's Delayed Words as a function of time to diagnosis (for progressors) or on the last 5 cognitive assessments (for non-progressors). A quadratic function best describes the distribution for the progressors: black line. No significant model is found in the non-progressors: dotted grey line.

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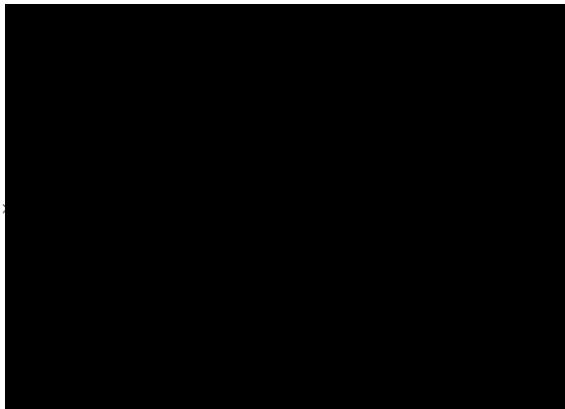
**Fig. 4.** Performance on spatial memory as a function of time to diagnosis (for progressors) or on the last 5 cognitive assessments (for non-progressors). A quadratic function best describes the distribution for the progressors: black line. No significant model is found in the non-progressors: dotted grey line.



**Inhibition (Stroop)**

| | | | | | |
|---|---|---|---|---|---|
| **Non-Progressors:** | 24 | 38 | 49 | 74 | 70 |
| **Progressors:** | 9 | 17 | 23 | 46 | 46 |
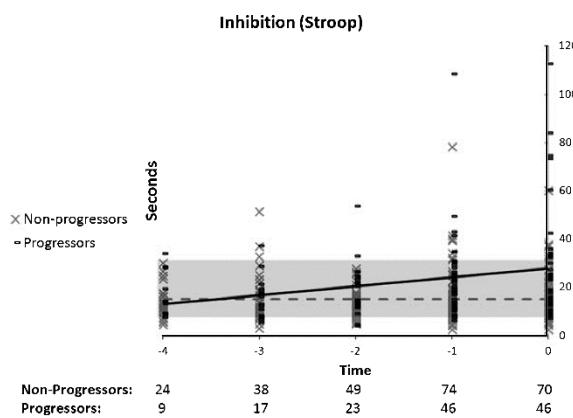
**Fig. 5**. Performance on the inhibition component of the Stroop Test as a function of time to diagnosis (for progressors) or on the last 5 cognitive assessments (for non-progressors). A linear function best describes the distribution for the progressors: black line. No significant model is found in the non-progressors: dotted grey line.
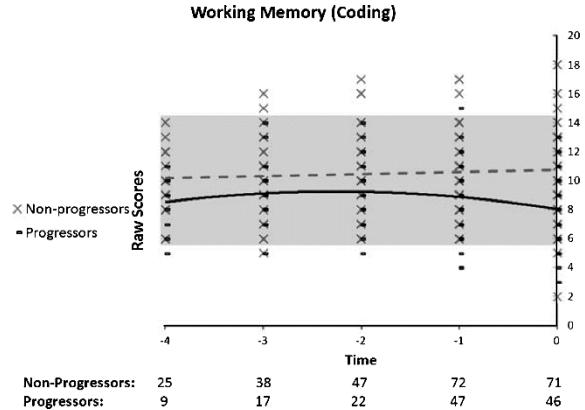
**Fig. 6.** Performance on working memory (coding) as a function of time to diagnosis (for progressors) or on the last 5 cognitive assessments (for non-progressors). A quadratic function best describes the distribution for the progressors: black line. A linear function best describes the distribution for the non-progressors: dotted grey line.
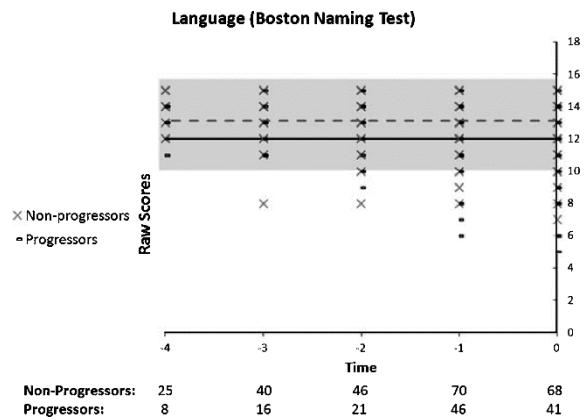


**Fig. 7.** Performance on the Boston Naming Test as a function of time to diagnosis (for progressors) or on the last 5 cognitive assessments (for non-progressors). No significant model is found in the progressors: black line, or in the non-progressors: dotted grey line.
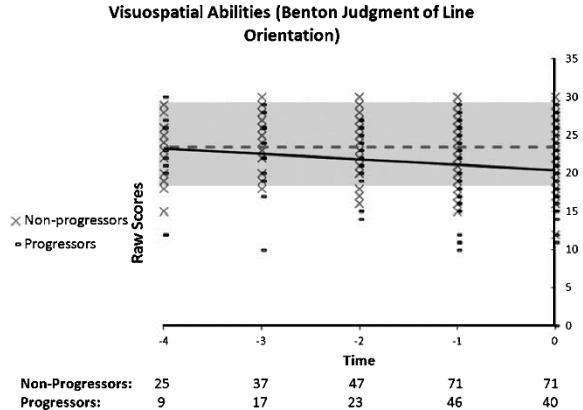
**Fig. 8.** Performance on the Benton Judgment of Line Orientation as a function of time to diagnosis (for progressors) or on the last 5 cognitive assessments (for non-progressors). A linear function best describes the distribution for the progressors: black line. No significant model is found in the non-progressors: dotted grey line.

*Episodic memory*

The regression analysis indicated a significant linear model for immediate recall of the verbal memory test in the progressor group, but none were found to be significant in the non-progressors group. This indicates a gradual decline of immediate recall in progressors and no change in non-progressors (See Fig. 2). The Group by Time ANOVA on the immediate recall indicated a Group effect, (F(1, 68) = 19.06, $p < 0.01$) as progressors ($n = 22$) recalled less words than non-progressors ($n = 48$) overall. There was no Time or Group by Time interaction. Combining the two analyses indicates that decline in progressors was very gradual and that they differed from non-progressors on all time periods.

The quadratic model best describes the data pertaining to the progressor group for the delayed recall (Fig. 3). This suggests there is a presence of one fracture in the pattern of decline. None of the models were found to be significant in the non-progressors group. The Group by Time ANOVA indicated a significant Group by Time interaction (F(2, 138) = 11.31,

$p < 0.01$). Time was significant in the progressor group ($n = 22$) ($F_{(2, 42)} = 14.61, p < 0.01$), but not in the non-progressors group ($n = 49$) ($F_{(2, 96)} = 0.4, p = 0.65$). *Post-hoc* comparisons with Bonferroni adjustments of measurement times in progressors indicated that T0 (M = 4.5) differed from T-2 (M = 7.5) and T-1 (M = 6.3) but that T-2 and T-1 did not differ one from another. Thus, a fast decline occurs just prior to diagnosis. Progressors differed from non-progressors on all time periods. Combining the two analyses indicates that the progressors are significantly impaired at baseline but that there is an accelerated decline one year prior to diagnosis.

A quadratic polynomial model best explained nonverbal memory performance (Fig. 4) in progressors, suggesting the presence of one fracture in the pattern of decline. Examination of Fig. 4 shows that performance in progressors is stable before suffering an accelerated decline. The Group by Time ANOVA indicated a significant interaction ($F_{(2, 124)} = 3.23, p = 0.045$) due to the fact that the Time effect was only significant in the progressor ($n = 19$) group, ($F_{(2, 36)} = 6.7, p = 0.008$), but not significant in the non-progressors ($n = 45$) group ($F_{(2, 88)} = 1.77, p = 0.18$). In progressors, the difference between T-2 (M = 12.2) and T0 (M = 8.2) was significant but T-1 (M = 11) did not differ from T0. Furthermore, the groups were different on all times. The regression in combination with the ANOVA indicates that progressors and non-progressors' performance on spatial memory was similar at entry, and that progressors began their accelerated decline two years prior to diagnosis, at which point the groups showed significant differences.

*Executive functions*

The regression analyses revealed a significant linear decline in the case of the Stroop

test (Fig. 5) for progressors whereas no model fitted the data in non-progressors. The Group by Time ANOVA indicated a significant Group effect, $F_{(1, 67)} = 22.58$, $p < 0.01$, but no Time or Group by Time interaction. Thus, executive function gradually worsened in progressors ($n = 21$), who displayed lower performance than non-progressors ($n = 48$) on all time periods.

*Working memory*

Regarding the Coding task (Fig. 6), the quadratic trend was significant in progressors, whose performance remained stable for some years before presenting an accelerated decline just prior to diagnosis. A positive linear trend explained performance in non-progressors, suggesting an improvement over time in that group. The Group by Time ANOVA indicated the presence of a main Group effect ($F_{(1, 65)} = 13.05$, $p = 0.01$), which was qualified by a significant interaction ($F_{(2, 130)} = 8.38$, $p = 0.001$). The interaction was explained by the presence of a Time effect in the progressor group ($n = 22$) ($F_{(2, 42)} = 5.4$, $p = 0.014$), as well as in the non-progressors group ($n = 45$) ($F_{(2, 88)} = 4.67$, $p = 0.014$). *Post-hoc* comparisons indicated a significant difference between T-1 ($M = 9.2$) and T0 ($M = 8.2$) for the progressors, and a significant difference between T-2 ($M = 10.78$) and T0 ($M = 11.42$) for the non-progressors. Also, the groups significantly differed on all time points. By combining the two analyses, it was thus revealed that on working memory, the progressors' performance was impaired at baseline compared to non-progressors and presented an accelerated decline in the year preceding the diagnosis of dementia. It was also revealed that the non-progressors showed a significant improvement on this task in the last 3 years of the follow-up.

*Language*

When analyzing the Boston Naming Test (Fig. 7) in the progressor and non-progressors groups, none of the models were significant, suggesting that both groups had a stable performance over time. However, the Group by Time ANOVA revealed a significant Group effect, $F (1, 60) = 5.92$, $p = 0.018$, as non-progressors ($n = 45$) performed better than progressors ($n = 17$) overall. There was no Time or Group by Time interaction.

*Visual-spatial abilities*

The progressor group's performance on the Benton Judgement of Line Orientation (Fig. 8) was best described by a linear model, which suggested a gradual and fairly slow progression. None of the models were found to be significant for non-progressors. The Group by Time ANOVA indicated a significant interaction, $F (2, 118) = 4.62$, $p = 0.014$. Bonferroni *post-hoc* revealed a significant difference between the groups only on T0, which supports the presence of a very slow decline in the progressors ($n = 18$), but not in the non-progressors $n = 43$) with the groups diverging only on the year of the diagnosis.

**DISCUSSION**

The goal of this study was to examine the trajectories of decline during the MCI phase that precedes a diagnosis of dementia as a function of cognitive domains. The study is innovative compared to other natural history studies as it contrasts a group of patients with dementia and non-progressor MCI group, it analyzes the data as a function of time of diagnosis rather than study entry and it compares decline as a function of the cognitive domain. Also, it explores more complex statistical models, which allowed for a better representation of how the decline really unfolds during the pre-dementia phase.

The data lead to clear findings in relation to our initial objectives. First, cognitive deficits vary as a function of whether MCI participants later progress to AD or not. The non-progressors presented an improvement in working memory, which could reflect practice effects, and remain stable on all other cognitive measures, whereas the progressors show a decline on almost all cognitive domains. Second, the different cognitive domains have strikingly different patterns of trajectory changes. Linear decline is not the norm and a more complex quadratic pattern occurs frequently with a period of stability or very mild decline followed by an acceleration of decline one or two years prior to diagnosis. Our findings indicate three major types of cognitive trajectories. 1) *Stable impairment* was observed for language and is characterized by an impaired performance with no signs of deterioration as patients progress toward dementia. 2) *Gradual appearance of impairment* was found for immediate recall, inhibition, and visuo-spatial abilities and is characterized by an initially normal performance followed by a very gradual linear decline. 3) *Stable followed by accelerated decline* was found for delayed recall, visuo-spatial memory, and working memory (coding) and is characterized by a stable performance followed by a fast decline prior to conversion. These findings are discussed below as a function of the more precise pattern of change observed for cognitive domains.

Episodic memory and working memory are the cognitive domains that are the most impaired and that presented the fastest decline in the MCI progressor group: they are already impaired many years prior to diagnosis and present a fast decline right before the conversion year. This is consistent with the observation that MCI is mainly characterized by memory deficits (Petersen, Stevens, et al., 2001; Small et al., 2000), and that both episodic memory and working memory are impaired early in the disease process and are predictors of conversion from MCI to

AD (Belleville, Gauthier, et al., 2014; Peters, Villeneuve, & Belleville, 2014) (for a review, see (Belleville, Fouquet, Duchesne, Collins, & Hudon, 2014)) and from healthy aging to MCI (Rizk-Jackson et al., 2013).

Importantly, our study showed that memory is not the only cognitive domain that is impaired in MCI progressing toward AD. Many other domains show impairment that increases in severity. One of them is the domain of executive functions. This differs from the study of Bennett et al. (Bennett et al., 2002), which failed to observe a deterioration of executive functions. This difference might be due to the fact that Bennet et al. had used   a composite measure for executive functions whereas we relied on the inhibition portion of the Stroop test. There is increasing evidence that the executive domain reflects a range of cognitively and neurologically distinct processes (de Frias, Dixon, & Strauss, 2009; Miyake et al., 2000; Sylvain-Roy, Lungu, & Belleville, 2014). So perhaps, not all of these domains are equally sensitive to AD (Belleville, Chertkow, & Gauthier, 2007). Among them, inhibition and working memory appeared to be particularly sensitive and were reported to be severely impaired in MCI (Belanger & Belleville, 2009; Belanger, Belleville, & Gauthier, 2010; Johns et al., 2012; Zheng et al., 2012). One other crucial difference between the two studies is that we differentiated non-progressor from progressor MCI. Some studies have indicated that executive functions and inhibition are more impaired in progressors than in non-progressor MCIs (Belanger & Belleville, 2009; Rainville, Lepage, Gauthier, Kergoat, & Belleville, 2012; N. L. Saunders & Summers, 2010; N. L. J. Saunders & Summers, 2011) and predictive models that are most sensitive and specific often include executive function measures (Belleville, Gauthier, et al., 2014) (for a review, see (Belleville, Fouquet, et al., 2014)). Our results support this literature as executive

functions were found to differ between non-progressor and progressor MCI and only the latter showed increased impairment.

While progressor MCIs are globally impaired on the Boston naming test, we did not find any significant decline for language. These results contrast with the decline on semantic memory previously reported for individuals with MCI (Bennett et al., 2002; Gardini et al., 2013; Price et al., 2012). It should be noted, though, that many of the previous studies used a verbal fluency task to measure language, a task that has some executive component. The test that we used to evaluate language was a picture-naming task. It is possible that it reflects dimensions of language that do not decline as much as those measured by tests of verbal fluency. Our results indicate that episodic memory and working memory are significantly impaired many years preceding dementia but then show no change for a period of time before presenting an accelerated decline just prior to dementia. This pattern, which we found only for these two cognitive domains, supports the plateau model proposed by Twamley and colleagues (Twamley et al., 2006) for memory, and the data from Smith et al. (Smith et al., 2007) and Backman et al. (Backman et al., 2001). This pattern of decline was suggested to result from the fact that compensatory processes are particularly active during the very early phase of MCI and support memory maintenance. As the patient progresses toward dementia, however, there is a failure in compensatory mechanisms. A similar hypothesis has been proposed to account for the presence of hyperactivation in fMRI followed by hypoactivation as patients progress toward dementia (Clement & Belleville, 2010, 2012; Clement, Gauthier, & Belleville, 2013). The fact that this finding is only present in MCI progressors and not in non-progressor MCIs indicates that this pattern arises as a result of the underlying pathology and is not a mere reflection of older adults with reduced memory capacities. Our findings also indicate that different cognitive domains have

different cognitive trajectories. Non-progressors showed virtually no change in their cognition whereas progressors manifested decline in nearly all domains confirming that the presence of a cognitive decline might be an indication of future progression. Note however, absence of decline does not constitute a perfect indicator of protection against con- version to dementia as decline varies across domains and across time. For instance, performance on naming remained stable up to dementia diagnosis, even in those who developed AD. Similarly, while episodic memory suffers important decline one to two years prior to diagnosis, it can remain stable for a while when tested many years prior. These results stress the importance of carefully considering the types of measures to be included when one intends to assess cognitive change with composite aggregates, as including measures that are not sensitive to change will reduce the power to detect change in populations. Sensitivity to change might also depend on where patients stand on the severity continuum. The quadratic pattern found in many instances indicates that domains that remain stable at some point in time during the progression can be those showing the largest changes at other time points. As a result, measures such as delayed recall and inhibition might be particularly sensitive to change in the years close to the diagnosis. Thus, more studies will be needed before we can ascertain that cognitive change is a reliable indicator at all stages of the disease.

*Limitations*

This study has certain limitations that should be acknowledged. First, the diagnosis was based on clinical criteria and we did not include biomarkers. For this reason, we are unable to draw conclusions regarding the etiology of the disease in these individuals, as the more recent research criteria of the National Institute on Aging for MCI and AD include the presence of biomarkers confirmed by imaging (Albert et al., 2011; McKhann et al., 2011). Furthermore, the

conventional Petersen/Winbald criteria were used for MCI diagnosis, but more recent criteria based on the neuropsychological method of actuarial diagnostic decision-making (Jak/Bondi criteria) were shown to improve diagnostic precision and to be less susceptible to false positives (Bondi et al., 2014). Second, we did not include healthy older adults to serve as a control group, as our goal was to examine the natural history of a clinical cohort as a function of future progression to dementia. As a result, it is not possible to know whether non-progressor MCIs are impaired relative to a comparative group of older adults with no complaint. It is of note, however, that mean performance levels indicate that, apart from verbal memory, the non-progressors present a performance similar to that of healthy older adults (Dion et al., 2015; Fastenau, Denburg, & Hufford, 1999; Hudon et al., 2009). The fact that we used a retrospective design is a strength, as it allows us to distinguish individuals who will receive a diagnosis of AD from those who do not progress, and to compare their cognitive profiles. However, it also introduces challenges on a methodological level. One is that different time points do not benefit from the same amount of practice across individuals, as they are defined retrospectively with respect to diagnosis time. In addition, we had to arbitrarily determine that the last assessment for the non-progressors represented T0. Because time to diagnosis (or time between study entry and diagnosis) varies across subjects, the number of participants decreased as time to diagnosis increased. These are caveats that we believe are compensated by the fact that we knew precisely the year of conversion to dementia, which allowed for a more accurate description of the natural history of the cognitive symptoms in MCI in the years preceding a diagnosis of AD. Also, even though the results of the polynomial regression analyses and the ANOVAs generally agree and are coherent, we found a significant linear decline in the progressors with the polynomials analyses for immediate words recall and executive functions, but no time effect with the

ANOVAs. This discrepancy may be explained by the fact that the polynomial regressions included more times and more participants, which increases the statistical power. Finally, factors that may influence cognitive decline in older adults were not considered in the analyses because they were unavailable. For example, genetic factors such as the presence of the E4 variant of the apolipoprotein gene can increase the risk of converting to AD (Liu, Kanekiyo, Xu, & Bu, 2013). We know that there is a relationship between high level of vascular burden, diseases and executive deficits (Villeneuve et al., 2009). In addition, for future studies, it would be important to consider sleep habits, as we know that poor sleep quality in the preclinical phase of AD is associated with aggregates of amyloid-þ peptide, which is characteristic of this type of dementia (Ju et al., 2013).

*Conclusion and implications*

Cognition declines in individuals with MCI as they progress toward dementia. However, the decline trajectory varies between cognitive domains. While some domains (immediate recall, visuo-spatial abilities, and inhibition) present a slow linear decline (linear trend), delayed recall, spatial memory, and working memory (coding) remain stable for a while but exhibit a large and accelerated decline just prior to diagnosis (quadratic trend). By contrasting the profiles of change of individuals with non-progressor MCI and of those who progressed to dementia, this study identified a profile of change that characterizes individuals who will progress toward dementia. A fast decline on episodic memory and working memory accompanied by impairment on language emerges as a profile that could reflect individuals presenting an elevated risk of converting to dementia in the near future. Another important finding is that decline was more pervasive and of a larger magnitude when patients were very close to the time at which they met the classification criteria for dementia, suggesting that the point of diagnosis might represent the

time at which the amount of brain damage is severe enough to yield a form of compensation failure which has a catastrophic effect on cognition and precipitates dementia (Clement & Belleville, 2010, 2012).

## ACKNOWLEDGMENTS

## References

Ahmed, S., Mitchell, J., Arnold, R., Nestor, P. J., & Hodges, J. R. (2008). Predicting rapid clinical progression in amnestic mild cognitive impairment. *Dement Geriatr Cogn Disord, 25*(2), 170-177. doi:10.1159/000113014

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., . . . Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 270-279. doi:10.1016/j.jalz.2011.03.008

American Psychiatric Association., & American Psychiatric Association. Task Force on DSM-IV. (2000). *Diagnostic and statistical manual of mental disorders : DSM-IV-TR* (4th ed.). Washington, DC: American Psychiatric Association.

Amieva, H., Jacqmin-Gadda, H., Orgogozo, J.-M., Le Carret, N., Helmer, C., Letenneur, L., . . . Dartigues, J.-F. (2005). The 9 year cognitive decline before dementia of the Alzheimer type: a prospective population-based study. *Brain, 128*, 1093-1101. doi:10.1093/brain/awh451

Backman, L., Small, B. J., & Fratiglioni, L. (2001). Stability of the preclinical episodic memory deficit in Alzheimer's disease. *Brain, 124*(Pt 1), 96-102.

Ballard, C., Gauthier, S., Corbett, A., Brayne, C., Aarsland, D., & Jones, E. (2011). Alzheimer's disease. *Lancet, 377*(9770), 1019-1031. doi:10.1016/S0140-6736(10)61349-9

Belanger, S., & Belleville, S. (2009). Semantic inhibition impairment in mild cognitive impairment: a distinctive feature of upcoming cognitive decline? *Neuropsychology, 23*(5), 592-606. doi:10.1037/a0016152

Belanger, S., Belleville, S., & Gauthier, S. (2010). Inhibition impairments in Alzheimer's disease, mild cognitive impairment and healthy aging: effect of congruency proportion in a Stroop task. *Neuropsychologia, 48*(2), 581-590. doi:10.1016/j.neuropsychologia.2009.10.021

Belleville, S., Chertkow, H., & Gauthier, S. (2007). Working memory and control of attention in persons with Alzheimer's disease and mild cognitive impairment. *Neuropsychology, 21*(4), 458-469. doi:10.1037/0894-4105.21.4.458

Belleville, S., Fouquet, C., Duchesne, S., Collins, D. L., & Hudon, C. (2014). Detecting Early Preclinical Alzheimer's Disease via Cognition, Neuropsychiatry, and Neuroimaging: Qualitative Review and Recommendations for Testing. *J Alzheimers Dis*. doi:10.3233/JAD-141470

Belleville, S., Gauthier, S., Lepage, E., Kergoat, M. J., & Gilbert, B. (2014). Predicting decline in mild cognitive impairment: A prospective cognitive study. *Neuropsychology, 28*(4), 643-652. doi:10.1037/neu0000063

Bennett, D. A., Wilson, R. S., Schneider, J. A., Evans, D. A., Beckett, L. A., Aggarwal, N. T., . . . Bach, J. (2002). Natural history of mild cognitive impairment in older persons. *Neurology, 59*, 198-205.

Benton, A. L., Hamsher, K., Varney, N. R., & Spreen, O. (1983). Contributions to neuropsychological assessment. . *New York: Oxford University Press*.

Bondi, M. W., Edmonds, E. C., Jak, A. J., Clark, L. R., Delano-Wood, L., McDonald, C. R., . . . Salmon, D. P. (2014). Neuropsychological criteria for mild cognitive impairment improves diagnostic precision, biomarker associations, and progression rates. *J Alzheimers Dis, 42*(1), 275-289. doi:10.3233/JAD-140276

Bossuyt, P. M., Reitsma, J. B., Bruns, D. E., Gatsonis, C. A., Glasziou, P. P., Irwig, L. M., . . . Standards for Reporting of Diagnostic Accuracy, G. (2003). The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. The Standards for Reporting of Diagnostic Accuracy Group. *Croat Med J, 44*(5), 639-650.

Chen, P., Ratcliff, G., Belle, S. H., Cauley, J. A., DeKosky, S. T., & Ganguli, M. (2001). Patterns of cognitive decline in presymptomatic Alzheimer disease: a prospective community study. *Arch Gen Psychiatry, 58*(9), 853-858.

Clement, F., & Belleville, S. (2010). Compensation and disease severity on the memory-related activations in mild cognitive impairment. *Biol Psychiatry, 68*(10), 894-902. doi:10.1016/j.biopsych.2010.02.004

Clement, F., & Belleville, S. (2012). Effect of disease severity on neural compensation of item and associative recognition in mild cognitive impairment. *J Alzheimers Dis, 29*(1), 109-123. doi:10.3233/JAD-2012-110426

Clement, F., Gauthier, S., & Belleville, S. (2013). Executive functions in mild cognitive impairment: emergence and breakdown of neural plasticity. *Cortex, 49*(5), 1268-1279. doi:10.1016/j.cortex.2012.06.004

de Frias, C. M., Dixon, R. A., & Strauss, E. (2009). Characterizing executive functioning in older special populations: from cognitively elite to cognitively impaired. *Neuropsychology, 23*(6), 778-791. doi:10.1037/a0016743

Dion, M., Potvin, O., Belleville, S., Ferland, G., Renaud, M., Bherer, L., . . . Rouleau, I. (2015). Normative data for the Rappel libre/Rappel indicé à 16 items (16-item Free and Cued Recall) in the elderly Quebec-French population. *Clin Neuropsychol, 28*(sup1), 1-19.

Dupéré, V., Lacourse, E., Vitaro, F., & Tremblay, R. E. (2007). Méthodes d'analyse du changement fondés sur les trajectoires de développement individuel. *Bulletin de méthodologie sociologique, 95*, 26-57.

Eubank, R. L. (1999). *Nonparametric regression and spline smoothing* (2nd ed.). New York: Marcel Dekker.

Fastenau, P. S., Denburg, N. L., & Hufford, B. J. (1999). Adult norms for the Rey-Osterrieth Complex Figure Test and for supplemental recognition and matching trials from the Extended Complex Figure Test. *Clin Neuropsychol, 13*(1), 30-47. doi:10.1076/clin.13.1.30.1976

Fellows, L., Bergman, H., Wolfson, C., & Chertkow, H. (2008). Can clinical data predict progression to dementia in amnestic mild cognitive impairment? *Can J Neurol Sci, 35*(3), 314-322.

Field, A. P. (2013). *Discovering statistics using IBM SPSS statistics : and sex and drugs and rock 'n' roll* (4th ed.). Los Angeles: Sage.

Gainotti, G., Quaranta, D., Vita, M. G., & Marra, C. (2014). Neuropsychological predictors of conversion from mild cognitive impairment to Alzheimer's disease. *J Alzheimers Dis, 38*(3), 481-495. doi:10.3233/JAD-130881

Gardini, S., Cuetos, F., Fasano, F., Pellegrini, F. F., Marchi, M., Venneri, A., & Caffarra, P. (2013). Brain structural substrates of semantic memory decline in mild cognitive impairment. *Curr Alzheimer Res, 10*(4), 373-389.

Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R. C., Ritchie, K., Broich, K., . . . Winblad, B. (2006). Mild cognitive impairment. *Lancet, 367*, 1262-1270.

Hudon, C., Potvin, O., Turcotte, M. C., D'Anjou, C., Dube, M., Preville, M., & Brassard, J. (2009). [Normative date for the Mini-Mental State Examination (MMSE) in a sample of community dwelling French speaking residents from Quebec aged 65 and older]. *Can J Aging, 28*(4), 347-357. doi:10.1017/S0714980809990171

Johns, E. K., Phillips, N. A., Belleville, S., Goupil, D., Babins, L., Kelner, N., . . . Chertkow, H. (2012). The profile of executive functioning in amnestic mild cognitive impairment: disproportionate deficits in inhibitory control. *J Int Neuropsychol Soc, 18*(3), 541-555. doi:10.1017/S1355617712000069

Ju, Y. E., McLeland, J. S., Toedebusch, C. D., Xiong, C., Fagan, A. M., Duntley, S. P., . . . Holtzman, D. M. (2013). Sleep Quality and Preclinical Alzheimer Disease. *JAMA Neurol*, 1-7. doi:10.1001/jamaneurol.2013.2334

Kaplan, E. F., Goodglass, H., & Weintraub, S. (1983). The Boston Naming Test (2nd ed.). *Philadelphia, PA: Lea & Febiger*.

Lindeboom, J., & Weinstein, H. (2004). Neuropsychology of cognitive ageing, minimal cognitive impairment, Alzheimer's disease, and vascular cognitive impairment. *Eur J Pharmacol, 490*(1-3), 83-86. doi:10.1016/j.ejphar.2004.02.046

Liu, C. C., Kanekiyo, T., Xu, H., & Bu, G. (2013). Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nat Rev Neurol, 9*(2), 106-118. doi:10.1038/nrneurol.2012.263

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr., Kawas, C. H., . . . Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 263-269. doi:10.1016/j.jalz.2011.03.005

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. *Cogn Psychol, 41*(1), 49-100. doi:10.1006/cogp.1999.0734

Peters, F., Villeneuve, S., & Belleville, S. (2014). Predicting progression to dementia in elderly subjects with mild cognitive impairment using both cognitive and neuroimaging predictors. *J Alzheimers Dis, 38*(2), 307-318. doi:10.3233/JAD-130842

Petersen, R. C., Doody, R., Kurz, A., Mohs, R. C., Morris, J. C., Rabins, P. V., . . . Winblad, B. (2001). Current concepts in mild cognitive impairment. *Arch Neurol, 58*(12), 1985-1992.

Petersen, R. C., Stevens, J. C., Ganguli, M., Tangalos, E. G., Cummings, J. L., & DeKosky, S. T. (2001). Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology, 56*(9), 1133-1142.

Price, S. E., Kinsella, G. J., Ong, B., Storey, E., Mullaly, E., Phillips, M., . . . Perre, D. (2012). Semantic verbal fluency strategies in amnestic mild cognitive impairment. *Neuropsychology, 26*(4), 490-497. doi:10.1037/a0028567

Rainville, C., Lepage, E., Gauthier, S., Kergoat, M. J., & Belleville, S. (2012). Executive function deficits in persons with mild cognitive impairment: a study with a Tower of London task. *J Clin Exp Neuropsychol, 34*(3), 306-324. doi:10.1080/13803395.2011.639298

Regard, M. (1981). Cognitive rigidity and flexibility: A neuropsychological study. PhD dissertation. *University of Victoria, Canada*.

Rey, A. (1959). Test de copie d'une figure complexe: Manuel. *Paris: Les Éditions du Centre de Psychologie Appliquée.*

Rizk-Jackson, A., Insel, P., Petersen, R., Aisen, P., Jack, C., & Weiner, M. (2013). Early indications of future cognitive decline: stable versus declining controls. *PLoS One, 8*(9), e74062. doi:10.1371/journal.pone.0074062

Salmon, D. P., & Bondi, M. W. (2009). Neuropsychological assessment of dementia. *Annu Rev Psychol, 60*, 257-282. doi:10.1146/annurev.psych.57.102904.190024

Saunders, N. L., & Summers, M. J. (2010). Attention and working memory deficits in mild cognitive impairment. *J Clin Exp Neuropsychol, 32*(4), 350-357. doi:10.1080/13803390903042379

Saunders, N. L. J., & Summers, M. J. (2011). Longitudinal Deficits to Attention, Executive, and Working Memory in Subtypes of Mild Cognitive Impairment. *Neuropsychology, 25*, 237-248. doi:10.1037/a0021134

Small, B. J., Fratiglioni, L., Viitanen, M., Winblad, B., & Backman, L. (2000). The course of cognitive impairment in preclinical Alzheimer disease: three- and 6-year follow-up of a population-based sample. *Arch Neurol, 57*(6), 839-844.

Smith, G. E., Pankratz, V. S., Negash, S., Machulda, M. M., Petersen, R. C., Boeve, B. F., . . . Ivnik, R. J. (2007). A plateau in pre-Alzheimer memory decline: evidence for compensatory mechanisms? *Neurology, 69*(2), 133-139. doi:10.1212/01.wnl.0000265594.23511.16

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., . . . Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease:

recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 280-292. doi:10.1016/j.jalz.2011.03.003

Sylvain-Roy, S., Lungu, O., & Belleville, S. (2014). Normal Aging of the Attentional Control Functions That Underlie Working Memory. *J Gerontol B Psychol Sci Soc Sci*. doi:10.1093/geronb/gbt166

Twamley, E. W., Ropacki, S. A., & Bondi, M. W. (2006). Neuropsychological and neuroimaging changes in preclinical Alzheimer's disease. *J Int Neuropsychol Soc, 12*(5), 707-735. doi:10.1017/S1355617706060863

Van der Linden, M., Adam, S., Agniel, A., Baisset-Mouly, C., Bardet, F., Coyette, F., & al., e. (2004). L'évaluation de troubles de la mémoire: présentation de quatre tests de mémoire épisodique (avec étalonnage). *Marseille: Solal.*

Villeneuve, S., Belleville, S., Massoud, F., Bocti, C., & Gauthier, S. (2009). Impact of Vascular Risk Factors and Diseases on Cognition in Persons with Mild Cognitive Impairment. *Dementia and Geriatric Cognitive Disorders, 27*, 375-381. doi:10.1159/000209965

Wechsler, D. (1997). Weschsler Adult Intelligence Scale. *San Antonio*.

Wilson, R. S., Aggarwal, N. T., Barnes, L. L., Mendes de Leon, C. F., Hebert, L. E., & Evans, D. A. (2010). Cognitive decline in incident Alzheimer disease in a community population. *Neurology, 74*, 951-955.

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L. O., . . . Petersen, R. C. (2004). Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med, 256*(3), 240-246. doi:10.1111/j.1365-2796.2004.01380.x

Zheng, D., Dong, X., Sun, H., Xu, Y., Ma, Y., & Wang, X. (2012). The overall impairment of core executive function components in patients with amnestic mild cognitive impairment: a cross-sectional study. *BMC Neurol, 12*, 138. doi:10.1186/1471-2377-12-138

**Chapitre IV**
**Article 3:** *Trajectories of Decline on Instrumental Activities of Daily Living Prior to Dementia in Persons with Mild Cognitive Impairment*

**Article 3: Trajectories of decline on instrumental activities of daily living prior to dementia in persons with mild cognitive impairment**

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**<u>En préparation</u>**

**KEY POINTS**

**Question:** When do deficits in instrumental activities of daily living (iADL) occur and how do they change over time in the mild cognitive impairment (MCI) phase?

**Findings:** MCI progressors experience many years of iADL stable performance but they show a rapid decline of complex iADL about two years prior to the clinical diagnosis of dementia, a pattern which is not found in stable MCI.

**Meaning:** Performance on iADL declines in late MCI, especially for complex tasks, and observing a change on these activities, particularly when combined with lower performance on neuropsychological tests, signals imminent progression to dementia in the following one or two years.

**ABSTRACT**

**Importance:** Very few studies have investigated the trajectories of decline on instrumental activities of daily living (iADL) in the years preceding a diagnosis of dementia.

**Objective:** The main objective was to determine the trajectory of iADL decline in persons with mild cognitive impairment (MCI) who progressed towards dementia or more severe cognitive symptoms relative to persons with MCI who remained stable. Relevant iADL dimensions were based on a principal components analysis. Polynomial analyses were then used to identify the function that best describe change on those dimensions.

**Design:** This is a longitudinal case-control observational study.

**Setting:** Patients were recruited from memory clinics.

**Participants:** At study entry, all participants met criteria for MCI. Based on the follow-up, 47 participants later converted to dementia and were identified as progressors. Sixteen participants, identified as decliners, presented a significant cognitive decline but did not reach the criteria for dementia within the study timeframe. Stable MCI remained cognitively stable during the 5-year follow-up; $n = 58$.

**Exposure:** Participants completed a yearly assessment using clinical tests/questionnaires, clinical neuropsychological measures and functional autonomy assessment until they met criteria for dementia. The average number of months for the follow-up was 34.

**Main Outcomes and Measures:** The principal components analysis of responses on the Functional Autonomy Measurement System scale identified two iADL domains: *complex activities* and *housekeeping-related activities*.

**Results:** A quadratic function, i.e. many years of stable performance followed by an accelerated decline just prior to diagnosis, was observed for complex activities for progressors. No change was found for stable MCI and a gradual linear decline characterized decliners. The *housekeeping-related activities* component showed a linear decline in progressors and did not change in stable and decliner MCI. We propose a predictive model that includes significant predictors of dementia conversion with a high diagnostic accuracy the following year (area under the curve = .94 (95% confidence level; lower bound: .87, upper bound: 1)).

**Conclusions and Relevance:** It is critical to assess iADL that reflect complex activities in the evaluation of MCI individuals as their impairment, combined with change on cognitive markers, indicates a higher risk of dementia progression one or two years later. Close monitoring of complex iADL in persons at risk for dementia can be used to assess imminent progression.

**BACKGROUND**

Dementias are a group of major neurocognitive disorders that are defined by a decline from previous levels of functioning and a cognitive impairment involving at least two cognitive domains [1]. Alzheimer's disease (AD) is the most common type of dementia. AD is characterized by an insidious onset and is known to have a long prodromal phase during which cognitive symptoms are mild or absent. The term mild cognitive impairment (MCI) is used to describe individuals whose performance on neuropsychological tests is abnormal for their age and education level. Persons with MCI don't meet the criteria for dementia because the cognitive deficits are not severe enough to significantly interfere with activities of daily living (ADL) [2-4]. Yet, the disease is progressive and as cognitive deficits accumulate, patients may experience growing problems in their ability to perform activities of daily living (ADL) particularly instrumental ADL (iADL) such as financial management, use of telephone or cooking, as these require more advanced skills [5].

There is some evidence that MCI participants are significantly more impaired on iADL than healthy older adults [6]. Difficulties with executive functions, which include the cognitive abilities used to control actions and goal-oriented behavior, have been consistently associated with difficulties in performing iADL in early dementia [7-10]. Similar difficulties can occur for MCI individuals, since executive functions are already impaired during that phase [11-13]. It has been found that individuals with MCI are impaired relative to controls on complex iADL related to frontal/executive functioning, such as keeping appointments and managing belongings [14]. Even when performance scores on iADL scales are similar to controls, some subtle but still notable difficulties were found during MCI, such as a reduced speed in telephone

use or medication management [15]. Subtle changes in the ability to perform iADL have been observed up to 10 years before the clinical diagnosis of dementia [16].

Given that iADL are impaired early in the disease process and may index future decline, it is critical to know the moment at which those difficulties appear. It is also critical to describe their trajectory and how they change over time because changes in functions is often considered as a more sensitive and specific marker of future decline than performance level at a single timepoint. Since cognitive deficits increase in severity and breadth during the MCI phase [17, 18], the magnitude of the functional impact is likely to change as well. However, there are few longitudinal studies investigating the trajectory of iADL change in the years preceding the AD diagnosis and as a result, little is known regarding the way iADL impairment unfolds over time.

Regarding cognition, the trajectory is characterized by a rapid and severe decline of episodic and working memory just prior to diagnosis [17, 19]. Since the ability to perform iADL depend largely on executive functions and memory capacities, their impairment may follow a similar trajectory, that is years of stable performance followed by a rapid decline just prior to the diagnosis. Furthermore, as not all MCI will progress to dementia, it is important to compare the trajectory in those who progressed to a dementia diagnosis (MCI progressors) relative those who did not progress (MCI non-progressors). No study, to our knowledge, has examined the natural history of the decline in iADL for a clinical cohort of MCI individuals as a function of whether they progressed to dementia or remained stable.

Thus, the objective of this study was to assess the trajectory of decline in iADL for MCI progressors and compare this trajectory with the one found in MCI non-progressors. This was done using mixed model analysis with polynomial regressions to assess with more precision the

way the ability to perform iADL change over time. A second objective was to determine if combining information on iADL and cognitive performance may offer a sensitive model to predict future progression [20].

## METHODS

*Design*

Patients were recruited consecutively from memory clinics and were identified as meeting criteria for MCI by experienced clinicians (HC, MJK, SG). They were then referred to participate to a longitudinal study on cognition in MCI, which lasted for a period of 8 years [21]. At study entry and at yearly follow-up, participants completed a comprehensive clinical and neuropsychological examination. All measures were taken in a single testing session. The referring clinicians determined the clinical status on follow-up assessments, independent from the experimental tests, and experimental follow-up was interrupted the year a patient received a diagnosis of dementia. Thus, the last assessment corresponds to the year of dementia diagnosis.

T0 represents the year of conversion, i.e., the year when participants received the diagnosis of dementia for those who declined to AD. T -1, T -2, T -3, and T -4 represent the data collected one, two, three, and four years prior to diagnosis respectively. The last year of evaluation is labelled as T0 for non-progressors (decliners and stable MCI) and in this case, T -1, T -2, T -3, and T -4 represent the data collected one, two, three, and four years prior to the last assessment. Patients were followed for as long as they failed to progress to dementia up to the end of the cohort study, with a maximum follow-up of 94 months (average=33.88 months).

*Participants*[1]

One-hundred and fifty-one participants were recruited from memory clinics and met the criteria [3, 22] for amnestic MCI at entry. Thirty participants only had one assessment and were excluded from the analyses. Following study entry, participants received a yearly clinical follow-up that allowed to identify those who had progressed, hereby progressors. Progressors (N=47) were found to meet the clinical *DSM–IV* criteria for dementia of the Alzheimer type [23] at any point over the course of the follow-up. Amongst the non-progressors, some showed a significant cognitive decline (more than 1,5 SD from one year to the other) on neuropsychological tests and were thus classified as decliners (N=16). It is hypothesized that these individuals are in an earlier stage of the disease process and had not yet reached the point at which they could meet the criteria for dementia over the course of the follow-up. They were thus examined as a group of interest. The remaining of the non-progressors were classified as stable MCI (N=58).

*Cognitive measures*

Six neuropsychological tests were used to assess the cognitive profile of the participants: the RL/RI [24] (Free-Recall and Cued word Recall), the Rey complex geometrical figure test, 3 min-delay score [25] the Stoop-Victoria test [26], the Coding-subtest of the WAIS-R [27] the Benton Judgment of line orientation [28] and the 15-item version of the Boston Naming test [29]. For a detailed description of the cognitive tests, see Cloutier et al. [18]. The inclusion of these neuropsychological tests in the cognitive battery was based on 3 criteria : 1) they are

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[1] The same cohort of participants was part of a previous study investigating the patterns of cognitive decline prior to dementia [18].

standard tasks used in clinical setting; 2) they were shown to be sensitive in detecting cognitive impairment associated with AD [30]; and 3) they cover multiple cognitive domains, mainly episodic memory, executive functions, working memory, language and visuospatial processing.

*Instrumental Activities of Daily Living*

The instrumental subscale of the *Système de mesure de l'automie fonctionnelle* (SMAf; a French-language functional autonomy questionnaire) was used to assess performance in iADL. This scale was chosen since it was shown to have good inter-rater agreement and test-retest reliability [31]. It includes eight iADL items (cleaning, cooking, shopping, laundry, telephone use, use of transportation, in medication intake and budget management) scored between 0 and 3 (0 representing no self-reported impairment and 3 a significant handicap; e.g. for the budget item: 0 = Can manage budget alone; 1= Needs help with major transactions; 2= Needs help with daily transactions but is able to use pocket money; 3= Cannot manage a budget) by the participant. Thus, scores on individual item range from 0 to 3 and total scores range from 0 to 24. The clinical classification and dementia diagnosis of the participants were independent from the results of the SMAf instrument.

*Analysis*

We determined the outcomes by assessing which SMAf-8 items were grouped into subdomains of iADL using a principal components analysis on the scores obtained for each item on T0 using data from the whole group. This was done because it was expected that different iADL domains would have a different progression trajectory.

We then ran polynomial regression analyses (growth curves, mixed linear model analysis) to determine which model best fits the data over the 5-year follow-up period. This was

done for each group (progressors, decliners, stable) separately. The dependent variables were the total score on the SMAf (0-24) and the average score for the items clustering on the PCA determined factors. The data was analyzed as a function of time from diagnosis. We first verified whether a linear model was significant for each group and if it was, we proceeded to test more sophisticated models: the quadratic function, a second-order polynomial characterized by one fracture in the curve and the cubic function, a third-order polynomial. We also included age, gender, and education as controlled variables in the model. Time was considered in the models as repeated effects with a compound symmetry correlation matrix.

Following the regression analyses, we used separate 2 (Groups: progressors, non-progressors) x 3 (Time: T0, T -1, T -2) mixed analyses of variance (ANOVA) for each dependent variable to identify more precisely at what time the groups differed from one another. Here, the stable MCI group and the decliners were combined into a non-progressor group, so that the sample meets the postulate for group comparisons using parametric analysis. Only three years were used in order to maximize the number of participants, as ANOVA is not resistant to missing data and it was done with only the participants with at least three years of follow-up prior to diagnosis. The adjusted F was used to correct sphericity by removing the part of the effect that is explained by the systematic error. Greenhouse-Geisser's estimates were used to correct for error of the first kind.

We assess predictive accuracy of the models, that is the accuracy to predict future progression to dementia, by combining logistic regressions (Wald backward elimination stepwise selection) with receive operating characteristic (ROC) curve analyses. The cognitive

measures as well as the iADL scores were entered as predictors. The regressions were performed on each of the three years prior to dementia conversion.

Finally, to test whether the cognitive performance was predictive of the impairment on the iADL subdomains found with the PCA, we entered the scores on each of the cognitive tests in a mixed model analysis. Age, gender and education were entered in the regressions as controls. Since the data were collected using a longitudinal design, the repeated effects (Time) were considered in the model as random effects, using a compound symmetry covariance matrix.

**RESULTS**

*Socio-demographic and clinical characteristics*

The data from 121 participants (74 women) was analyzed. Demographic and clinical data are presented in Table 1.

Table 1. Clinical and demographic characteristics at entry and on T0 (Mean, SD in parentheses)

|  | Stable | Decliners | Progressors | p |
|---|---|---|---|---|
| **Age** |  |  |  |  |
| At entry | 68.09 (9.2) | 74.63 (6.4) | 71.47 (7.3) | **< 0.05** |
| On T0* | 72.53 (9) | 76.43 (6.4) | 74.11 (7.3) | .21 |
| **Education (years)** | 14.69 (3.9) | 14.31 (5.3) | 14.23 (4.1) | .85 |
| **N (Men/Women)** | 58 (22/36) | 16 (8/8) | 47 (17/30) | .61 |
| **Length of follow-up (months)** | 39.98 (17.7) | 20.88 (12.6) | 30.77 (19.6) | **< 0.01** |
| **GDS** |  |  |  |  |
| At entry | 1.23 (1.2) | 1.5 (1.3) | 1.05 (1.3) | .46 |
| On T0 | 1.26 (1.3) | 1.4 (1.5) | 1.21 (1.1) | .89 |
| **MMSE on T0** | 28.08 (2) | 27.47 (1.9) | 26.07 (2.6) | **< 0.01** |
| **MATTIS on T0** | 137.52 (2.9) | 130.47 (8.2) | 126.17 (10.1) | **< 0.01** |

* corresponds to the year of dementia progression in progressors and last year of testing for decliners and stable

*Principal Component Analysis for iADL*

Two components explained 57,64 % of the variance. The items that cluster on component 1 are Telephone use, medication intake, use of transportation, budget management and shopping suggesting that component 1 reflects the ability to carry on "complex iADL". The items cleaning, laundry and cooking loaded on Component 2 which was interpreted as reflecting a general "housekeeping iADL" factor.

*Growth curve models for Total iADL*

The regression analysis for total iADL indicated a significant quadratic trend for the progressors and a significant linear trend for the decliners (see Figure 1A). None of the models were found significant for the stable group. The ANOVA on the total iADL score indicated a significant Group x Time interaction ($F_{(2, 122)} = 14.83$, $p < 0,05$). The interaction was due to Time being significant for progressors (N = 24) ($F_{(2, 46)} = 10.43$, $p < 0,05$), but not for the non-progressors (N = 39). Post-hoc comparisons with Bonferroni adjustments in progressors indicate that T0 (M = 3,21) differed from T-1 (M = 1,67) and T-2 (M = 1,04), but T-1 and T-2 did not differ from each other. Furthermore, the difference between progressors and non-progressors was significant on both T0 and T-1.

*Growth curve models for Housekeeping-related iADL*

The regression analysis for *Housekeeping-related iADL* indicated a significant linear trend for the progressors (see Figure 1B). None of the models were found significant for the stable group. The ANOVA on housekeeping-related iADL indicated a significant Group x Time interaction ($F_{(2, 106)} = 6.3$, $p < 0,05$). The interaction was due to Time being significant for progressors (N = 21) ($F_{(2, 40)} = 4.06$, $p < 0,05$), but not for non-progressors (N = 34).

Furthermore, post-hoc comparisons indicated that the difference between progressors and non-progressors for the housekeeping-related iADL was significantly different on T0 only.

*Complex iADL*

The regression analysis for complex iADL indicated a significant quadratic trend for the progressors and a significant linear trend for the decliners (see Figure 1C). None of the models were found significant for the stable group. The ANOVA on complex iADL indicated a significant Group x Time interaction (F $(2, 106)$ = 6.51, p < 0,05). Time was significant for the progressors (N = 21) (F $(2, 40)$ = 5.27, p < 0,05), but not for non-progressors (N = 34). Post-hoc comparisons with Bonferroni adjustments in progressors indicated that T0 (M = 0,43) differed from T-2 (M = 0,17). Furthermore, the progressors significantly differed from non-progressors on both T0 and T-1.

**Figure 1.** Trajectories of decline in stable (dotted lines), decliners (broken line) and progressors (full line) as a function of time to diagnosis on A) total iADL; B) houskeeping and c) Complex iADL.
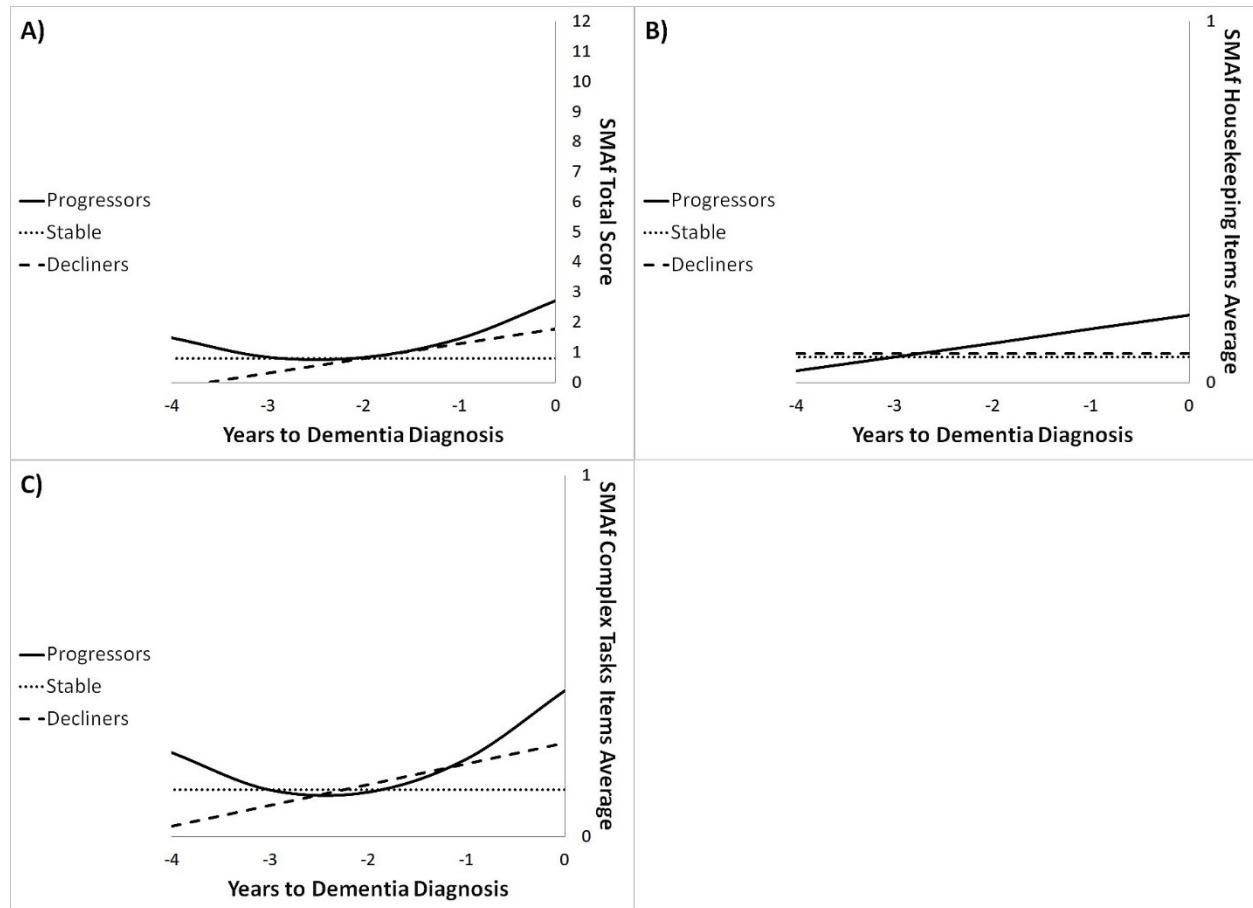


A. Score on SMAf total (sum of the 8 items) as a function of time to diagnosis (for progressors) or on the last 5 cognitive assessments (for the decliners and stable). Note that a higher score represents more functional impact. A quadratic function best describes the distribution for the progressors: black line. A linear function best describes the distribution for the decliners: big dots line. No significant model for stable: small dots line.

B. Score on the housekeeping-related iADL items as a function of time to diagnosis (for progressors) or on the last 5 cognitive assessments (for the decliners and stable). Note that a higher score represents more functional impact. A linear function best describes the distribution for the progressors: black line. No significant model for the declines (big dots line) and the stable: small dots line.

C. Score on the complex iADL items as a function of time to diagnosis (for progressors) or on the last 5 cognitive assessments (for the decliners and stable). Note that a higher score represents more functional impact. A quadratic function best describes the

distribution for the progressors: black line. A linear function best describes the distribution for the decliners: big dots line. No significant model for stable: small dots line.

*Predictive Diagnostic Accuracy*

The results of the logistic regression analysis (see Table 2) indicated that 3 years prior to dementia conversion (T -3), only the score of the delayed words recall was a significant predictor of dementia progression. On T -2, both delayed words recall and cognitive inhibition (Stroop) were significant predictors, whereas on T -1, the significant predictors of dementia progression were delayed word recall, cognitive inhibition, working memory (Coding) and complex iADLs. By combining the results of the logistic regression analysis with the trajectories of decline found using the polynomial regression analysis, we proposed a theoretical model of progression from MCI to dementia (see Figure 2).

Table 2. Logistic regressions for dementia conversion prediction

|  | B (SE) | p |
|---|---|---|
| **T-3** |  |  |
| Constant | 2.697 (.615) | **.000** |
| Delayed Word Recall | -.384 (.072) | **.000** |
| **T-2** |  |  |
| Constant | .613 (1.249) | .624 |
| Delayed Word Recall | -.353 (.113) | **< 0.01** |
| Stroop Inhibition | .143 (.053) | **< 0.01** |
| **T-1** |  |  |
| Constant | 3.054 (1.337) | **< 0.05** |
| Delayed Word Recall | -.366 (.085) | **< 0.01** |
| Stroop Inhibition | .06 (.026) | **< 0.05** |
| Coding | -.249 (.119) | **< 0.05** |
| Complex iADL | 4.477 (2.169) | **< 0.05** |
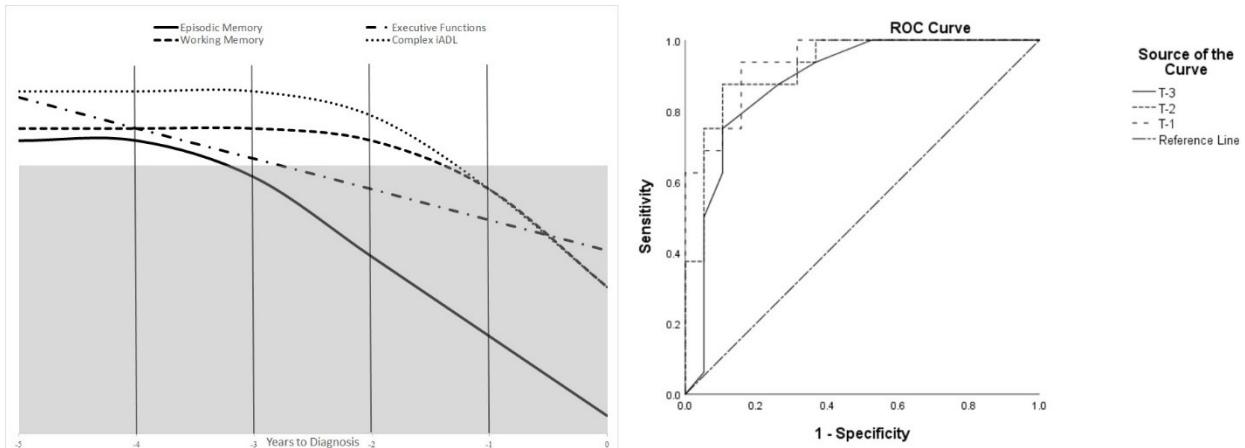
**Figure 2.** Prediction Model of Progression from MCI to Dementia (left) and Diagnostic Accuracy of this model (right). The grey area represents the significant predictors of conversion, based on the logistic regression analysis. ROC curve analysis indicated a good accuracy 3 years prior the diagnosis (Area under the curve (AUC) = .88 (95% confidence level; lower bound: .76, upper bound: 1)) and an excellent accuracy 2 years (AUC = .92 (95% confidence level; lower bound: .84, upper bound: 1)) and 1 year (AUC = .94 (95% confidence level; lower bound: .87, upper bound: 1)) before diagnosis.

The prediction accuracy of this model was assessed using ROC curve analysis (see Figure 2). Three years prior to the diagnosis, the performance of delayed words recall alone has a good predictive accuracy (area under the curve (AUC) = .88). The predictive accuracy increases to excellent (AUC = .92) 2 years prior to dementia progression when we include the performance on the executive functions task (cognitive inhibition). The diagnosis accuracy is also very high (AUC = .94) the year preceding dementia conversion when we include the significant predictors (episodic memory, executive functions, working memory and complex iADL scores).

*Relation between cognitive performance and iADL scores*

Performance on working memory (Coding) and episodic memory (spatial (Rey Complex figure) and verbal (immediate and delayed recall)) was a significant predictor for the scores in complex iADL (see Table 3). Thus, the worse was the performance on these cognitive tasks, the

greater was the impairment on complex iADL, all throughout the follow-up assessments. For the housekeeping-related activities domain, only the verbal episodic memory tasks (immediate and delayed recall) were significant predictors.

Table 3.

*CognitiveTests and iADL impairment (F values)*

|  | Complex iADL | Housekeeping-related activities |
| --- | --- | --- |
| Boston Naming Test | 3.67 | .16 |
| Coding | **3.89*** | .10 |
| Benton Judgment of Lines Orientation | .23 | .11 |
| Rey Complex Figure Test | **8.59**** | 1.04 |
| Stroop | .002 | 1.44 |
| Immediate Recall | **15.2**** | **6.2*** |
| Delayed Recall | **19.19**** | **8.59**** |

* $p < 0.05$
** $p < 0.01$

**DISCUSSION**

The goal of this study was to determine the decline trajectories of iADL in MCI in the years preceding a diagnosis of dementia. The study innovates by analyzing the data as a function of time to diagnosis rather than study entry and by examining complex models of decline in addition to the more traditional linear model.

A significant proportion of the participants (39%) progressed to dementia during the course of the study. MCI participants who progressed to dementia started to experience a

significant decline in their total iADL score about 2 years prior to the year they received their diagnosis. As a result, the impairment on iADL was apparent and statistically significant at least one year prior to their diagnosis. Even though the groups did not differ 2 years prior the progressors's diagnosis, a decline was nevertheless observed during that time. Indeed, we found that the trajectory followed a quadratic trend. In other words, scores on iADL remained stable for many years before presenting the rapid decline found in the 2 years before diagnosis.

A group of participants were identified as decliners. Those MCI did not meet the clinical criteria of dementia during the follow-up of the study, but still showed a significant cognitive decline over the years. They nevertheless experience a decline in iADL but it is slower and more gradual than in those who received their diagnosis within the timeframe of this study. It is likely that decliners are in an earlier phase of the disease than progressors. Thus, the linear decline might represent a prior state which we may not have been able to observe in progressors as their assessment may not have extended far back enough.

Importantly, the two iADL categories progress differently during the MCI phase. The trajectory of decline found for the total iADL score and described above seems to be explained by complex iADL. Indeed, this category of iADL follows the exact same trajectory, that is a quadratic trend for progressors, a linear trend for decliners and no effect of time for the stable MCI.

The results of the principal component analysis identified two broad iADL categories: housekeeping-related activities (cleaning, cooking and laundry) and complex iADL (telephone use, medication intake, use of transportation, budget management and shopping). This complex iADL category contains activities that have been related to cognitive decline and they were

found to be predictive of conversion to dementia the following year, in a large longitudinal population study [32, 33]. This category of iADL is also very similar to the Barberger-Gateau's 4-iADL (telephone use, transportation, medication intake and budget management). A functional impairment on these 4-iADL was suggested to represent an early marker of incident dementia up to 3 years before the diagnosis in a population cohort [34]. Our finding that the same domains are impaired with a very similar timeline in a clinical cohort is important because it indicates that the effect is independent of recruitment source and characteristics. Thus, the component analysis used here appears to have identified a clinically and empirically valid distinction among iADL, which brings external support to our approach.

One of our goals was to combine the complex iADL scores with the performance in cognition [17] to assess the diagnostic accuracy of a prediction model of progression from MCI to dementia. We observed that a significant impairment of episodic memory predicts progression three years prior to the diagnosis. We obtain an excellent diagnostic accuracy two years before dementia progression, by combining the performance on both memory and executive functions task (significant predictors). This is unsurprising, since we know that episodic memory and executive functions are both impaired early in the disease process and are predictors of conversion from MCI to AD [21, 35]. Cognitive tests have been shown to be excellent at predicting MCI individuals who will progress to dementia, and the predictive accuracy seems to be the highest when combining memory measures with a small set of other domains [36]. Our model reflects these findings since multi-domain impairment increases the risk of MCI to dementia conversion.

The year prior to the diagnosis, we observe that, on top of memory and executive functioning impairment, a decline in working memory and complex iADL contribute to predict progression. Thus, changes on complex iADL are accompanied by changes in working memory and preceded by a significant decline in executive functioning. This is consistent with data showing that executive functions are good predictors of functional impact in patients with relatively mild dementia [37], in patients with frontal lesions and in community-dwelling older adults [38, 39]. Our findings on the relationship between cognitive impairment and the decline in iADL, particularly for complex tasks, support the already established evidence from the literature. Our model proposes that a change in the ability to perform complex iADL may signal imminent conversion the following year. This is clinically relevant and may help the clinicians to implement interventions and accommodations as early as possible for their at risk patients and their family.

The strength of this model is that it relies on a very simple clinical assessment which is relatively cheap and readily available for family doctors' practice. This is a notable advantage over more complex investigations that include imaging and biomarkers.

*Limitations*

Some limitations must be acknowledged. First, the diagnosis was based on clinical criteria and we did not include biomarkers. For this reason, we are unable to draw conclusions regarding the etiology of the disease in these individuals [1, 40]. Second, we did not include healthy older adults to serve as a control group, as our goal was to examine the natural history of a clinical cohort as a function of future progression to dementia. As a result, it is not possible to know whether non-progressors (stable/decliners) MCIs are impaired relative to a comparative

group of older adults with no complaint. It is of note, however, that when comparing mean performance levels to those provided by normative values, stable MCI participants present a performance very similar to that of healthy older adults, apart from verbal memory which is impaired by design.

To measure everyday functioning, we used and 8-item self-reported questionnaire. Though, this has the advantage of simplicity of use, it may be biased by the participant's own impression of their abilities. Furthermore, the ecological validity of the measure is not assured as it is not a performance-based score. Also, the questionnaire may lack sensitivity to subtle difficulties expressed by MCI participants. Note however that we did nevertheless observe a reasonable range of values and were able to derive statistically valid models. Furthermore, it is important to mention that the ADL measure was not used for the dementia diagnosis. Thus, our findings are not counfounded by a dependence between dementia diagnosis and performance on the iADL scale.

*Conclusion and implications*

This study provides new information regarding the trajectory of iADL change during the MCI phase. Most prior studies have assumed a linear change function and change scores are typically derived using formula that don't consider the trajectory of change. Here we found that complex iADL are characterized by a quadratic function, that is years of stable performance followed by decline just prior to dementia progression. This highlights the importance of including iADL in the evaluation of MCI individuals and further challenge the idea that performance on activities of daily living is intact and does not change during the MCI phase.

# References

1.  McKhann, G.M., et al., *The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.* Alzheimers Dement, 2011. **7**(3): p. 263-9.

2.  Gauthier, S., et al., *Mild cognitive impairment.* Lancet, 2006. **367**(9518): p. 1262-70.

3.  Petersen, R.C., et al., *Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology.* Neurology, 2001. **56**(9): p. 1133-42.

4.  Sperling, R.A., et al., *Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.* Alzheimers Dement, 2011. **7**(3): p. 280-92.

5.  Pedretti, L.W., H.M. Pendleton, and W. Schultz-Krohn, *Pedretti's occupational therapy : practice skills for physical dysfunction.* 6th ed. 2006, St. Louis, Mo.: Mosby/Elsevier. xv, 1262 p.

6.  Gold, D.A., *An examination of instrumental activities of daily living assessment in older adults and mild cognitive impairment.* J Clin Exp Neuropsychol, 2012. **34**(1): p. 11-34.

7.  Marshall, G.A., et al., *Executive function and instrumental activities of daily living in mild cognitive impairment and Alzheimer's disease.* Alzheimers Dement, 2011. **7**(3): p. 300-8.

8.  Cahn-Weiner, D.A., P.A. Boyle, and P.F. Malloy, *Tests of executive function predict instrumental activities of daily living in community-dwelling older individuals.* Appl Neuropsychol, 2002. **9**(3): p. 187-91.

9.  Jefferson, A.L., et al., *Evaluating elements of executive functioning as predictors of instrumental activities of daily living (IADLs).* Arch Clin Neuropsychol, 2006. **21**(4): p. 311-20.

10. Martyr, A. and L. Clare, *Executive function and activities of daily living in Alzheimer's disease: a correlational meta-analysis.* Dement Geriatr Cogn Disord, 2012. **33**(2-3): p. 189-203.

11. Clement, F., S. Gauthier, and S. Belleville, *Executive functions in mild cognitive impairment: emergence and breakdown of neural plasticity.* Cortex, 2013. **49**(5): p. 1268-79.

12.     Rainville, C., et al., *Executive function deficits in persons with mild cognitive impairment: a study with a Tower of London task.* J Clin Exp Neuropsychol, 2012. **34**(3): p. 306-24.

13.     Johns, E.K., et al., *The profile of executive functioning in amnestic mild cognitive impairment: disproportionate deficits in inhibitory control.* J Int Neuropsychol Soc, 2012. **18**(3): p. 541-55.

14.     Ahn, I.S., et al., *Impairment of instrumental activities of daily living in patients with mild cognitive impairment.* Psychiatry Investig, 2009. **6**(3): p. 180-4.

15.     Wadley, V.G., et al., *Mild cognitive impairment and everyday function: evidence of reduced speed in performing instrumental activities of daily living.* Am J Geriatr Psychiatry, 2008. **16**(5): p. 416-24.

16.     Peres, K., et al., *Natural history of decline in instrumental activities of daily living performance over the 10 years preceding the clinical diagnosis of dementia: a prospective population-based study.* J Am Geriatr Soc, 2008. **56**(1): p. 37-44.

17.     Cloutier, S., et al., *Patterns of Cognitive Decline Prior to Dementia in Persons with Mild Cognitive Impairment.* J Alzheimers Dis, 2015. **47**(4): p. 901-13.

18.     Henneges, C., et al., *Describing the Sequence of Cognitive Decline in Alzheimer's Disease Patients: Results from an Observational Study.* J Alzheimers Dis, 2016. **52**(3): p. 1065-80.

19.     Twamley, E.W., S.A. Ropacki, and M.W. Bondi, *Neuropsychological and neuroimaging changes in preclinical Alzheimer's disease.* J Int Neuropsychol Soc, 2006. **12**(5): p. 707-35.

20.     Luck, T., et al., *Impact of impairment in instrumental activities of daily living and mild cognitive impairment on time to incident dementia: results of the Leipzig Longitudinal Study of the Aged.* Psychol Med, 2011. **41**(5): p. 1087-97.

21.     Belleville, S., et al., *Predicting decline in mild cognitive impairment: a prospective cognitive study.* Neuropsychology, 2014. **28**(4): p. 643-52.

22.     Winblad, B., et al., *Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment.* J Intern Med, 2004. **256**(3): p. 240-6.

23.     American Psychiatric Association., *Diagnostic criteria from DSM-IV-TR.* 2000, Washington, D.C.: American Psychiatric Association. xii, 370 p.

24.     Van der Linden, M., et al., *L'évaluation de troubles de la mémoire: présentation de quatre tests de mémoire épisodique (avec étalonnage).* Marseille: Solal., 2004.

25. Rey, A., *Test de copie d'une figure complexe: Manuel.* Paris: Les Éditions du Centre de Psychologie Appliquée., 1959.

26. Regard, M., *Cognitive rigidity and flexibility: A neuropsychological study. PhD dissertation.* University of Victoria, Canada, 1981.

27. Wechsler, D., *Weschsler Adult Intelligence Scale.* San Antonio, 1997.

28. Benton, A.L., et al., *Contributions to neuropsychological assessment. .* New York: Oxford University Press, 1983.

29. Kaplan, E.F., H. Goodglass, and S. Weintraub, *The Boston Naming Test (2nd ed.).* Philadelphia, PA: Lea & Febiger, 1983.

30. Strauss, E., et al., *A compendium of neuropsychological tests : administration, norms, and commentary*. 3rd ed. 2006, Oxford ; New York: Oxford University Press. xvii, 1216 p.

31. Hébert, R., et al., *Le système de mesure de l'autonomie fonctionnelle (SMAF).* La Revue de Gériatrie, 2003. **28**(4): p. 323-336.

32. Barberger-Gateau, P., et al., *Instrumental activities of daily living as a screening tool for cognitive impairment and dementia in elderly community dwellers.* J Am Geriatr Soc, 1992. **40**(11): p. 1129-34.

33. Barberger-Gateau, P., J.F. Dartigues, and L. Letenneur, *Four Instrumental Activities of Daily Living Score as a predictor of one-year incident dementia.* Age Ageing, 1993. **22**(6): p. 457-63.

34. Barberger-Gateau, P., et al., *Functional impairment in instrumental activities of daily living: an early clinical sign of dementia?* J Am Geriatr Soc, 1999. **47**(4): p. 456-62.

35. Peters, F., S. Villeneuve, and S. Belleville, *Predicting progression to dementia in elderly subjects with mild cognitive impairment using both cognitive and neuroimaging predictors.* J Alzheimers Dis, 2014. **38**(2): p. 307-18.

36. Belleville, S., et al., *Neuropsychological Measures that Predict Progression from Mild Cognitive Impairment to Alzheimer's type dementia in Older Adults: a Systematic Review and Meta-Analysis.* Neuropsychol Rev, 2017. **27**(4): p. 328-353.

37. Razani, J., et al., *Relationship between executive functioning and activities of daily living in patients with relatively mild dementia.* Appl Neuropsychol, 2007. **14**(3): p. 208-14.

38. Vaughan, L. and K. Giovanello, *Executive function in daily life: Age-related influences of executive processes on instrumental activities of daily living.* Psychol Aging, 2010. **25**(2): p. 343-55.

39.     Bell-McGinty, S., et al., *Standard measures of executive function in predicting instrumental activities of daily living in older adults.* Int J Geriatr Psychiatry, 2002. **17**(9): p. 828-34.

40.     Albert, M.S., et al., *The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.* Alzheimers Dement, 2011. **7**(3): p. 270-9.

**Chapitre V**
**Article 4:** *Perspectives on a Collaborative Canada-China Research Program on Diagnostic Biomarkers for Pre-Dementia Stages of Alzheimer's Disease*

# Article 4: Perspectives on a Collaborative Canada-China Research Program on Diagnostic Biomarkers for Pre-Dementia Stages of Alzheimer's Disease

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**Abstract**

As biomarkers are important in the early diagnosis of Alzheimer's disease (AD), the first collaborative work of recruiting early-onset familial AD (EO- FAD) families in Canada and China was initiated in 2012. The registration networks have collected hundreds of pedigrees, for which genetic screening, neuropsychological tests and amyloid and tau imaging was used to study diagnostic biomarkers for preclinical and mild cognitive impairment (MCI) stages of AD. Besides identifying pedigrees with novel mutations in *presenilins (PSENs)/amyloid precursor protein* (*APP*), the program has benefited training of Chinese research fellows, AD clinical trials for prevention, the ethical concerns for clinical findings, and other collaborative projects with Chinese investigators. Further research of the collaborative program may facilitate the testing and clinical use of novel treatments for EOFAD and late onset AD and contribute to dementia prevention strategies in Canada and China.

**Introduction**

The importance of biomarkers and their utility in the early diagnosis of Alzheimer's disease (AD) was initially proposed by the International Working Group (Dubois et al., 2007), with criteria being subsequently defined by the National Institutes of Aging and Alzheimer Association working groups for each stage of the disease including preclinical AD (Sperling et al., 2011), mild cognitive impairment (MCI) (Albert et al., 2011), and dementia (McKhann et al., 2011). Initiated in 2012, the collaborative research program between Canada and China has been made possible by joint funding from the Canadian Institutes of Health Research and the National Natural Science Foundation of China.

**Design of the research program**

The original study, as submitted to the Canadian and Chinese funding agencies, had three aims: ① to develop a Canada-China database registry to integrate Canadian and Chinese resources for large-scale genetic and biomarker studies; ② to characterize dynamic biomarkers and cognitive changes over time in carriers of presenilin-1 (*PSEN1*), presenilin 2 (*PSEN2*), and amyloid precursor protein (*APP*)mutations at the preclinical and MCI stages of AD; ③ to search for novel causative mutations for early onset familial Alzheimer's disease (EOFAD).

The original hypotheses were ① amyloidosis is present in carriers of *PSEN1*, *PSEN2*, and *APP* mutations regardless of disease stage or the age at onset among relatives; ② a higher rate of decline of synaptic function measured by [18F]FDG-PET and resting fMRI is a hallmark of the preclinical stage of EOFAD; and ③ brain atrophy using MRI is the most important biomarker change at the MCI stage.

The study methodology was to recruit EOFAD families in Canada and China, including individuals with known *PSEN1*, *PSEN2* and *APP* mutations as well as informative families without a known mutation. The latter were to have exome sequencing to detect mutations in known or novel genes. Neuropsychological assessments were to be correlated with pathophysiological and neurodegenerative biomarkers as well as clinical stage of AD.

**Results specific to the research program**

*Recruitment of families*

The enrollment of informative families has been rapid showing a steady increase in Beijing (N=457) and Canada (N=77). Of these 77 families, 34 were ascertained through Montreal (DNA samples from 60 individuals) and 43 from Vancouver (DNA samples from 108 individuals).

*Pattern of mutations*

As expected, the most common mutations detected were in *PSEN1*, followed by *APP* and *PSEN2*. Sequencing of *PSEN1*/*PSEN2*/*APP* families in Beijing led to the discovery of 5 novel mutations (manuscript in preparation). Tab. 1 lists published results to date of novel mutations. Further genetic analysis using the whole exome sequencing is ongoing for the families in Beijing with no known mutations. To conduct this study, Dr. Jia and colleagues developed a national FAD registration network: Chinese Familial Alzheimer's Disease network (CFAN, https://www.chinacfan.org/), which comprises of 7 general hospitals around China. One hundred sixty FAD families have been recruited from CFAN from Jan 2013 to Dec 2014 from which 22 pedigrees were identified with mutations in *PSEN1*, *PSEN2* or *APP*. Specifically, 13/22 (59.1%) had *PSEN1* mutations (4 novel and 9 previously reported), 8

(36.4%) had *APP* mutations (1 novel and 7 reported), and 1 (4.5%) had a *PSEN2* reported

mutation.

**Tab. 1 Novel mutations in *PSEN1/APP* identified
in families in Beijing**

| Family number | Proband's age at onset, years | Gene | Exon | Amino acid change | Reference |
|---|---|---|---|---|---|
| 1 | 42 | *APP* | 17 | M722K | Wang et al. 2015 |
| 2 | 69,77 | *PSEN1* | 9 | K311R | Dong et al. 2017 |

*Neuropsychological testing*

Neuropsychological tests used in this cohort were validated in English, French and

Mandarin (Tab. 2).

**Tab. 2 Canada-China familial Alzheimer's
disease project's cognitive battery**

| Memory | |
|---|---|
| Rey Auditory Verbal Learning Test | (Schmidt. 1996) |
| Logical Memory, Story A (WMS-III) | (Wechsler. 1997) |
| Rey Complex Figure Test | (Rey. 1959) |
| | |
| Attention & Perceptual Speed | |
| Coding (WAIS-III) | (Wechsler. 1997) |
| Digit Span (WAIS-III) | (Wechsler. 1997) |
| | |
| Language | |
| Verbal Fluency, Animals (D-KEFS) | (Delis et al. 2001) |
| Boston Naming Test | (Kaplan et al. 1983) |
| Working Memory and Executive Functions | |
| Stroop (D-KEFS) | (Delis et al. 2001) |
| Color Trails Test | (D'Ellia et al. 1996) |
| Hayling Task | (Belleville et al. 2006) |
| | |
| Visuospatial | |

| | |
|---|---|
| Orientation Match Task (BORB) | (Riddoch & Humphreys. 1993) |
| Block Design Test (WAIS-III) | (Wechsler. 1997) |
| | |
| Cognitive Reserve | |
| Bartrés-Faz Cognitive Reserve Questionnaire | (Sole-Padulles et al. 2009) |
| Vocabulary (WAIS-III) | (Wechsler. 1997) |

Note: This set of neuropsychological tests is being considered for use by the DIAN-TU-2 team for treatment of families with EOFAD in China

*Biomarker studies*

PET studies are ongoing in Canada and China using the best validated ligands for amyloid and tau. Tau PET imaging proved to be quite a challenge because of non-specificity of some of the ligands (Ng et al., 2017). Work is ongoing to correlate data from PET imaging with CSF measures of relevant biomarkers.

**Broader results of the research program**

*Research training of Chinese research fellows*

Since 2012, there has been a steady flow of excellent research fellows from China to the McGill Center for Studies in Aging in Montreal. The productivity of these fellows can be seen in resultant publications (Tab. 3).

Of special interest is the ability of these research fellows to access and analyze large databases such as the Alzheimer Disease Neuroimaging Initiative (ADNI), and correlate clinical symptoms with regional biomarkers. This ability will expand as the scientific world is moving to an open access strategy.

## Tab. 3 List of articles published with the Chinese research fellows

Wu L, Rosa-Neto P, Hsiung GYR, Sadovnick AD, Masellis M, Black SE, Jia J, Gauthier S. Early-onset familial Alzheimer's disease (EOFAD). Canadian Journal of Neurological Sciences, 2012,39: 436-445.

Gauthier S, Wu L, Rosa-Neto P, Jia J. Prevention strategies for Alzheimer's disease. Translational Neurodegeneration, 2012. DOI:10.1186/2047-9158-1-13.

Wu L, Rowley J, Mohades S, Leuzy A, Dauar MT, Shin M, Fonov V, Jia J, Gauthier S, Rosa-Neto P, the Alzheimer's Disease Neuroim- aging Iinitiative. Dissociation between brain amyloid deposition and metabolism in early mild cognitive impairment. PLoS ONE, 2012, 7(10): e47905. doi:10.1371/journal.pone.0047905, 2012.

Rowley J, Fonov V, Wu O, eskildsen S, Scoemaker D, Wu L, Mohades S, Shin M, Sziklas V, Shmuel A, Dagher A, Gauthier S, Rosa-Ne- to P, the Alzheimer's Disease Neuroimaging Initiative. White matter abnormalities and structural hippocampal disconnections in AD, naMCI and aMCI. PloS ONE, 2013, 8: e74776.

Wu L, Soder RB, Shoemaker D, Carbonell F, Sziklas V, Rowley J, Mohades S, Fonov V, Bellec P, Dagher A, Sziklas V, Schmuel A, Jia J, Gauthier S, Rosa-Neto P. Resting state executive control network adaptations in amnestic mild cognitive impairment. Journal of Alzheimer Disease, 2014, 40:993-1004.

Ba M, Kong M, Li X, Ng KP, Rosa-Neto P, Gauthier S. Is apoE ε 4 a good biomarker for amyloid pathology in late onset Alzheimer's disease? Translational Neurodegeneration, 2016, 5:20. DOI:10.1186/s40035-016-0067-z.

Li X, NG KP, Ba M, Rosa-Neto P, Gauthier S. Dementia and bioethics// Chiu H, Shulman K. Mental health and illness in the elderly. Singapore: Springer Nature, 2017.DOI: 10.1007/978-981-10-0370_6-1.

Ba M, Li X, Ng KP, Pascoal TA, Mathotaarachchi S, Rosa-Neto P, Gauthier S, the Alzheimer Disease Neuroimaging Initiative. The prevalence and biomarker characteristics of rapidly progressive Alzheimer's disaease from the Alzheimer's Disease Neuroimaging Initiative database. Alzheimer's & Dementia: Translational Research & Clinical Interventions, 2017,3:107

113.

Ng KP, Pascoal T, Mathotaarachechi S, Chung CO, Benedet AL, Shin M, Kang MS, Li X, Ba M, Kandiah N, Rosa-Neto P, Gauthier S, the Alzheimer's Disease Neuroimaging Initiative. Neuropsychiatric symptoms predict hypometabolism in preclinical Alzheimer's disease. Neurology, 2017, 88:1814-1821.

Ng KP, Pascoal TA, Li X, Rosa-Neto P, Gauthier S. Patient benefits and ethical considerations: clinical meaningfulness of biomarkers endpoints. Biomarkers for preclinical Alzheimer's disease. //Perneczky R. Neuromethods. Wolfgang Walz Series Editor, Springer. (In press)

Li X, Ba M, Ng KP, Mathotaarachchi S, Pascoal TA, Rosa-Neto P, Gauthier S, the Alzheimer's Disease Neuroimaging Initiative. Char- acterizing biomarker features of cognitively normal individuals with ventriculomegaly. Alzheimer's & dementia (Amsterdam, Nether- lands), 2017,10: 12-21. Doi.org/10.1016/j.dadm.2017.08.001.

Gauthier S, Ng KP, Pascoal T, Zhang H, Rosa-Neto, P. Targeting AD at the right time and the right place: validation of a personalized approach to diagnosis and treatment. Journal of Alzheimer's Disease. Doi/10.3233/JAD-179924

*Participation in DIAN-TU*

The availability of a registry of potential participants in Montreal and Vancouver has allowed enrolment of interested family members for the DIAN-TU program (Bateman et al., 2017). DIAN-TU participants are currently ending the second year of randomization to solazenumab, crenezumab, or placebo with biomarkers as primary outcomes. As well, an additional drug arm will soon be available (DIAN-TU-2). We anticipate that this study will be possible in China thanks to the experience gained with our collaborative Canada-China research program.

**Ethical considerations**

Due to the sensitive issue of genetic carrier status which may or may not be known

to the participants, a high level of ethical considerations is required when man- aging

registries in EOFAD. Some of our study investigators are involved in the Ethical, Legal,

Social Impact (ELSI) committees of large observational studies, which look issues such as

disclosure of clinically relevant incidental findings.

**Other collaborative projects with Chinese investigators**

A number of collaborative projects have taken place with principal investigator Jianping

Jia and other Chinese investigators (Tab. 4).

### Tab. 4 Other collaborative projects and related publications since 2012

Lee WJ, Tsai CF, Gauthier S, Wang SJ, Fuh JL. The association between cognitive impairment and neuropsychiatric symptoms in pa- tients with Parkinson's disease dementia. International Psychogeriatrics, 2012, 24 :1980-1987.

Liu WJ, Wang LN, Tan JP, Ji P, Gauthier S, Zhang YL, Ma TX, Liu SN. Burden, anxiety and depression in caregivers of veterans with dementia in Beijing. Archives of Gerontology and Geriatrics, 2012, 55: 560-563.

Jia J, Zhou A, Wei C, Jia X, Wang F, Li F, Wu X, Mok V, Gauthier S, Tang M, Chu L, Zhou Y, Zhou C, Cui Y, Wang Q, Wang W, Yin P, Hu N, Zuo X, Song H, Qin W, Wu L, Li D, Jia L, Song J, Han Y, Xing Y, Yang P, Li Y, Qiao Y, Tang Y, Lv J, Dong X. The prevalence of mild cognitive impairment and its etiological subtypes in elderly Chinese. Alzheimer's & Dementia, 2014, 10: 439-447.

Gauthier S, Proano JV, Jia J, Froelich L, Vester J, Doppler E. Cerebrolysin in mild-to-moderate Alzheimer's disease: a meta-analysis of randomized clinical trials. Dementia & Geriatric Cognitive Disorders, 2015, 39: 332-347.

Jia J, Gauthier S, Pallotta S, Ji Y, Wei W, Xiao S, Peng D, Guo Q, Wu L, Chen S, Kuang W, Zhang J, Wei C, Tang Y. Consensus-based recommendations for the management of rapid cognitive decline due to Alzheimer's disease. Alzheimer's & Dementia, 2017, 13: 592- 597.

Wilcock G, Gauthier S, Frisoni GB, Jia J, Hardlund JH, Moebius HJ, Bentham P, Kook KA, Schelter BO, Wischik DJ, Davis CS, Staff RT, Vuksanovic V, Aheam T, Bracoud L, Shamsi K,

Marek K, Seildel J, Reindel G, Storey JM, Harrington CR, Wischik C. Potential of low dose leuco-methylthioninium bis(hydromethanesulfonate) (LMTM) monotherapy for treatment of mild Alzheimer's disease: cohort analysis as modified primary outcome in a phase 3 clinical trial. Journal of Alzheimer's Disease. Doi 103233/JAD-170560.

Jia J, Wei C, Chen C, Li F, Tang Y, Qin W, Zhao L, Jin H, Xu H, Wang F, Zhou A, Zuo X, Wu L, Han Y, Han Y, Huang L, Wang Q, Li D, Chu C, Shi L, Ging M, Du Y, Zhang J, Zhang J, Zhou C, Ly J, Lv Y, Xie H, Ji Y, Li F, Yu E, Luo B, Wang Y, Yang S, Qu Q, Guo Q, Liang F, Zhang J, Tan L, Shen L, Zhang K, Zhang J, Peng D, Tang M, Lv P, Fang B, Chu L, Jia L, Gauthier S. The cost of Alzheimer's disease in China and re-estimation of costs world-wide. Alzheimer's & Dementia. (In press) (ADJ-D-17-00332R2).

Jia J, Wei C, Chen S, Li F, Tang Y, Qin W, Shi L, Gong M, Xu H, Li F, He J, Song H, Yang S, Zhou A, Wang F, Zuo X, Chu C, Liang J, Jia L, Gauthier S. Efficacy and safety of thye Chinese medicine SaiLuoTong in vascular dementia: a randomized, controlled, double-blind, parallel-arm trial. New England Journal of Medicine. (Submitted)

## Discussion

This collaborative program has accelerated research in EOFAD in both Canada and China, leading to advances in registry development, genetic analysis and biomarker validation. This has also enabled enrollment of participants into treatment trial programs such as DIAN-TU.

As an international collaborative group, we look forward to further research endeavors to facilitate the testing and clinical use of novel treatments for EOFAD and late onset AD, thus contributing to dementia prevention strategies in Canada and China.

## References

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., . . . Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 270-279. doi:10.1016/j.jalz.2011.03.008

Bateman, R. J., Benzinger, T. L., Berry, S., Clifford, D. B., Duggan, C., Fagan, A. M., . . . Network, D.-T. P. C. f. t. D. I. A. (2017). The DIAN-TU Next Generation Alzheimer's

prevention trial: Adaptive design and disease progression model. *Alzheimers Dement, 13*(1), 8-19. doi:10.1016/j.jalz.2016.07.005

Belleville, S., Rouleau, N., & Van der Linden, M. (2006). Use of the Hayling task to measure inhibition of prepotent responses in normal aging and Alzheimer's disease. *Brain Cogn, 62*(2), 113-119. doi:10.1016/j.bandc.2006.04.006

D'Ellia, L. F., Satz, P., Uchiyama, C. L., & White, T. (1996). Color Trails Test. Professional manual. *Psychological Assessment Resources, Odessa, FL*.

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). Delis-Kaplan Executive Function System™ (D-KEFS™). *Psychological Corporation*.

Dong, J., Qin, W., Wei, C., Tang, Y., Wang, Q., & Jia, J. (2017). A Novel PSEN1 K311R Mutation Discovered in Chinese Families with Late-Onset Alzheimer's Disease Affects Amyloid-beta Production and Tau Phosphorylation. *J Alzheimers Dis, 57*(2), 613-623. doi:10.3233/JAD-161188

Dubois, B., Feldman, H. H., Jacova, C., Dekosky, S. T., Barberger-Gateau, P., Cummings, J., . . . Scheltens, P. (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol, 6*(8), 734-746. doi:10.1016/S1474-4422(07)70178-3

Kaplan, E. F., Goodglass, H., & Weintraub, S. (1983). The Boston Naming Test (2n ed.). *Philadelphia, PA: Lea & Febiger*.

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr., Kawas, C. H., . . . Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 263-269. doi:10.1016/j.jalz.2011.03.005

Ng, K. P., Pascoal, T. A., Mathotaarachchi, S., Therriault, J., Kang, M. S., Shin, M., . . . Rosa-Neto, P. (2017). Monoamine oxidase B inhibitor, selegiline, reduces (18)F-THK5351 uptake in the human brain. *Alzheimers Res Ther, 9*(1), 25. doi:10.1186/s13195-017-0253-y

Rey, A. (1959). Test de copie d'une figure complexe: Manuel. *Paris: Les Éditions du Centre de Psychologie Appliquée.*

Riddoch, J. M., & Humphreys, G. W. (1993). BORB: Birmingham Object Recognition Battery. *Psychology Press*.

Schmidt, M. (1996). Rey Auditory Verbal Learning Test: A Handbook. *Western Psychological Services*.

Sole-Padulles, C., Bartres-Faz, D., Junque, C., Vendrell, P., Rami, L., Clemente, I. C., . . . Molinuevo, J. L. (2009). Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging, 30*(7), 1114-1124. doi:10.1016/j.neurobiolaging.2007.10.008

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., . . . Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 280-292. doi:10.1016/j.jalz.2011.03.003

Wang, Q., Jia, J., Qin, W., Wu, L., Li, D., Wang, Q., & Li, H. (2015). A Novel AbetaPP M722K Mutation Affects Amyloid-beta Secretion and Tau Phosphorylation and May Cause Early-Onset Familial Alzheimer's Disease in Chinese Individuals. *J Alzheimers Dis, 47*(1), 157-165. doi:10.3233/JAD-143231

Wechsler, D. (1997a). Wechsler Adult Intelligence Scale–Third Edition. *San Antonio: The Psychological Corporation.*

Wechsler, D. (1997b). Wechsler Memory Scale (3rd edn.). *Psychological Corporation, San Antonio, TX*

**Chapitre VI**

**Article 5:** *Canada-China Familial Alzheimer's Disease (CCFAD) Project: Cognitive Data from the Canadian Cohort with PSEN1 Mutations*

# Article 5: Canada-China Familial Alzheimer's Disease (CCFAD) Project: Cognitive Data from the Canadian Cohort with PSEN1 Mutations

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**En préparation**

**Canada-China Familial Alzheimer's Disease (CCFAD): Cognitive Data from the Canadian Cohort with PSEN1 mutations**

**Introduction**

Worldwide, it is estimated that more than 24 million people have AD, and as life expectancy increases, so is the prevalence of this disease (Ballard et al., 2011). Furthermore, it represents an important public health issue, being the 6th leading cause of death in older adults (Thies, Bleiler, & Alzheimer's, 2013). AD had an estimated socioeconomical cost of more than 167 billion dollars in 2015 (Jia et al., 2018). Thus, it is necessary to find a robust and valid way to distinguish the persons who will progress to AD from those who won't, given that the earlier the diagnosis, the greater the chances of effective interventions. One possible way to achieve this objective is by carefully studying the onset and progression of cognitive symptoms in persons who do not yet meet the criteria for dementia.

Familial type AD (fAD) offers a unique opportunity to study the brain pathology, the biomarkers and the cognitive profile of individuals who will progress to AD, many years prior to their diagnosis. Familial AD is an autosomal, dominantly inherited form of AD, associated with gene mutations on presenilin1 (PSEN1), preseinilin2 (PSEN2), and the amyloid precursor gene (APP). Contrary to other genetic mutations that were shown to increase the risk of AD conversion (Bettens, Sleegers, & Van Broeckhoven, 2013), such as the allele e4 of the apolipoprotein E (APOE) gene (Mullan et al., 1996), these mutations are highly penetrant (from 95% to 100%) (Bird, 2012). PSEN1, PSEN2 and APP genes are directly or indirectly implicated in the production of beta-amyloid (Bettens et al., 2013), a finding that has provided critical empirical support to the amyloid hypothesis for AD (Hardy & Selkoe, 2002; Jack et al., 2010). Most of fAD cases are caused by PSEN1 mutations, PSEN2 mutations being the rarest. Clinical

and cognitive heterogeneity depending on the mutations location (APP, PSEN1 or PSEN2) have been reported (Wu et al., 2012). PSEN1 mutations carriers generally present an earlier AD onset, more atypical cognitive symptoms, such as language and dysexecutive presentations (Ryan et al., 2016), and more neurological features, such as myoclonus and seizures (Janssen et al., 2000). PSEN2 mutations are associated with a later onset and a longer disease duration (Jayadev et al., 2010). There may also be some ethnics differences in the mutation spectrum and clinical features of fAD (Shea et al., 2016). Thus, it is important to consider these factors since they may have a significant impact on the clinical progression of the disease.

Familial AD cases represent less than 1% of all AD cases (Bekris, Yu, Bird, & Tsuang, 2010; Campion et al., 1999). Despite this low prevalence, families with fAD are an ideal population for studying the early phases of AD (Bateman et al., 2011; Dubois et al., 2016). First, the certainty of the diagnosis makes it possible to study the cognitive profile well before the first symptoms. Second, the age at which the parent was diagnosed is a good estimate of the age at which the mutation-carrying participant will meet AD criteria, since there is a strong correlation between the estimated age of onset based on the age of the parent's diagnosis and the effective age of onset (Ryman et al., 2014). Third, fAD is associated with an early onset; less than 60 years for most, can be as early as mid-20s (Bateman et al., 2011; Snider et al., 2005). Thus, comorbidity with other medical conditions, which could explain part of the cognitive deficits and complicate the etiology (Doraiswamy, Leon, Cummings, Marin, & Neumann, 2002), is less present than in older patients with sporadic AD. Importantly, familial AD seems to unfold in a very similar way to sporadic AD. For cognition, both are characterized by early episodic memory and judgment impairments. For brain pathology and imaging markers, both forms present hippocampal atrophy, tempo-parietal cortical loss, temporo-parietal hypometabolism,

significant amyloid deposition, especially in the precuneus/posterior cingulate and prefrontal cortex, as well as neurofibrillary tangles on neuropathology. For cerebrospinal fluid (CSF) biomarkers, both forms show a decrease in CSF Aβ42 and an increase in CSF tau (Bateman et al., 2011; Shepherd, McCann, & Halliday, 2009).  Thus, studying fAD can contribute to understanding the more common, sporadic form of AD and this motivated an active research field which investigated the phenotype in young individuals, carriers of fAD mutations in the years preceding their diagnosis.

The dominantly inherited form of AD being so rare, recruiting a significant number of families with members who are often spread over a large territory represents a challenge for researchers interested in studying the clinical presentation of the disease. A multi-centric collaborative approach, such as the *Dominantly Inherited Alzheimer Network (DIAN),* can optimize the number of participants recruited. DIAN is multi-centric and longitudinal international collaboration with the goal of studying the early markers of AD, by developing a large register of fAD mutations carriers and their non-carriers family relatives (Morris et al., 2012).

DIAN reported clinical and biomarkers changes in AD that supports the hypothetical model of dynamic biomarkers proposed by Jack et al. (2010). About 25 years prior to the estimated age of onset in the family (EAO), a decrease in the concentration of CSF Aβ42 is observed and thus represents of the earliest markers of the disease (Bateman et al., 2012). Fifteen years before the EAO, beta-amyloid accumulation can be detected, which is followed (10 years to EAO) by hypometabolism and episodic memory impairment. Global cognition impairment (MMSE, CDR) is observed about 5 years prior to the EAO.

**Neuropsychological findings in the familial type Alzheimer's disease**

Considering its low prevalence, very few studies have characterized how the cognitive deficits unfold in fAD, especially during the preclinical phases of the disease. Newman, Warrington, Kennedy, and Rossor (1994) published one of the first studies that looked at the cognitive profile of a fAD mutation-carrying individual, before the diagnosis. They followed a woman with confirmed APP mutations and performed 3 comprehensive neuropsychological assessments between July 1991 and October 1992. One of the earliest deficit (low percentile compared to population norms) was found in verbal memory followed by a decline in spatial memory. Language and reading abilities were spared over the entire follow-up. Godbolt et al. (2004) reported similar results in a longitudinal study including 19 subjects with fAD: reading and spelling abilities were relatively spared, whereas memory and general intelligence were the most impaired, even before the dementia diagnosis. A 6-years prospective group study including 63 participants at-risk for autosomal dominantly inherited AD (Fox, Warrington, Seiffer, Agnew, & Rossor, 1998) reported early impairment in verbal memory when comparing participants who later progressed to dementia, compared to the non-progressors, as well as lower performance IQ (visuoperceptual speed and spatial reasoning abilities). More recent studies also seem to suggest that short-term memory binding deficits is a sensitive marker of fAD, even for asymptomatic mutations carrier (Liang et al., 2016; Parra, Abrahams, Logie, & Della Sala, 2010; Parra et al., 2015). Note that subjective cognitive complaints has been suggested to precede the mild cognitive symptoms in fAD as is suggested to be the case for sporadic AD (Ardila et al., 2000).

Storandt, Balota, Aschenbrenner, and Morris (2014) described the clinical and cognitive characteristics of the DIAN cohort at study entry: 249 participants divided into 3 groups (non-carriers, asymptomatic carriers and carriers with mild cognitive impairment (MCI)). A

significant group x time (to EAO) interaction was found for logical memory, Simon's Task reaction time and Digit Symbol: the closer to the EAO, the more impaired the mutation carrier participants were on these tasks. Furthermore, asymptomatic mutations carriers significantly differed from controls (non-carriers) for categorization and logical memory at all EAO. Thus, fAD mutations carriers seem to be more cognitively vulnerable, especially for episodic memory, tough it is possible that other factors than the genotype, such as education, occupation or life activities may explain part of this vulnerability. In contrast, familial AD mutations non-carriers enrolled in DIAN showed no impairment, no matter their age, from 30 years before the EAO to 20 years after (Bateman et al., 2012).

Most of the studies reporting the neuropsychological profiles of fAD associated mutations carriers have assumed that the cognitive decline is linear, which may not necessarily be the case. Some cognitive domains may follow more complex trajectories, such as a plateau followed by a decline, starting in the few years before the age of onset. Furthermore, DIAN includes research groups in Australia, Europe and the United States, so there was a need for a similar collaborative approach in Canada and China. The Canada-China Familial Alzheimer's Disease Project (CCFAD) is a collaborative research program between Canada and China, funded by the Canadian Institutes of Health Research and the National Natural Science Foundation of China since 2012 (Gauthier et al., 2017).

**Canada-China Familial Alzheimer's Disease Project (CCFAD)**

Canada-China Familial Alzheimer's Disease (CCFAD) project aims to pool the resources of Canada and China to develop a registry of fAD participants, to characterize biomarkers and cognitive changes associated with PSEN1, PSEN2 and APP mutations at the

preclinical and MCI stages of AD and to search for novel fAD mutations (Gauthier et al., 2017). This program includes the collaboration between research centers in Montreal, a bi-cultural city with both a French- and English-speaking population (McGill Center for Studies on Aging, Montreal Geriatrics Institute and Montreal Neurological Institute), Vancouver (endMS Western Pacific Research and Training Center), Toronto (Sunnybrook Research Center) and Beijing (Beijing Institute for Brain Disorders Alzheimer's Disease Center and Capital University). Several articles related to this collaboration have already been published (Gauthier et al., 2017) and novel mutations were found for families in China (Dong et al., 2017; Wang et al., 2015). The CCFAD project includes a clinical evaluation, a neuropsychological assessment using a standardized battery with tests available in English, French and Mandarin (see Neuropsychological Assessment of CCFAD Participants section), a blood sample for genotyping, MRI for brain atrophy, PET with ligands for amyloid and tau and a lumbar puncture for CSF biomarkers.

For the purpose of this paper, we will report the cognitive data of the Canadian cohort with PSEN1 mutations. More precisely, the goals of this study were: 1) to compare the cognitive profile of PSEN1 mutations carriers to their non-carrying family members; 2) to assess the effect of the time to the estimated age of onset (EAO) on the cognitive performance in mutations carriers; and 3) to determine what form the trajectory of time to EAO takes (linear, plateau followed by an accelerated decline just prior to EAO, etc.).

**Methodology**

Participants, mutations and estimated age of onset

Individuals with a familial history of early onset AD were referred to the CCFAD registry. They consented for a medical appointment with a neurologist, a blood sample for

genetic analyzes and an interview with a genetic counselor, for a precise history of the age of symptoms onset in the family. Thirty-two participants from the Canadian registry for familial AD were recruited for the neuropsychological study and were genotyped for known fAD mutations. Since our sample was mainly composed of PSEN1 mutations carriers and considering the clinical heterogeneity associated with the mutations' genes location (APP, PSEN1, PSEN2), we excluded one APP mutation carrier and their non-carriers family members (N = 5). Also, the goal of this study was to characterize the preclinical phases of AD, up until the beginning of symptoms onset (MCI/mild dementia). Thus, we excluded 2 symptomatic carriers and 1 non-carrier that were at more than 10 years following the estimated age of onset (EAO). Seven participants (carriers, N = 3) had 2 cognitive assessments, with at least 12 months between each session. The second assessment was scheduled around the same time of the PET scans, so that we may compare their cognitive function with amyloid and tau imaging markers. In total, 15 carriers' data points (12 carriers + 3 with 2 neuropsychological assessments) and 15 non-carriers' data points (11 non-carriers + 4 with 2 neuropsychological assessments) were included in this study.

Table 1 presents the 2 PSEN1 mutations of the sample. The first one is H163R protein change (A>G). This mutation was first described in 1995, in conjunction with the cloning of the PSEN1 gene. The estimated age of onset (EAO) for the French-Canadian families is 45 years old (Sherrington et al., 1995), which is also what we found in our sample. Thus, this mutation appears to be highly penetrant around the age of 45 years old, which we used to compute the EAO for the asymptomatic carriers and the non-carriers. The second identified mutation is F175L protein change (C>G). This mutation is classified as having uncertain clinical significance regarding AD pathogenicity (Karbassi et al., 2016) but is a known mutation

included in DIAN. The mean age of onset in the families for the F175L mutation in our sample was older (around 50 years old), but more importantly was highly variant (standard deviation of 7 years with a range between 43 and 62 years old). Thus, we used the age of onset of the parent to compute the time to EAO. For both mutations, we used the effective age of onset for symptomatic carriers, which was derived from a clinical interview, independent of the cognitive assessment.

**Table 1.** PSEN1 mutations of the Canadian Families

| Mutation | Non-Carriers | Carriers | Mean age of onset families (SD) |
|----------|--------------|----------|--------------------------------|
| H163R (A>G) | 4 | 4 | 45.75 (1.41) |
| F175L (C>G) | 7 | 8 | 50.14 (6.96) |

Neuropsychological Assessment of CCFAD Participants

The participants received a thorough cognitive assessment, performed in one session. The examiner was blind for both the genetic mutation carrying status and the clinical classification. The CCFAD neuropsychological tests were selected based on a few important criteria. First, the tests battery had to allow harmonization with other, similar, major clinical studies, especially DIAN (Morris et al., 2012). Second, the battery was partly harmonized with that of the *Consortium pour l'identification précoce de la maladie d'Alzheimer-Québec* (CIMA-Q) cognitive battery which includes tests sensitive and specific to progression from MCI to dementia (Belleville, Fouquet, Duchesne, Collins, & Hudon, 2014). Third, the cognitive measures had to be sensitive enough to detect subtle cognitive changes in a young population, considering the younger age of onset associated with fAD. Fourth, the tests had to be available in French, English and Mandarin. Finally, and importantly, the tests had to be appropriate for

use in the context of China. Thus, the neuropsychological team in Montreal worked in collaboration with neuropsychologists from Dr. Jia's team in Beijing to make sure that the selected tests were available in Mandarin and culturally appropriate for use in mainland China. Table 1 presents the CCFAD project's neuropsychological battery, divided by cognitive domain (memory, attention/perceptual speed, language, working memory/executive functions, visuospatial). The battery also included a measure of cognitive reserve proxy.

**Table 2.** CCFAD Project's Cognitive Battery

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**Memory**
Rey Auditory Verbal Learning Test  (RAV                                (Schmidt, 1996)
Logical Memory, Story A (WMS-III)                              (Wechsler, 1997b)
Rey Complex Figure Test                                       (Rey, 1959)

**Attention & Perceptual Speed**
Coding (WAIS-III)                                             (Wechsler, 1997a)
Digit Span (WAIS-III)                                         (Wechsler, 1997a)

**Language**
Boston Naming Test                        (Kaplan, Goodglass, & Weintraub, 1983)
Vocabulary (WAIS-III)                                         (Wechsler, 1997a)

**Working Memory and Executive Functions**
Stroop (D-KEFS)                                (Delis, Kaplan, & Kramer, 2001)
Color Trails Test                          (D'Ellia, Satz, Uchiyama, & White, 1996)
Hayling Task                      (Belleville, Rouleau, & Van der Linden, 2006)
Verbal Fluency (D-KEFS)                                      (Delis et al., 2001)

**Visuospatial**
Orientation Match Task (BORB)                              (Riddoch & Humphreys, 1993)
Block Design Test (WAIS-III)                                 (Wechsler, 1997a)

**Cognitive Reserve proxy**
Bartrés-Faz Cognitive Reserve Questionnaire                (Sole-Padulles et al., 2009)

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Neuropsychological battery's Norms

Cognitive abilities assessed by neuropsychological testing are, in part, culturally determined (Ardila, 1995). Education and culture have an impact on cognitive performance, even in non-verbal tests (Rosselli & Ardila, 2003). Therefore, it is necessary to use cognitive tests that have been normalized for the population of interest and that consider factors such as language and education, to make more accurate and fairer cross-cultural comparisons (Manly, 2008; Pedraza & Mungas, 2008). Most of the CCFAD Project's cognitive tests have available norms for the English population, French-Canadian population (St-Hilaire et al., 2017; St-Hilaire et al., 2016; Tremblay et al., 2015; Vanier, 1991; Wechsler, 2005) and the Chinese population (Q Guo, 2007; Qihao Guo, Zhao, Chen, Ding, & Hong, 2009; Weschler, Chen, & Chen, 2002). The French-Canadian norms are part of a series of studies in Quebec that published normative data and equations to derive Z scores for commonly used neuropsychological tests in dementia research, by computing the age, gender and level of education of elderly participants (Callahan et al., 2014; Dion et al., 2015; Escudier et al., 2016; Larouche et al., 2016; Lavoie et al., 2013).

<u>Statistical analysis</u>

For each of the cognitive tests, we ran a mixed model analysis. The dependent variables were Z scores, derived from the best available normative data. For verbal memory recognition, the raw scores were used, to consider both the number of words recognized and the number of false positives (e.g. a participant who recognized correctly all of the 15 target words (15/15) but committed 10 false positives would obtain a score of 40/50). The fixed effects were the mutation carrying status, the time to EAO and the interaction term (mutation x time to EAO). We also controlled for education and for age in the case of verbal memory recognition. Since the performance of members from a same family is expected to be correlated (intraclass covariance),

the models included this factor as a random effect, with a compound symmetry covariance matrix. When the interaction was significant, we looked at the simple effects of the time to EAO for each group (carriers and non-carriers). We also assessed whether more complex trajectories, such a second-order polynomial (quadratic trend), were significantly better models to represent the data distribution.

**Results**

Table 3 presents the demographics data of the participants. The groups were well matched, since the non-carriers did not significantly differ from the carriers for gender distribution, age, education, time to EAO and vocabulary (a proxy measure of cognitive reserve and premorbid functioning).

**Table 3.** Demographics Data of the Canadian Cohort

|  | **Non-Carriers** | **Carriers** | **p** |
|---|---|---|---|
| N (Men/Women) | 15 (8/7) | 15 (8/7) | .642 |
| Age (SD) | 38.73 (5.79) | 42.47 (7.45) | .137 |
| Education (SD) | 12.87 (1.46) | 13.13 (2.33) | .71 |
| Time to EAO (SD) | -11.61 (8.59) | -6.02 (10.02) | .112 |
| Vocabulary* (WAIS-III) | -.38 (.76) | -.57 (.63) | .466 |

* Z scores derived from normative data

When analyzing cognitive performance, we found a significant interaction (mutation x time to EAO) for the RAVLT immediate recall (F = 8.79, p < 0.01), the RAVLT delayed recall (F = 17.99, p < 0.01), the RAVLT recognition (F = 30.57, p < 0.01), the semantic fluency test (F = 15.51, p < 0.01) and the block design test (F = 10.9, p < 0.01). For all these measures, the effect of the time to EAO was found to be significant only in the carriers' group. For a summary of the simple effects by group, see tables 4 (non-carriers) and 5 (carriers).

When assessing the model that relates time to cognitive performance in carriers, we found a significant linear trend for RAVLT immediate recall (F = 19.27, p < 0.01, figure 1), semantic fluency (F = 5.35, p < 0.05, figure 2) and block design (F = 14.2, p < 0.01, figure 3). A quadratic trend (an initial plateau followed by a significant negative trajectory) was found to account for the relation between time to EAO for verbal memory delayed recall (F = 24.33, p < 0.01, figure 4) and recognition (F = 8.62, p < 0.05, figure 5).

**Table 4.** Summary table for the mixed model analyses of performance in the non-carriers' group

| Cognitive Tests | β | F | Significant Model |
|---|---|---|---|
| RAVLT, List A 1-5 | -.003 | .007 | N.S. |
| RAVLT, Delayed Recall | .007 | .062 | N.S. |
| RAVLT, Recognition | -.031 | .315 | N.S. |
| Semantic Fluency | .041 | .51 | N.S. |

| | | | |
|---|---|---|---|
| Block Design | -.019 | 1.108 | N.S. |

**Table 5.** Summary table for the mixed model analyses of performance in the carriers' group

| Cognitive Tests | β | F | Significant Model |
|---|---|---|---|
| RAVLT, List A 1-5 | -.092 | **19.27\*\*** | Linear |
| RAVLT, Delayed Recall | -.237 | **121.813\*\*** | Quadratic |
| RAVLT, Recognition | -.743 | **67.531\*\*** | Quadratic |
| Semantic Fluency | -.065 | **5.347\*** | Linear |
| Block Design | -.082 | **14.201\*\*** | Linear |

\*p < 0.05
\*\*p < 0.01
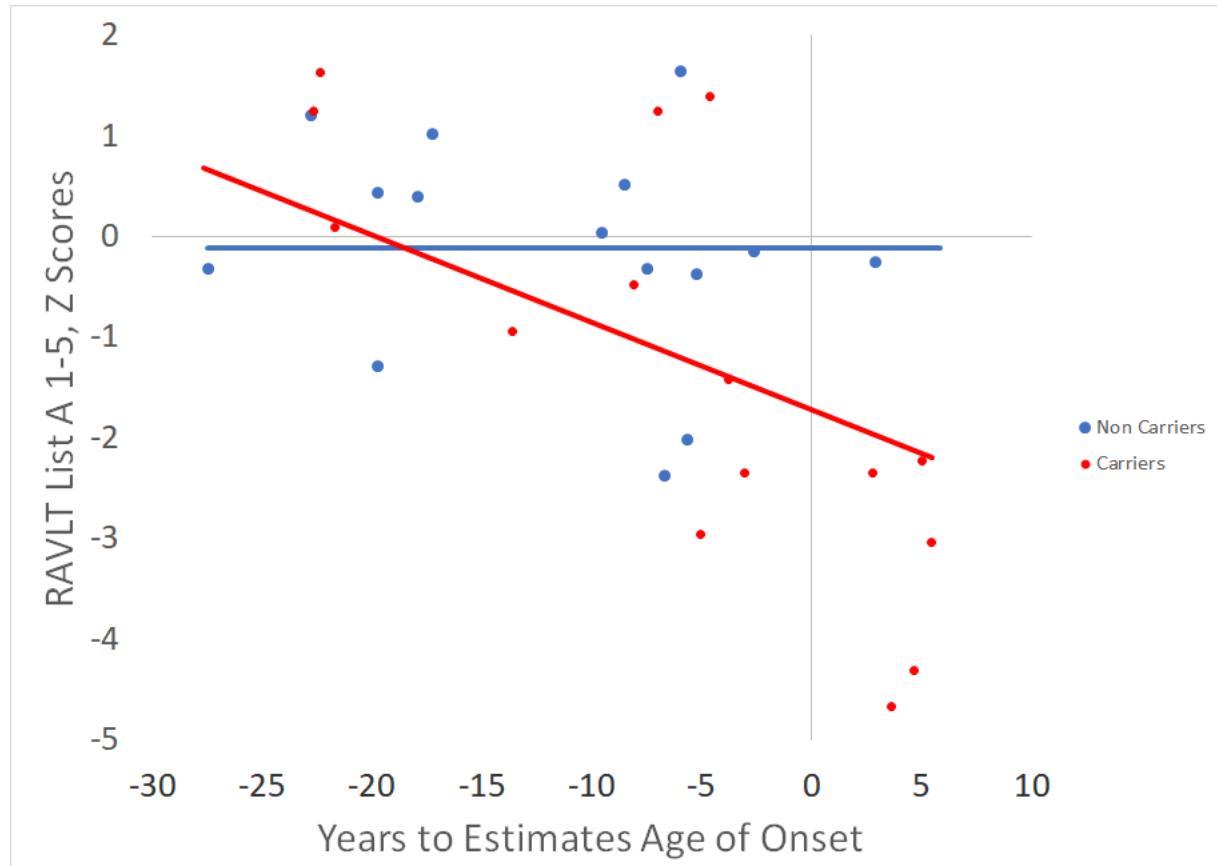
**Figure 1.** Performance on the RAVLT immediate recall (Z scores) as a function of years to EAO. There was a significant effect of time to EAO only in the carriers' group (red), and this effect followed a linear trend. Based on this model, the expected time for a significant impairment (z=-1) is estimated at -7 years to EAO in the carriers.
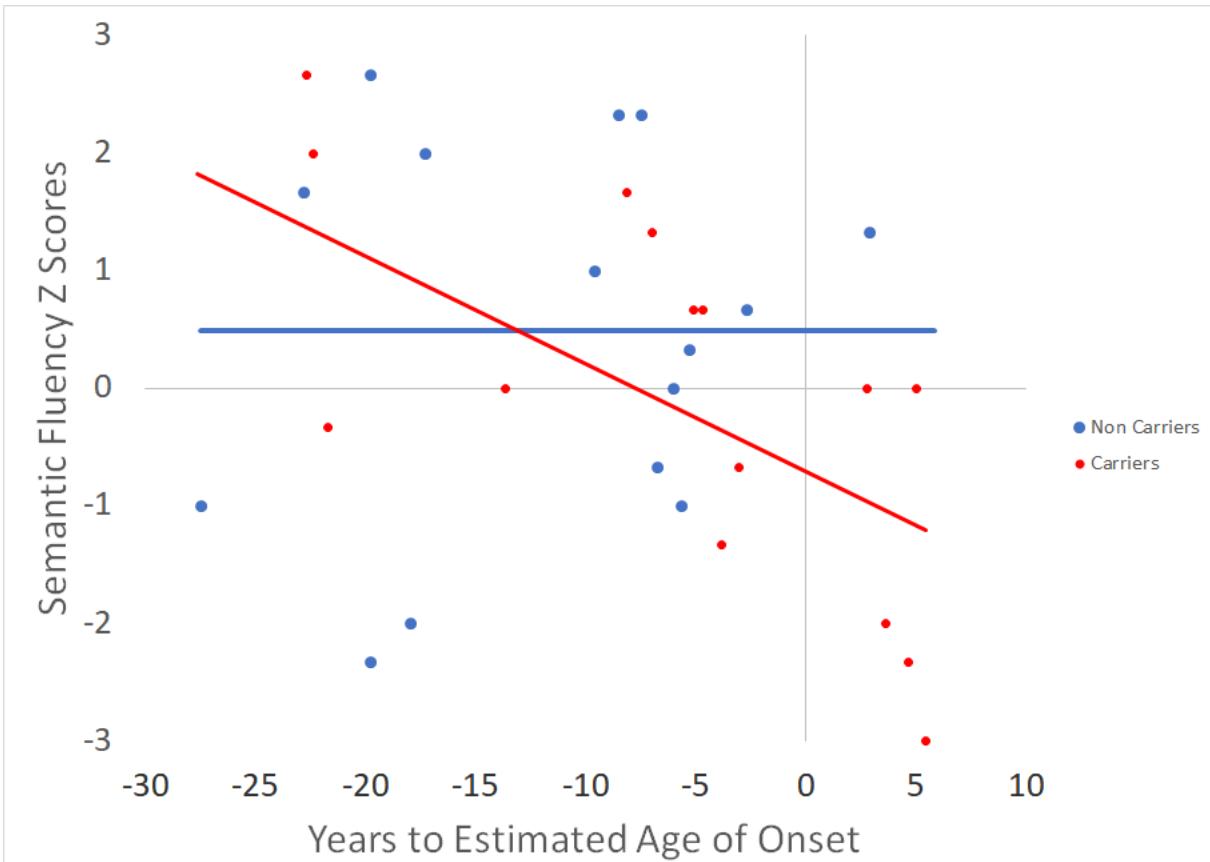
**Figure 2.** Performance on the semantic fluency task (Z scores) as a function of years to EAO. There was a significant effect of time to EAO only in the carriers' group (red), and this effect followed a linear trend. Based on this model, the expected time for a significant impairment ($z=-1$) is estimated at 3 years after the EAO in the carriers.
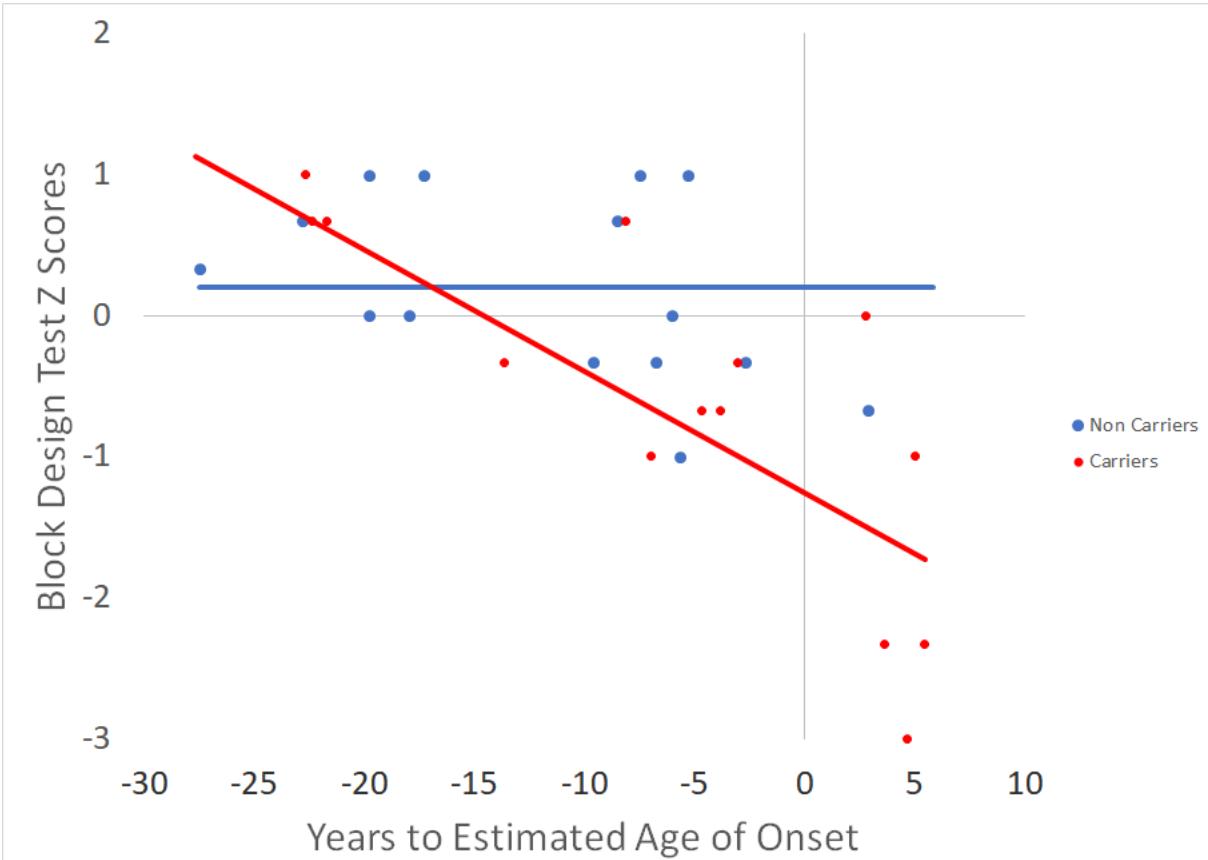
**Figure 3.** Performance on the Block Design Test (Z scores) as a function of years to EAO. There was a significant effect of time to EAO only in the carriers' group (red), and this effect followed a linear trend. Based on this model, the expected time for a significant impairment (z=-1) is estimated at 2 years after the EAO in the carriers.
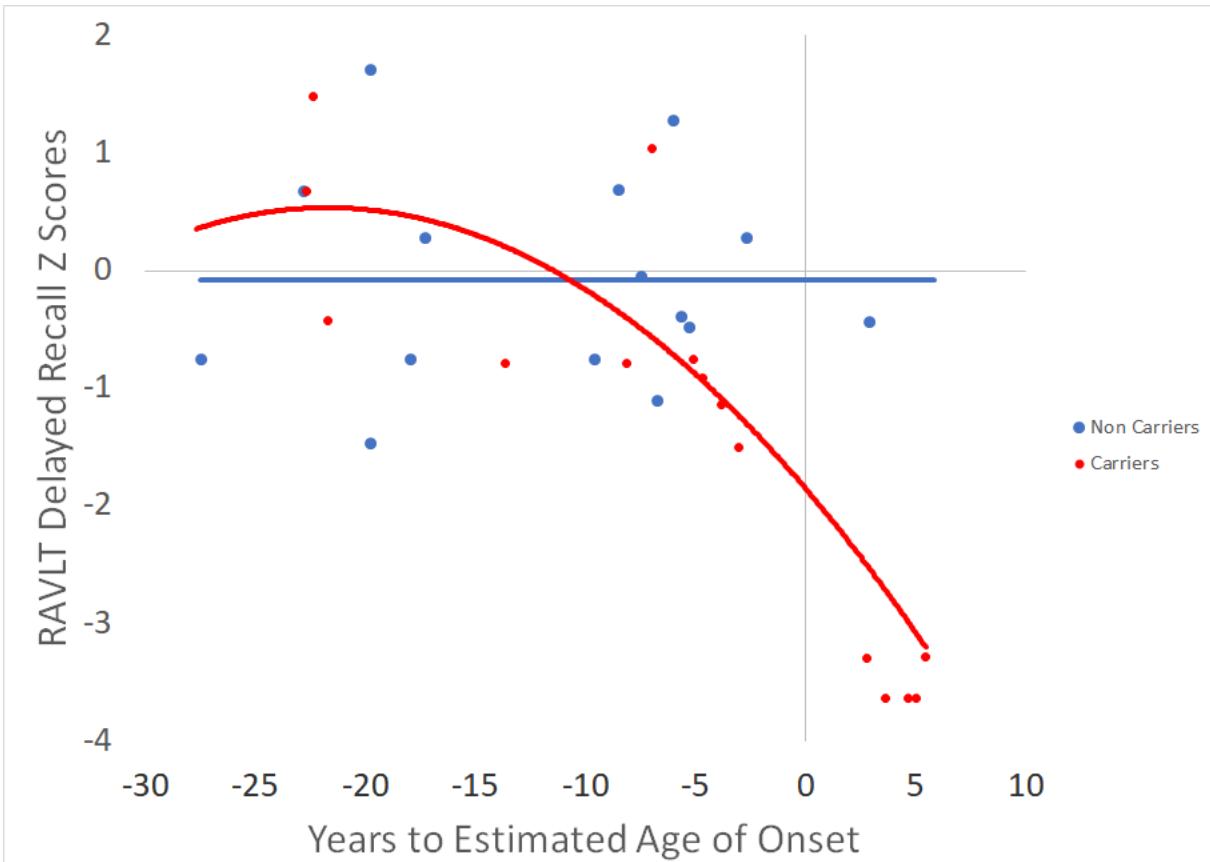
**Figure 4.** Performance on the RAVLT delayed recall (Z scores) as a function of years to EAO. There was a significant effect of time to EAO only in the carriers' group (red), and this effect followed a quadratic trend, with a significant decline starting at -16 years to EAO. Based on this model, the expected time for a significant impairment (z=-1) is estimated at -5 years to the EAO in the carriers.
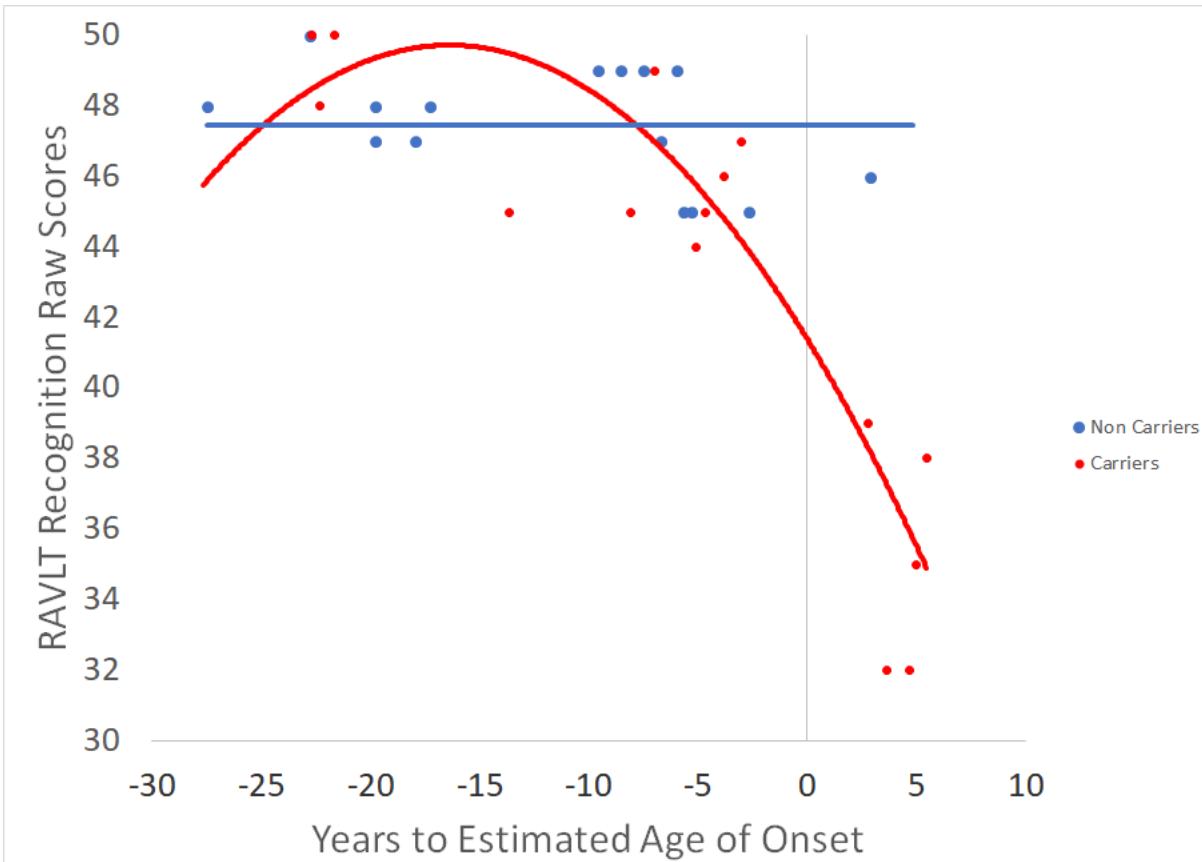
**Figure 5.** Performance on the RAVLT recognition (raw scores) as a function of years to EAO. There was a significant effect of time to EAO only in the carriers' group (red), and this effect followed a quadratic trend, with a significant decline starting at -17 years to EAO.

## Discussion

Familial AD offers a unique opportunity to study early biomarkers and neuropsychological changes in prodromal AD. A recent Canada-China collaboration on fAD research aims to pool the resources of these 2 countries to develop a fAD participants' registry with the goal of detecting early markers of the disease.

The goal of this study was to examine the trajectories of the time to EAO in the Canadian cohort with PSEN1 mutations, as a function of cognitive domains. First, the trajectory of cognitive deficits varies depending on the mutation carrying status. The non-carriers did not present a significant effect of the time to EAO for all the cognitive measures, whereas this effect

was significant for the mutations carriers for verbal episodic memory, semantic fluency and visuospatial abilities. Second, these cognitive domains had different patterns of trajectories for the time to EAO in the carriers.

We found a linear trend for verbal memory immediate recall, semantic fluency and visuospatial abilities. Thus, the deficits in these domains seem to appear more gradually as a function of time to EAO and are only impaired near the symptom's onset. This is consistent with the fact that dementia is a neurodegenerative disorder, with multi-domains impairments. As the disease progresses, the early memory deficits are followed and accompanied by impairments in other cognitive domains and the results indicate that semantic fluency and visuospatial tasks may be sensitive to detect progression to dementia. Semantic fluency deficits have consistently been associated with a higher risk of AD progression (Papp et al., 2016; Vaughan, Coen, Kenny, & Lawlor, 2018). Similarly, visuospatial measures were shown to have significant diagnostic and prognostic potential in dementia (Salimi et al., 2018).

A quadratic trend (an initial plateau followed by a significant negative trend) was a better fit for verbal memory delayed recall and recognition. This is consistent with a large body of literature indicating that verbal memory deficits are a predictor of conversion to AD and are found early in the disease progression (Belleville et al., 2014; Mortamais et al., 2017; Peters, Villeneuve, & Belleville, 2014; Rizk-Jackson et al., 2013). DIAN reported significant episodic memory impairment 10 years before the EAO (Bateman et al., 2012). In our sample, a negative trend was detected starting around 16 years to the EAO. We can hypothesize that the deficits must progressively appear in the years preceding the moment they can be detected with neuropsychological testing.

Interestingly, the trajectories found in this study are very similar to those reported in a longitudinal study of a clinical cohort of MCI participants in sporadic AD (Cloutier, Chertkow, Kergoat, Gauthier, & Belleville, 2015), with delayed memory following a quadratic trend and executive functions and visuospatial abilities presenting a more gradual, linear decline. Thus, even though the etiology is different, the neuropsychological markers associated with AD progression are comparable in the 2 forms of the disease, which brings support to the fact that the body of knowledge acquired by initiatives studying fAD may be useful to better understand the more common, sporadic form (Bateman et al., 2011).

Finally, this study contributed to thoroughly characterize Canadian families with PSEN1 mutations. We confirmed that the H163R protein change mutation is pathogenic and highly penetrant around the age of 45 years old, with low variability regarding the age of onset in the families. F175L mutation's mode of inheritance appears to be consistent with autosomal-dominant inheritance in the families, which supports that this mutation may be likely pathogenic for AD, especially since it was associated with significant amyloid and tau pathology. However, this mutation seems to be less penetrant than the H163R protein change and the age of onset presented a wider range in the families. Cases of reduced penetrance of fAD associated mutations, such as H163Y (Thordardottir et al., 2018) are reported and other genetic, epigenetic or environmental factors may contribute to modify the age of onset.

Limitations

This study has a few limitations that must be acknowledged. First, the sample was relatively small, which may impact statistical power. Considering the rarity of the disease, the number of participants with a thorough cognitive assessment was still significant. The carriers and non-carriers groups were equivalent, which made possible the comparison of their cognitive

performance as a function of time to EAO possible. Canadian families with PSEN1 mutations were not previously well characterized in the literature. This study contributed to report the neuropsychological profile of Canadian carriers of 2 rare PSEN1 mutations and brought support that the F175L PSEN1 mutation may be likely pathogenic for AD, considering the family history, the cognitive deficits typical of AD dementia and the evidence of amyloid and tau pathology associated with this mutation. Furthermore, it laid the foundations to the possibility of pooling the data from 2 populations with distinct cultures and languages (Canada and China). By elaborating a neuropsychological battery with appropriate norms, it will be possible to derive Z scores and combine the neuropsychological data of all the participants in this collaborative project. Second, the distribution of mutation carriers as a function of time to EAO shows that most of the participants were either very far from the EAO or close to the EAO. For instance, there was only one participant between -10 and -20 years to EAO. Considering that the goal of this study was to characterize the preclinical phases, there may be subtle cognitive markers in this period of the disease that we were not able to detect. Thus, the starting point of the negative trajectory found for verbal memory in this study (around -16 years to EAO) is not a precise measure and may shift along the time to EAO if more asymptomatic carriers were recruited and their data analyzed. Still, we found evidence that the time to EAO may present different trajectories depending on the cognitive domains. Third, many factors that may contribute to cognitive deficits, such as vascular risk factors, depressive symptoms, anxiety or sleep disorders were not included. It will be important to include these factors, not as exclusion criteria since it may further limit the already difficult recruitment of this population, but as controls or variables of interest in future studies. Finally, other pathologies sometimes associated with AD, such as white matter lesions, Lewy body pathology and neuroinflammation were not reported. However,

the focus of this study was first and foremost to characterize the neuropsychological markers of the Canadian cohort and how they relate to the AD pathology hallmarks biomarkers (amyloid and tau).

**Conclusion**

Carriers of PSEN1 mutations in Canadian families had significant cognitive deficits as a function of the time to EAO. The trajectories of the time to EAO depended on the cognitive domains. Verbal delayed memory deficits are an early cognitive marker of the disease and are characterized by a plateau far from the EAO, followed by a significant decline as the individuals get closer to the EAO. Verbal fluency and visuospatial abilities worsening performing as a function of time to EAO was also significant in the cognitive profile of the PSEN1 mutations' carriers. However, the effect of time to EAO was more gradual for these domains.

**References**

Ardila, A. (1995). Directions of research in cross-cultural neuropsychology. *J Clin Exp Neuropsychol, 17*(1), 143-150. doi:10.1080/13803399508406589

Ardila, A., Lopera, F., Rosselli, M., Moreno, S., Madrigal, L., Arango-Lasprilla, J. C., . . . Kosik, K. S. (2000). Neuropsychological profile of a large kindred with familial Alzheimer's disease caused by the E280A single presenilin-1 mutation. *Arch Clin Neuropsychol, 15*(6), 515-528.

Ballard, C., Gauthier, S., Corbett, A., Brayne, C., Aarsland, D., & Jones, E. (2011). Alzheimer's disease. *Lancet, 377*(9770), 1019-1031. doi:10.1016/S0140-6736(10)61349-9

Bateman, R. J., Aisen, P. S., De Strooper, B., Fox, N. C., Lemere, C. A., Ringman, J. M., . . . Xiong, C. (2011). Autosomal-dominant Alzheimer's disease: a review and proposal for the prevention of Alzheimer's disease. *Alzheimers Res Ther, 3*(1), 1. doi:10.1186/alzrt59

Bateman, R. J., Xiong, C., Benzinger, T. L., Fagan, A. M., Goate, A., Fox, N. C., . . . Dominantly Inherited Alzheimer, N. (2012). Clinical and biomarker changes in

dominantly inherited Alzheimer's disease. *N Engl J Med, 367*(9), 795-804. doi:10.1056/NEJMoa1202753

Bekris, L. M., Yu, C. E., Bird, T. D., & Tsuang, D. W. (2010). Genetics of Alzheimer disease. *J Geriatr Psychiatry Neurol, 23*(4), 213-227. doi:10.1177/0891988710383571

Belleville, S., Fouquet, C., Duchesne, S., Collins, D. L., & Hudon, C. (2014). Detecting Early Preclinical Alzheimer's Disease via Cognition, Neuropsychiatry, and Neuroimaging: Qualitative Review and Recommendations for Testing. *J Alzheimers Dis*. doi:10.3233/JAD-141470

Belleville, S., Rouleau, N., & Van der Linden, M. (2006). Use of the Hayling task to measure inhibition of prepotent responses in normal aging and Alzheimer's disease. *Brain Cogn, 62*(2), 113-119. doi:10.1016/j.bandc.2006.04.006

Bettens, K., Sleegers, K., & Van Broeckhoven, C. (2013). Genetic insights in Alzheimer's disease. *Lancet Neurol, 12*(1), 92-104. doi:10.1016/S1474-4422(12)70259-4

Bird, T. D. (2012). Early-Onset Familial Alzheimer Disease. In R. A. Pagon, M. P. Adam, H. H. Ardinger, T. D. Bird, C. R. Dolan, C. T. Fong, R. J. H. Smith, & K. Stephens (Eds.), *GeneReviews(R)*. Seattle (WA).

Callahan, B. L., Belleville, S., Ferland, G., Potvin, O., Tremblay, M.-P., Hudon, C., & Macoir, J. (2014). Normative data for a computer-assisted version of the auditory three-consonant Brown-Peterson paradigm in the elderly French-Quebec population. *Clin Neuropsychol, 28*(2), 317-332.

Campion, D., Dumanchin, C., Hannequin, D., Dubois, B., Belliard, S., Puel, M., . . . Frebourg, T. (1999). Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum. *Am J Hum Genet, 65*(3), 664-670. doi:10.1086/302553

Cloutier, S., Chertkow, H., Kergoat, M.-J., Gauthier, S., & Belleville, S. (2015). Patterns of cognitive decline prior to dementia in persons with mild cognitive impairment. *Journal of Alzheimer's Disease*.

D'Ellia, L. F., Satz, P., Uchiyama, C. L., & White, T. (1996). Color Trails Test. Professional manual. *Psychological Assessment Resources, Odessa, FL*.

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). Delis-Kaplan Executive Function System™ (D-KEFS™). *Psychological Corporation*.

Dion, M., Potvin, O., Belleville, S., Ferland, G., Renaud, M., Bherer, L., . . . Rouleau, I. (2015). Normative data for the Rappel libre/Rappel indicé à 16 items (16-item Free and Cued Recall) in the elderly Quebec-French population. *Clin Neuropsychol, 28*(sup1), 1-19.

Dong, J., Qin, W., Wei, C., Tang, Y., Wang, Q., & Jia, J. (2017). A Novel PSEN1 K311R Mutation Discovered in Chinese Families with Late-Onset Alzheimer's Disease Affects Amyloid-beta Production and Tau Phosphorylation. *J Alzheimers Dis, 57*(2), 613-623. doi:10.3233/JAD-161188

Doraiswamy, P. M., Leon, J., Cummings, J. L., Marin, D., & Neumann, P. J. (2002). Prevalence and impact of medical comorbidity in Alzheimer's disease. *J Gerontol A Biol Sci Med Sci, 57*(3), M173-177.

Dubois, B., Hampel, H., Feldman, H. H., Scheltens, P., Aisen, P., Andrieu, S., . . . Washington Dc, U. S. A. (2016). Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. *Alzheimers Dement, 12*(3), 292-323. doi:10.1016/j.jalz.2016.02.002

Escudier, F., Léveillé, E., Charbonneau, S., Cole, J., Hudon, C., Bédirian, V., & Scherzer, P. (2016). Evaluating decision-making: Validation and regression-based normative data of the judgment assessment tool. *Archives of Clinical Neuropsychology, 31*(8), 829-838.

Fox, N. C., Warrington, E. K., Seiffer, A. L., Agnew, S. K., & Rossor, M. N. (1998). Presymptomatic cognitive deficits in individuals at risk of familial Alzheimer's disease. A longitudinal prospective study. *Brain, 121 ( Pt 9)*, 1631-1639.

Gauthier, S., Jia, J., Belleville, S., Cloutier, S., Sadovnick, D., Guimond, C., . . . Rosa-Neto, P. (2017). Perspectives on a collaborative Canada-China research program on diagnostic biomarkers for pre-dementia stages of Alzheimer's disease. *Journal of Translational Neuroscience, 2*(3), 1-6. doi:10-3868/j. issn. 2096-0689. 2017. 03. 001

Godbolt, A. K., Cipolotti, L., Watt, H., Fox, N. C., Janssen, J. C., & Rossor, M. N. (2004). The natural history of Alzheimer disease: a longitudinal presymptomatic and symptomatic study of a familial cohort. *Arch Neurol, 61*(11), 1743-1748. doi:10.1001/archneur.61.11.1743

Guo, Q. (2007). Norm of auditory verbal learning test in the normal aged in China community. *Chinese Journal of Clinical Psychology, 15*(2), 132.

Guo, Q., Zhao, Q., Chen, M., Ding, D., & Hong, Z. (2009). A comparison study of mild cognitive impairment with 3 memory tests among Chinese individuals. *Alzheimer Disease & Associated Disorders, 23*(3), 253-259.

Hardy, J., & Selkoe, D. J. (2002). The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science, 297*(5580), 353-356. doi:10.1126/science.1072994

Jack, C. R., Jr., Knopman, D. S., Jagust, W. J., Shaw, L. M., Aisen, P. S., Weiner, M. W., . . . Trojanowski, J. Q. (2010). Hypothetical model of dynamic biomarkers of the

Alzheimer's pathological cascade. *Lancet Neurol, 9*(1), 119-128. doi:10.1016/S1474-4422(09)70299-6

Janssen, J. C., Hall, M., Fox, N. C., Harvey, R. J., Beck, J., Dickinson, A., . . . Rossor, M. N. (2000). Alzheimer's disease due to an intronic presenilin-1 (PSEN1 intron 4) mutation: A clinicopathological study. *Brain, 123 ( Pt 5)*, 894-907.

Jayadev, S., Leverenz, J. B., Steinbart, E., Stahl, J., Klunk, W., Yu, C. E., & Bird, T. D. (2010). Alzheimer's disease phenotypes and genotypes associated with mutations in presenilin 2. *Brain, 133*(Pt 4), 1143-1154. doi:10.1093/brain/awq033

Jia, J., Wei, C., Chen, S., Li, F., Tang, Y., Qin, W., . . . Gauthier, S. (2018). The cost of Alzheimer's disease in China and re-estimation of costs worldwide. *Alzheimers Dement, 14*(4), 483-491. doi:10.1016/j.jalz.2017.12.006

Kaplan, E. F., Goodglass, H., & Weintraub, S. (1983). The Boston Naming Test (2n ed.). *Philadelphia, PA: Lea & Febiger*.

Karbassi, I., Maston, G. A., Love, A., DiVincenzo, C., Braastad, C. D., Elzinga, C. D., . . . Higgins, J. J. (2016). A Standardized DNA Variant Scoring System for Pathogenicity Assessments in Mendelian Disorders. *Hum Mutat, 37*(1), 127-134. doi:10.1002/humu.22918

Larouche, E., Tremblay, M.-P., Potvin, O., Laforest, S., Bergeron, D., Laforce, R., . . . Belleville, S. (2016). Normative data for the Montreal Cognitive Assessment in middle-aged and elderly Quebec-French people. *Archives of Clinical Neuropsychology, 31*(7), 819-826.

Lavoie, M., Callahan, B., Belleville, S., Simard, M., Bier, N., Gagnon, L., . . . Hudon, C. (2013). Normative data for the Dementia Rating Scale-2 in the French-Quebec population. *Clin Neuropsychol, 27*(7), 1150-1166.

Liang, Y., Pertzov, Y., Nicholas, J. M., Henley, S. M. D., Crutch, S., Woodward, F., . . . Husain, M. (2016). Visual short-term memory binding deficit in familial Alzheimer's disease. *Cortex, 78*, 150-164. doi:10.1016/j.cortex.2016.01.015

Manly, J. J. (2008). Critical issues in cultural neuropsychology: profit from diversity. *Neuropsychol Rev, 18*(3), 179-183. doi:10.1007/s11065-008-9068-8

Morris, J. C., Aisen, P. S., Bateman, R. J., Benzinger, T. L., Cairns, N. J., Fagan, A. M., . . . Buckles, V. D. (2012). Developing an international network for Alzheimer research: The Dominantly Inherited Alzheimer Network. *Clin Investig (Lond), 2*(10), 975-984. doi:10.4155/cli.12.93

Mortamais, M., Ash, J. A., Harrison, J., Kaye, J., Kramer, J., Randolph, C., . . . Ritchie, K. (2017). Detecting cognitive changes in preclinical Alzheimer's disease: A review of its feasibility. *Alzheimers Dement, 13*(4), 468-492. doi:10.1016/j.jalz.2016.06.2365

Mullan, M., Scibelli, P., Duara, R., Fallin, D., Gold, M., Schinka, J., . . . Crawford, F. (1996). Familial and population-based studies of apolipoprotein E and Alzheimer's disease. *Ann N Y Acad Sci, 802*, 16-26.

Newman, S. K., Warrington, E. K., Kennedy, A. M., & Rossor, M. N. (1994). The earliest cognitive change in a person with familial Alzheimer's disease: presymptomatic neuropsychological features in a pedigree with familial Alzheimer's disease confirmed at necropsy. *J Neurol Neurosurg Psychiatry, 57*(8), 967-972.

Papp, K. V., Mormino, E. C., Amariglio, R. E., Munro, C., Dagley, A., Schultz, A. P., . . . Rentz, D. M. (2016). Biomarker validation of a decline in semantic processing in preclinical Alzheimer's disease. *Neuropsychology, 30*(5), 624-630. doi:10.1037/neu0000246

Parra, M. A., Abrahams, S., Logie, R. H., & Della Sala, S. (2010). Visual short-term memory binding in Alzheimer's disease and depression. *J Neurol, 257*(7), 1160-1169. doi:10.1007/s00415-010-5484-9

Parra, M. A., Saarimaki, H., Bastin, M. E., Londono, A. C., Pettit, L., Lopera, F., . . . Abrahams, S. (2015). Memory binding and white matter integrity in familial Alzheimer's disease. *Brain, 138*(Pt 5), 1355-1369. doi:10.1093/brain/awv048

Pedraza, O., & Mungas, D. (2008). Measurement in cross-cultural neuropsychology. *Neuropsychol Rev, 18*(3), 184-193. doi:10.1007/s11065-008-9067-9

Peters, F., Villeneuve, S., & Belleville, S. (2014). Predicting progression to dementia in elderly subjects with mild cognitive impairment using both cognitive and neuroimaging predictors. *J Alzheimers Dis, 38*(2), 307-318. doi:10.3233/JAD-130842

Rey, A. (1959). Test de copie d'une figure complexe: Manuel. *Paris: Les Éditions du Centre de Psychologie Appliquée.*

Riddoch, J. M., & Humphreys, G. W. (1993). BORB: Birmingham Object Recognition Battery. *Psychology Press*.

Rizk-Jackson, A., Insel, P., Petersen, R., Aisen, P., Jack, C., & Weiner, M. (2013). Early indications of future cognitive decline: stable versus declining controls. *PLoS One, 8*(9), e74062. doi:10.1371/journal.pone.0074062

Rosselli, M., & Ardila, A. (2003). The impact of culture and education on non-verbal neuropsychological measurements: a critical review. *Brain Cogn, 52*(3), 326-333.

Ryan, N. S., Nicholas, J. M., Weston, P. S. J., Liang, Y., Lashley, T., Guerreiro, R., . . . Fox, N. C. (2016). Clinical phenotype and genetic associations in autosomal dominant familial Alzheimer's disease: a case series. *Lancet Neurol, 15*(13), 1326-1335. doi:10.1016/S1474-4422(16)30193-4

Ryman, D. C., Acosta-Baena, N., Aisen, P. S., Bird, T., Danek, A., Fox, N. C., . . . And the Dominantly Inherited Alzheimer, N. (2014). Symptom onset in autosomal dominant Alzheimer disease: A systematic review and meta-analysis. *Neurology*. doi:10.1212/WNL.0000000000000596

Salimi, S., Irish, M., Foxe, D., Hodges, J. R., Piguet, O., & Burrell, J. R. (2018). Can visuospatial measures improve the diagnosis of Alzheimer's disease? *Alzheimers Dement (Amst), 10*, 66-74. doi:10.1016/j.dadm.2017.10.004

Schmidt, M. (1996). Rey Auditory Verbal Learning Test: A Handbook. *Western Psychological Services*.

Shea, Y. F., Chu, L. W., Chan, A. O., Ha, J., Li, Y., & Song, Y. Q. (2016). A systematic review of familial Alzheimer's disease: Differences in presentation of clinical features among three mutated genes and potential ethnic differences. *J Formos Med Assoc, 115*(2), 67-75. doi:10.1016/j.jfma.2015.08.004

Shepherd, C., McCann, H., & Halliday, G. M. (2009). Variations in the neuropathology of familial Alzheimer's disease. *Acta Neuropathol, 118*(1), 37-52. doi:10.1007/s00401-009-0521-4

Sherrington, R., Rogaev, E. I., Liang, Y., Rogaeva, E. A., Levesque, G., Ikeda, M., . . . St George-Hyslop, P. H. (1995). Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature, 375*(6534), 754-760. doi:10.1038/375754a0

Snider, B. J., Norton, J., Coats, M. A., Chakraverty, S., Hou, C. E., Jervis, R., . . . Morris, J. C. (2005). Novel presenilin 1 mutation (S170F) causing Alzheimer disease with Lewy bodies in the third decade of life. *Arch Neurol, 62*(12), 1821-1830. doi:10.1001/archneur.62.12.1821

Sole-Padulles, C., Bartres-Faz, D., Junque, C., Vendrell, P., Rami, L., Clemente, I. C., . . . Molinuevo, J. L. (2009). Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging, 30*(7), 1114-1124. doi:10.1016/j.neurobiolaging.2007.10.008

St-Hilaire, A., Blackburn, M. C., Wilson, M. A., Laforce, R. J., Hudon, C., & Macoir, J. (2017). Object decision test (BORB): normative data for the adult Quebec population and performance in Alzheimer's disease and the semantic variant of primary progressive aphasia. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*, 1-16. doi:10.1080/13825585.2017.1319901

St-Hilaire, A., Hudon, C., Vallet, G. T., Bherer, L., Lussier, M., Gagnon, J. F., . . . Macoir, J. (2016). Normative data for phonemic and semantic verbal fluency test in the adult French-Quebec population and validation study in Alzheimer's disease and depression. *Clin Neuropsychol, 30*(7), 1126-1150. doi:10.1080/13854046.2016.1195014

Storandt, M., Balota, D. A., Aschenbrenner, A. J., & Morris, J. C. (2014). Clinical and psychological characteristics of the initial cohort of the Dominantly Inherited Alzheimer Network (DIAN). *Neuropsychology, 28*(1), 19-29. doi:10.1037/neu0000030

Thies, W., Bleiler, L., & Alzheimer's, A. (2013). 2013 Alzheimer's disease facts and figures. *Alzheimers Dement, 9*(2), 208-245. doi:10.1016/j.jalz.2013.02.003

Thordardottir, S., Rodriguez-Vieitez, E., Almkvist, O., Ferreira, D., Saint-Aubert, L., Kinhult-Stahlbom, A., . . . Graff, C. (2018). Reduced penetrance of the PSEN1 H163Y autosomal dominant Alzheimer mutation: a 22-year follow-up study. *Alzheimers Res Ther, 10*(1), 45. doi:10.1186/s13195-018-0374-y

Tremblay, M. P., Potvin, O., Callahan, B. L., Belleville, S., Gagnon, J. F., Caza, N., . . . Macoir, J. (2015). Normative data for the Rey-Osterrieth and the Taylor complex figure tests in Quebec-French people. *Arch Clin Neuropsychol, 30*(1), 78-87. doi:10.1093/arclin/acu069

Vanier, M. (1991). Test d'apprentissage auditivoverbal de Rey-Taylor AVLT. Montreal: Institut de réadaptation de Montréal.

Vaughan, R. M., Coen, R. F., Kenny, R., & Lawlor, B. A. (2018). Semantic and Phonemic Verbal Fluency Discrepancy in Mild Cognitive Impairment: Potential Predictor of Progression to Alzheimer's Disease. *J Am Geriatr Soc, 66*(4), 755-759. doi:10.1111/jgs.15294

Wang, Q., Jia, J., Qin, W., Wu, L., Li, D., Wang, Q., & Li, H. (2015). A Novel AbetaPP M722K Mutation Affects Amyloid-beta Secretion and Tau Phosphorylation and May Cause Early-Onset Familial Alzheimer's Disease in Chinese Individuals. *J Alzheimers Dis, 47*(1), 157-165. doi:10.3233/JAD-143231

Wechsler, D. (1997a). Wechsler Adult Intelligence Scale–Third Edition. *San Antonio: The Psychological Corporation*.

Wechsler, D. (1997b). Wechsler Memory Scale (3rd edn.). *Psychological Corporation, San Antonio, TX*

Wechsler, D. (2005). Échelle d'intelligence de Wechsler pour adultes -III Version pour francophones du Canada - (WAIS-III-FR CDN).

Weschler, D., Chen, Y., & Chen, X. (2002). WAIS-III Chinese version technical manual. *San Antonio, TA: Psychological Corporation*.

Wu, L., Rosa-Neto, P., Hsiung, G. Y., Sadovnick, A. D., Masellis, M., Black, S. E., . . .
Gauthier, S. (2012). Early-onset familial Alzheimer's disease (EOFAD). *Can J Neurol Sci, 39*(4), 436-445.

# Chapitre VII

**Article 6:** *Short Communication: Canada-China Familial Alzheimer's Disease (CCFAD): Preliminary Amyloid and Tau Data from the Canadian Cohort with PSEN1 mutations*

**Article 6: Short Communication: Canada-China Familial Alzheimer's Disease (CCFAD): Preliminary Amyloid and Tau Data from the Canadian Cohort with PSEN1 mutations**

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**En préparation**

**Short Communication: Canada-China Familial Alzheimer's Disease (CCFAD):**

**Preliminary Amyloid and Tau Data from the Canadian Cohort with PSEN1 mutations**

**Introduction**

Familial type AD (fAD) offers a unique opportunity to study the brain pathology, the biomarkers and the cognitive profile of individuals who will progress to AD, many years prior to their diagnosis. Familial AD is an autosomal, dominantly inherited form of AD, associated with gene mutations on presenilin1 (PSEN1), preseinilin2 (PSEN2), and the amyloid precursor gene (APP). Contrary to other genetic mutations that were shown to increase the risk of AD conversion (Bettens, Sleegers, & Van Broeckhoven, 2013), such as the allele e4 of the apolipoprotein E (APOE) gene (Mullan et al., 1996), these mutations are highly penetrant (from 95% to 100%) (Bird, 2012). PSEN1, PSEN2 and APP genes are directly or indirectly implicated in the production of beta-amyloid (Bettens et al., 2013), a finding that has provided critical empirical support to the amyloid hypothesis for AD (Hardy & Selkoe, 2002; Jack et al., 2010). Most of fAD cases are caused by PSEN1 mutations, PSEN2 mutations being the rarest.

For brain pathology and imaging markers, both the sporadic and familial forms present hippocampal atrophy, tempo-parietal cortical loss, temporo-parietal hypometabolism, significant amyloid deposition, especially in the precuneus/posterior cingulate and prefrontal cortex, as well as neurofibrillary tangles on neuropathology. For cerebrospinal fluid (CSF) biomarkers, both forms show a decrease in CSF Aβ42 and an increase in CSF tau (Bateman et al., 2011; Shepherd, McCann, & Halliday, 2009).

**Canada-China Familial Alzheimer's Disease Project (CCFAD)**

Canada-China Familial Alzheimer's Disease (CCFAD) project aims to pool the resources of Canada and China to develop a registry of fAD participants, to characterize biomarkers and cognitive changes associated with PSEN1, PSEN2 and APP mutations at the preclinical and MCI stages of AD and to search for novel fAD mutations (Gauthier et al., 2017). This program includes the collaboration between research centers in Montreal, a bi-cultural city with both a French- and English-speaking population (McGill Center for Studies on Aging, Montreal Geriatrics Institute and Montreal Neurological Institute), Vancouver (endMS Western Pacific Research and Training Center), Toronto (Sunnybrook Research Center) and Beijing (Beijing Institute for Brain Disorders Alzheimer's Disease Center and Capital University). Several articles related to this collaboration have already been published (Gauthier et al., 2017) and novel mutations were found for families in China (Dong et al., 2017; Wang et al., 2015). The CCFAD project includes a clinical evaluation, a neuropsychological assessment using a standardized battery with tests available in English, French and Mandarin (see Neuropsychological Assessment of CCFAD Participants section), a blood sample for genotyping, MRI for brain atrophy, PET with ligands for amyloid and tau and a lumbar puncture for CSF biomarkers.

For the purpose of this short communication, we will report the preliminary amyloid and tau data of the Canadian cohort with PSEN1 mutations. More precisely, the goal of this study was to qualitatively report the progression of amyloid and tau pathology as a function of time to EAO.

**Methodology**

<u>Participants, mutations and estimated age of onset</u>

Individuals with a familial history of early onset AD were referred to the CCFAD registry. They consented for a medical appointment with a neurologist, a blood sample for genetic analyzes and an interview with a genetic counselor, for a precise history of the age of symptoms onset in the family. Thirty-two participants from the Canadian registry for familial AD were recruited for the neuropsychological study and were genotyped for known fAD mutations and a subset of 18 participants (10 carriers) underwent amyloid and tau imaging.

Table 1 presents the 2 PSEN1 mutations of the sample. The first one is H163R protein change (A>G). This mutation was first described in 1995, in conjunction with the cloning of the PSEN1 gene. The estimated age of onset (EAO) for the French-Canadian families is 45 years old (Sherrington et al., 1995), which is also what we found in our sample. Thus, this mutation appears to be highly penetrant around the age of 45 years old, which we used to compute the EAO for the asymptomatic carriers and the non-carriers. The second identified mutation is F175L protein change (C>G). This mutation is classified as having uncertain clinical significance regarding AD pathogenicity (Karbassi et al., 2016) but is a known mutation included in DIAN. The mean age of onset in the families for the F175L mutation in our sample was older (around 50 years old), but more importantly was highly variant (standard deviation of 7 years with a range between 43 and 62 years old). Thus, we used the age of onset of the parent to compute the time to EAO. For both mutations, we used the effective age of onset for symptomatic carriers, which was derived from a clinical interview, independent of the cognitive assessment.

**Table 1.** PSEN1 mutations of the Canadian Families

| Mutation | Non-Carriers | Carriers | Mean age of onset families (SD) |
|---|---|---|---|
| H163R (A>G) | 4 | 4 | 45.75 (1.41) |
| F175L (C>G) | 7 | 8 | 50.14 (6.96) |

Statistical analysis

PET scans were acquired with a Siemens High Resolution Research Tomograph (HRRT). [18F]MK6240 images were acquired 90–110 minutes post-injection and scans were reconstructed with the OSEM algorithm on a 4D volume with 4 frames (4 x 300s) 19. [18F]AZD4694 images were acquired 40–70 minutes post-injection and scans were reconstructed with the OSEM algorithm on a 4D volume with 3 frames (3 x 600s) 20. Immediately following each PET acquisition, a 6-minute transmission scan was conducted with a rotating 137Cs point source for attenuation correction. Additionally, the images underwent correction for dead time, decay, and random and scattered coincidences. T1-weighted images were non-uniformity and field-distortion corrected and processed using an in-house pipeline. Then, PET images were automatically registered to the T1-weighted image space, and the T1-weighted images were linearly and non-linearly registered to the ADNI template space. Subsequently, a PET non-linear registration was performed using the linear and non-linear transformations from the T1-weighted image to the ADNI space and the PET to T1-weighted image registration. The PET images were spatially smoothed to achieve a final resolution of 8mm full-width at half maximum. [18F]MK6240 standardized uptake value ratio (SUVR) maps were generated using the inferior cerebellar grey matter as a reference region and

[18F]AZD4694 SUVR maps were generated using the cerebellar grey matter as a reference region. Both for amyloid and for tau, positivity was determined visually.

**Results**

Table 2 presents the demographics data of the participants. Figure 1 presents the amyloid and tau imaging markers for 2 non-carriers (one far from the EAO and the other closer to the EAO). Both were not positive for amyloid or tau and their cognitive performance (delayed verbal memory) was within average. Figure 2 presents the amyloid and tau imaging markers for 4 carriers, as a function of time to EAO. Amyloid positivity is an earlier marker, even for asymptomatic carriers, whereas significant tau pathology seems to be closer to or after the EAO and is associated with significant cognitive impairment.

**Table 2.** Demographics Data of the Canadian Cohort with Amyloid and Tau Data

|  | **Non-Carriers** | **Carriers** | **p** |
|---|---|---|---|
| N (Men/Women) | 8 (6/2) | 10 (6/4) | .638 |
| Age (SD) | 41 (7.56) | 46.4 (7.9) | .161 |
| Education (SD) | 12.5 (1.6) | 12.8 (2.78) | .79 |
| Vocabulary* (WAIS-III) | -.52 (.69) | -.63 (.63) | .771 |

* Z scores derived from normative data
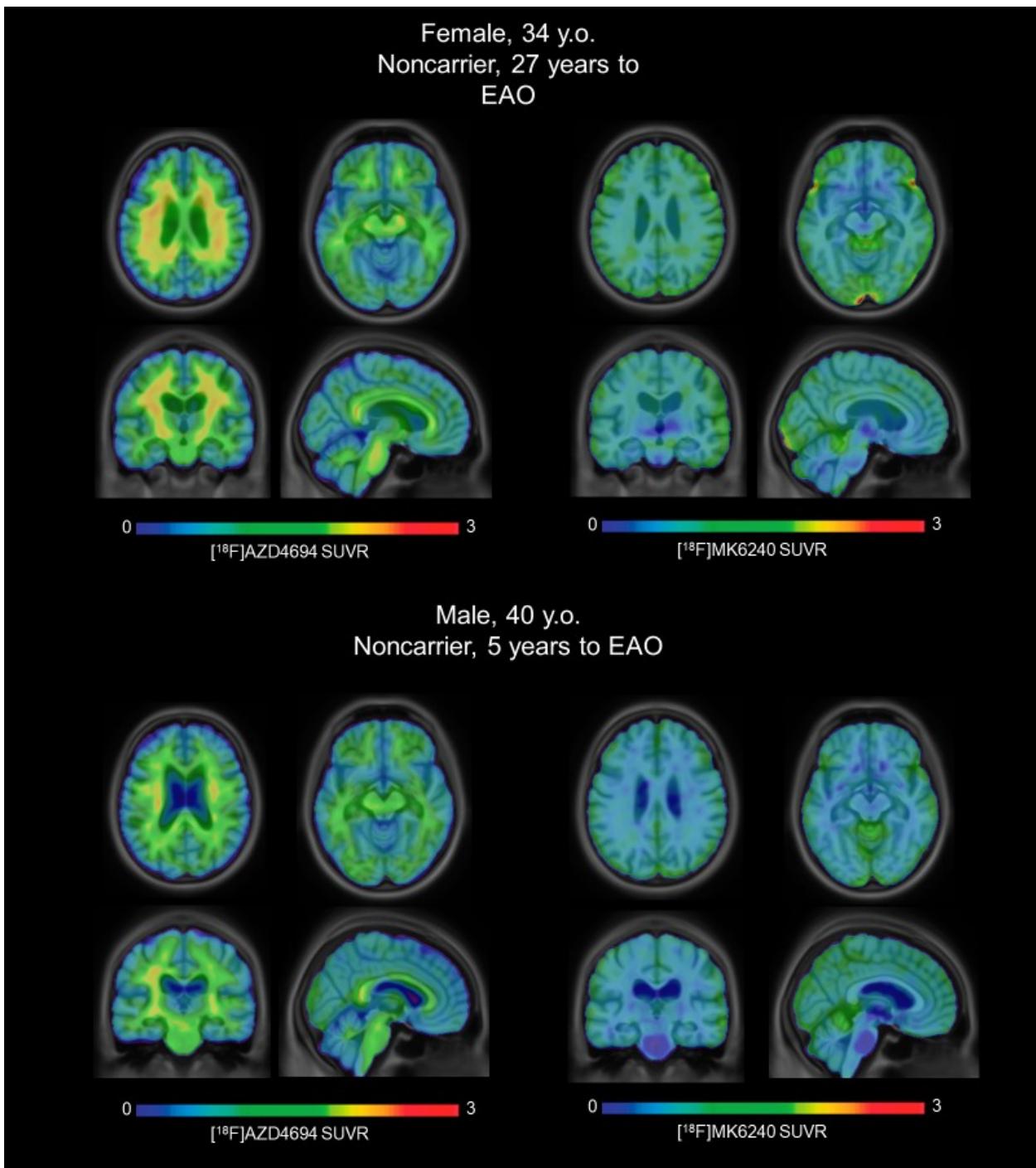
**Figure 1.** Amyloid (left) and Tau (right) imaging for 2 non-carriers. There was no significant amyloid or tau pathology whether the individual was far from the EAO (-27 years) or near the EAO (-5 years). Their performance for delayed verbal memory were within average (-0.75 and -0.48).

Female, 40 y.o.
Carrier, 22 years to EAO
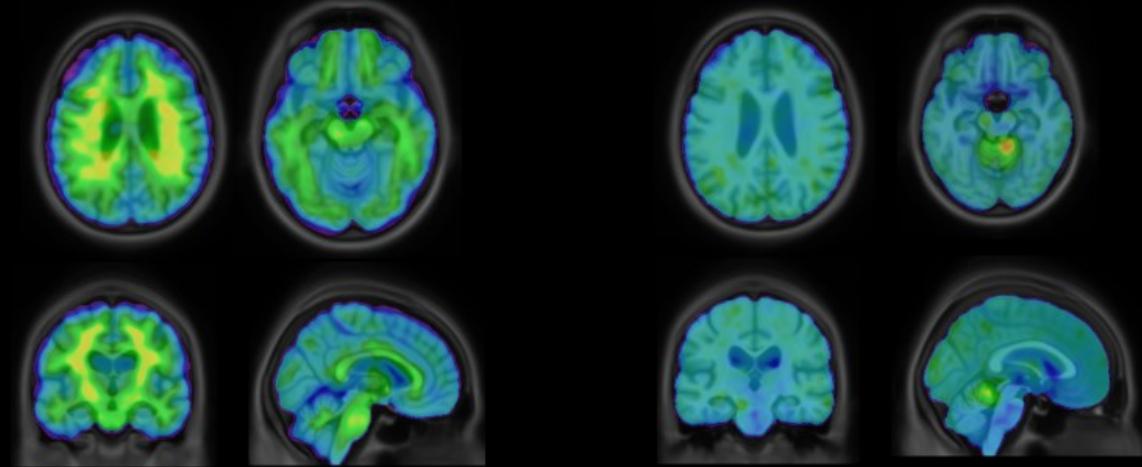
[¹⁸F]AZD4694 SUVR

[¹⁸F]MK6240 SUVR

Male, 48 y.o.
Carrier, 8 years to EAO
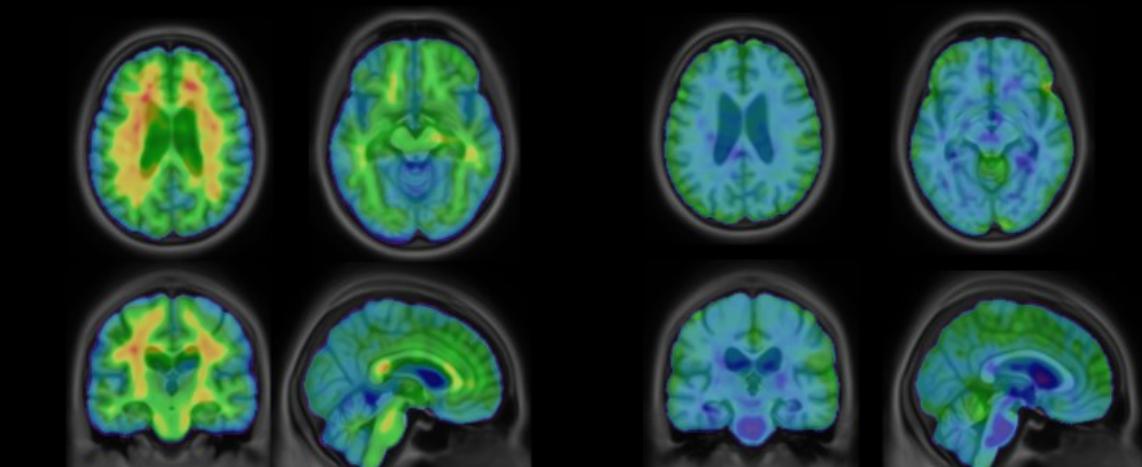
[¹⁸F]AZD4694 SUVR

[¹⁸F]MK6240 SUVR
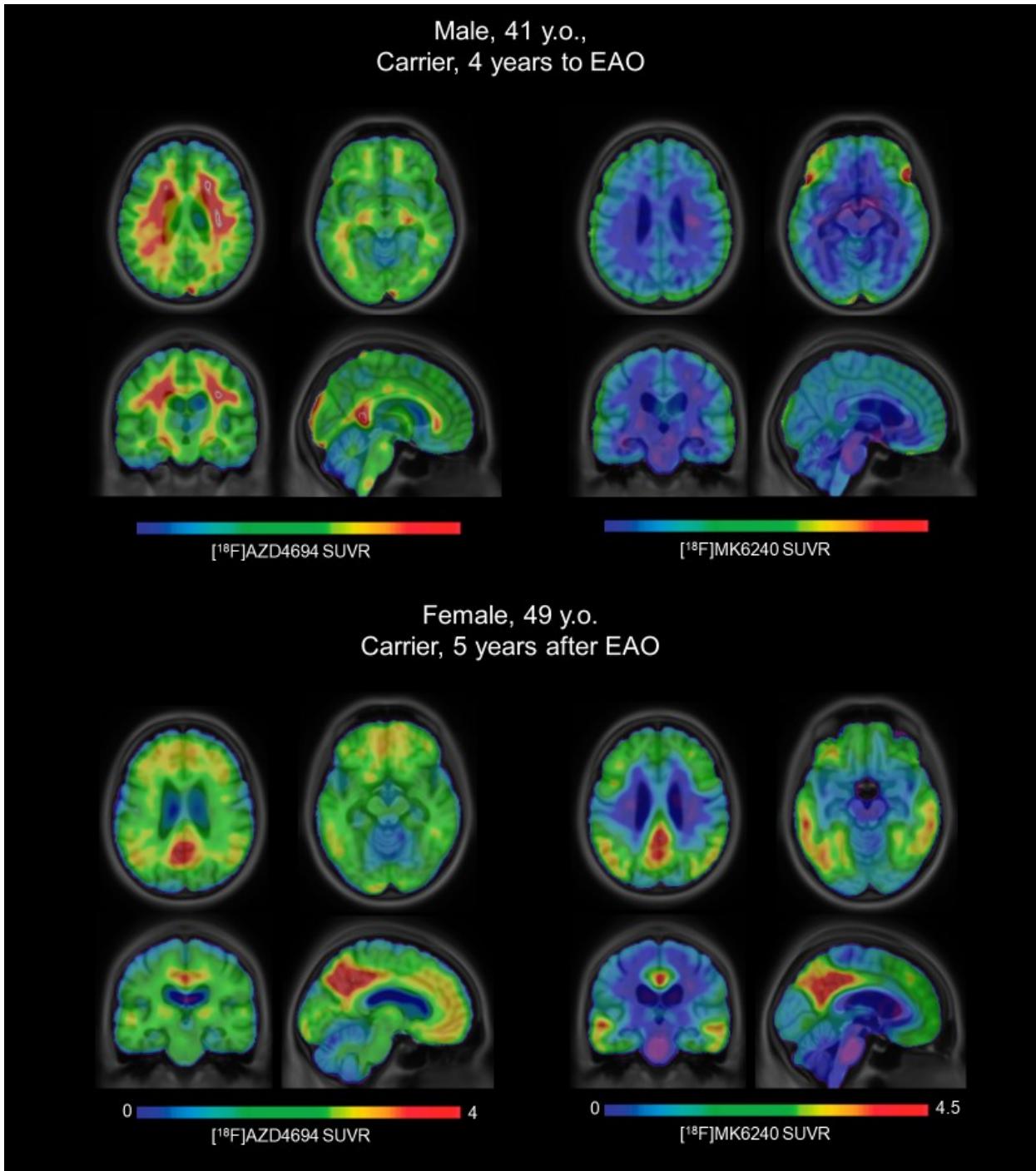
**Figure 2.** Amyloid (left) and Tau (right) imaging for 4 mutation carriers, as a function of time to EAO. There was no significant amyloid deposition or tau pathology for the carrier at -22 years to the EAO. The carriers at -8 years and -4 years to the EAO were positive for amyloid, but not for tau, whereas the symptomatic carrier at +5 years after the EAO was positive for both. Their performance for verbal memory delayed recall were, in order: -0.43, -0.79, -1.5 and -3.29.

**Conclusion**

Familial AD offers a unique opportunity to study early biomarkers in prodromal AD. A recent Canada-China collaboration on fAD research aims to pool the resources of these 2 countries to develop a fAD participants' registry with the goal of detecting early markers of the disease.

Regarding the biormarkers (amyloid and tau) as a function of time to EAO, we qualitatively observed that amyloid was an early marker, whereas significant tau pathology was found closer to the EAO and was associated with more cognitive deficits. Tau pathology is more strongly associated with clinical symptoms and cognitive impairments and it was proposed that it may be a better target for clinical trials (Giacobini & Gold, 2013; Hampel et al., 2015).

Cognitive deficits appeared to be more associated with tau pathology, compared to amyloid deposition, which was significant even in asymptomatic carriers many years to the EAO.

**References**

Bateman, R. J., Aisen, P. S., De Strooper, B., Fox, N. C., Lemere, C. A., Ringman, J. M., . . . Xiong, C. (2011). Autosomal-dominant Alzheimer's disease: a review and proposal for the prevention of Alzheimer's disease. *Alzheimers Res Ther, 3*(1), 1. doi:10.1186/alzrt59

Bettens, K., Sleegers, K., & Van Broeckhoven, C. (2013). Genetic insights in Alzheimer's disease. *Lancet Neurol, 12*(1), 92-104. doi:10.1016/S1474-4422(12)70259-4

Bird, T. D. (2012). Early-Onset Familial Alzheimer Disease. In R. A. Pagon, M. P. Adam, H. H. Ardinger, T. D. Bird, C. R. Dolan, C. T. Fong, R. J. H. Smith, & K. Stephens (Eds.), *GeneReviews(R)*. Seattle (WA).

Dong, J., Qin, W., Wei, C., Tang, Y., Wang, Q., & Jia, J. (2017). A Novel PSEN1 K311R Mutation Discovered in Chinese Families with Late-Onset Alzheimer's Disease Affects Amyloid-beta Production and Tau Phosphorylation. *J Alzheimers Dis, 57*(2), 613-623. doi:10.3233/JAD-161188

Gauthier, S., Jia, J., Belleville, S., Cloutier, S., Sadovnick, D., Guimond, C., . . . Rosa-Neto, P. (2017). Perspectives on a collaborative Canada-China research program on diagnostic biomarkers for pre-dementia stages of Alzheimer's disease. *Journal of Translational Neuroscience, 2*(3), 1-6. doi:10-3868/j. issn. 2096-0689. 2017. 03. 001

Giacobini, E., & Gold, G. (2013). Alzheimer disease therapy--moving from amyloid-beta to tau. *Nat Rev Neurol, 9*(12), 677-686. doi:10.1038/nrneurol.2013.223

Hampel, H., Schneider, L. S., Giacobini, E., Kivipelto, M., Sindi, S., Dubois, B., . . . Lista, S. (2015). Advances in the therapy of Alzheimer's disease: targeting amyloid beta and tau and perspectives for the future. *Expert Rev Neurother, 15*(1), 83-105. doi:10.1586/14737175.2015.995637

Hardy, J., & Selkoe, D. J. (2002). The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science, 297*(5580), 353-356. doi:10.1126/science.1072994

Jack, C. R., Jr., Knopman, D. S., Jagust, W. J., Shaw, L. M., Aisen, P. S., Weiner, M. W., . . . Trojanowski, J. Q. (2010). Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol, 9*(1), 119-128. doi:10.1016/S1474-4422(09)70299-6

Karbassi, I., Maston, G. A., Love, A., DiVincenzo, C., Braastad, C. D., Elzinga, C. D., . . . Higgins, J. J. (2016). A Standardized DNA Variant Scoring System for Pathogenicity Assessments in Mendelian Disorders. *Hum Mutat, 37*(1), 127-134. doi:10.1002/humu.22918

Mullan, M., Scibelli, P., Duara, R., Fallin, D., Gold, M., Schinka, J., . . . Crawford, F. (1996). Familial and population-based studies of apolipoprotein E and Alzheimer's disease. *Ann N Y Acad Sci, 802*, 16-26.

Shepherd, C., McCann, H., & Halliday, G. M. (2009). Variations in the neuropathology of familial Alzheimer's disease. *Acta Neuropathol, 118*(1), 37-52. doi:10.1007/s00401-009-0521-4

Sherrington, R., Rogaev, E. I., Liang, Y., Rogaeva, E. A., Levesque, G., Ikeda, M., . . . St George-Hyslop, P. H. (1995). Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature, 375*(6534), 754-760. doi:10.1038/375754a0

Wang, Q., Jia, J., Qin, W., Wu, L., Li, D., Wang, Q., & Li, H. (2015). A Novel AbetaPP M722K Mutation Affects Amyloid-beta Secretion and Tau Phosphorylation and May Cause Early-Onset Familial Alzheimer's Disease in Chinese Individuals. *J Alzheimers Dis, 47*(1), 157-165. doi:10.3233/JAD-143231

# CHAPITRE VIII : Discussion générale

# 1. Rappel des objectifs et synthèse des résultats

L'objectif général de ce travail était de caractériser les trajectoires de déclin cognitif et fonctionnel dans les phases précoces de la maladie d'Alzheimer (MA). Deux grandes approches, à la fois distinctes et complémentaires, ont permis d'atteindre cet objectif : l'étude du trouble cognitif léger (TCL) dans la MA sporadique et l'étude du phénotype cognitif d'individus porteurs de mutations autosomiques dominantes dans la MA familiale (MAf). Quatre articles empiriques ont découlé de ce travail. Un résumé de leurs objectifs respectifs et une synthèse des principaux résultats sont présentés dans la présente section.

Le premier article empirique visait à caractériser les différents domaines cognitifs (mémoire épisodique, fonctions exécutives, mémoire de travail, traitement visuospatial et langage) et leurs trajectoires dans le temps, chez des personnes avec un TCL, en distinguant celles qui ultérieurement progressent vers une démence, ou progresseurs, et celles qui ne progressent pas vers une démence, ou non-progresseurs. Pour cela, nous avons fait appel à un devis longitudinal dans lequel les participants étaient évalués annuellement par un clinicien et par une batterie neuropsychologique. Les cliniciens déterminaient le diagnostic clinique de démence et le suivi était cessé l'année où le participant recevait le diagnostic. Les non-progresseurs sont demeurés stables sur l'ensemble des domaines cognitifs évalués. En revanche, les progresseurs montrent un déclin cognitif sur presque toutes les fonctions évaluées. De plus, les trajectoires de déclin se distinguent selon le domaine cognitif. Une fonction quadratique (un plateau suivi d'un déclin accéléré) caractérise le rappel différé en mémoire épisodique et la mémoire de travail/vitesse de traitement de l'information. Une fonction linéaire (plus graduelle et progressive) caractérise le rappel immédiat en mémoire, les fonctions exécutives et les habiletés visuospatiales.

Les résultats de cette étude indiquent que la mémoire épisodique et la mémoire de travail/vitesse de traitement de l'information sont les domaines cognitifs les plus atteints et qui ont présenté le déclin le plus rapide chez les progresseurs : ces domaines sont déjà atteints plusieurs années avant le diagnostic clinique de démence et ont présenté un déclin accéléré juste avant l'année de conversion. Ceci est cohérent avec des observations que le TCL est surtout caractérisé par des déficits en mémoire (Petersen, Stevens, et al., 2001; Small, Fratiglioni, Viitanen, Winblad, & Backman, 2000) et que les déficits en mémoire épisodique et pour la mémoire de travail sont précoces dans le continuum de la maladie (Belleville, Gauthier, Lepage, Kergoat, & Gilbert, 2014; Peters, Villeneuve, & Belleville, 2014) et sont des prédicteurs de conversion du TCL à la MA (Belleville, Fouquet, et al., 2014) et du vieillissement normal au TCL (Rizk-Jackson et al., 2013).

Cette étude montre aussi que la mémoire n'est pas le seul domaine cognitif atteint dans le TCL en progression vers la MA. Plusieurs autres domaines montrent une atteinte dont la sévérité augmente avec le temps. Un de ces domaines consiste en les fonctions exécutives. Ce résultat diffère avec ceux de l'étude de Bennett et al. (2002), qui n'a pas observé une détérioration par rapport aux fonctions exécutives. Cette différence pourrait être expliquée par le fait que Bennett et al. (2002) ont utilisé un score composite pour les fonctions exécutives, alors que nous avons mesuré la composante « inhibition » du test de Stroop. Les fonctions exécutives reflètent un ensemble de processus cognitivement et neurologiquement distincts (de Frias, Dixon, & Strauss, 2009; Miyake et al., 2000; Sylvain-Roy, Lungu, & Belleville, 2015). Il est possible que certains de ces processus ne soient pas sensibles pour la MA (Belleville et al., 2007). Parmi ceux-ci, l'inhibition et la mémoire de travail semblent être celles qui sont particulièrement sensibles et précocement atteintes dans le TCL (Belanger & Belleville, 2009;

Belanger, Belleville, & Gauthier, 2010; Johns et al., 2012; Zheng et al., 2012). Une autre différence entre ces études est le fait que nous avons distingué les progresseurs des non-progresseurs. Certaines études ont montré que les fonctions exécutives et l'inhibition sont davantage atteintes chez les progresseurs que chez les non-progresseurs dans le TCL (Belanger & Belleville, 2009; Rainville et al., 2012; Saunders & Summers, 2010, 2011). Les résultats de notre étude supportent cette littérature, puisque seuls les progresseurs présentent un déclin significatif dans ce domaine.

Enfin, malgré le fait que les progresseurs sont significativement plus atteints par rapport à leur performance au *Boston Naming Test*, nous n'avons pas trouvé de déclin significatif pour le langage. Ces résultats diffèrent des études ayant rapporté un déclin par rapport à la mémoire sémantique dans le TCL (Bennett et al., 2002; Gardini et al., 2013; Price et al., 2012). Il faut noter toutefois que, dans la plupart des études ayant montré un tel déclin, une tâche de fluence verbale, qui présente aussi une composante exécutive, était utilisée pour évaluer le langage. Dans notre étude, nous avons utilisé une tâche de dénomination d'images, qui pourrait refléter des dimensions du langage qui demeurent plus stables dans le TCL que celles évaluées par une tâche de fluence.

Dans le cadre de la seconde étude empirique, nous nous sommes intéressés aux trajectoires de déclin des capacités à réaliser les activités de la vie quotidienne instrumentales (AVQi) chez ces mêmes individus ayant un TCL qui ont progressé vers une démence et de comparer ces trajectoires à celles que l'on retrouve chez les individus avec un TCL n'ayant pas progressé. Les participants ont été divisés en 3 groupes : les progresseurs ont reçu un diagnostic de démence au cours de l'étude, les déclineurs ont présenté un déclin cognitif significatif sans rencontrer les critères de démence au cours de l'étude et les stables n'ont pas présenté de déclin

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cognitif et n'ont pas progressé vers un diagnostic de démence.  Nous faisons l'hypothèse que les déclineurs sont sans doute dans une phase moins sévère que les progresseurs puisque leurs atteintes n'ont pas progressé suffisamment lors du suivi pour qu'ils rencontrent les critères de démence. De façon générale, les capacités autorapportées à réaliser les AVQi suivent une trajectoire quadratique chez les progresseurs, linéaire chez les déclineurs et n'ont pas changé à travers le temps chez les stables. Cela suggère que le déclin pourrait d'abord être linéaire et graduel puis décliner rapidement lorsque les patients sont proches du stade de démence. Lorsqu'on distingue les activités complexes (p.ex. gérer le budget) et les activités de l'entretien de la maison (p.ex. faire la lessive), on observe la même trajectoire quadratique pour les activités complexes chez les progresseurs, mais une trajectoire linéaire chez les déclineurs et aucun changement chez les stables. En revanche, les activités reliées à l'entretien de la maison suivent une trajectoire linéaire pour les progresseurs et non-significative pour les déclineurs et les stables. Cela confirme que les activités complexes sont atteintes plus rapidement et que les déclineurs sont sans doute dans une phase moins avancée que les progresseurs.

Cette étude a identifié deux grandes catégories d'AVQi : les activités de l'entretien de la maison (ménage, cuisine et lessive) et les AVQi complexes (utiliser un téléphone, gérer la médication, gérer le budget, utiliser le transport et faire des achats). Cette dernière catégorie contient des activités qui étaient associées au déclin cognitif et prédisaient la conversion vers la démence l'année suivante, dans une large étude de population longitudinale (Barberger-Gateau et al., 1992; Barberger-Gateau, Dartigues, & Letenneur, 1993). Cette catégorie est également similaire au groupe de 4-AVQi de Barbeger-Gateau (utilisation du téléphone, transport, gestion de la médication et gestion du budget). Un déficit fonctionnel sur ces 4 AVQi représentait un marqueur précoce de démence, jusqu'à 3 ans précédant le diagnostic, dans une cohorte de

personnes âgées (Barberger-Gateau, Fabrigoule, Helmer, Rouch, & Dartigues, 1999). Ceci apporte donc un support à notre approche, c'est-à-dire l'étude des trajectoires selon le type d'AVQi.

La troisième étude empirique examinait l'apparition et l'évolution des atteintes cognitives dans la MAf, en distinguant les personnes porteuses de mutations menant à un diagnostic de démence de celles non-porteuses de ces mutations. Les performances ont été évaluées en tenant compte de l'âge estimé de conversion vers la MA. L'âge estimé correspond à l'âge prédit par la mutation ou alors à l'âge du diagnostic du parent. La distance au diagnostic correspond au nombre d'années entre l'évaluation cognitive et l'âge estimé du diagnostic. Comme les participants n'avaient pas tous le même âge, il a été possible ainsi de mesurer indirectement l'effet de la distance au diagnostic sur la trajectoire cognitive. Cette étude a permis de caractériser des familles canadiennes avec mutations PSEN1, qui n'étaient pas bien étudiées et représentées dans la littérature. Les membres non porteurs des mutations n'ont pas présenté d'effet du temps estimé au diagnostic, pour l'ensemble des domaines cognitifs. Chez les porteurs de mutation, le temps estimé au diagnostic suit une trajectoire quadratique pour le rappel différé et la reconnaissance en mémoire épisodique et une trajectoire linéaire pour le rappel immédiat en mémoire, la fluence verbale sémantique/catégorielle et les habiletés visuoconstructives.

Les déficits dans les domaines des fonctions exécutives (fluence verbale) et des habiletés visuoconstructives semblent donc apparaître de manière plus graduelle par rapport au temps estimé au diagnostic et sont significatifs seulement près du moment de conversion vers la démence. Ceci est cohérent avec le fait que la démence est un trouble neurodégénératif, avec des atteintes multi domaines. Au fur et à mesure que la maladie progresse, les déficits mnésiques précoces sont suivis et accompagnés par des déficits dans d'autres domaines et les résultats de

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cette étude indiquent que la fluence verbale et les habiletés visuoconstructives pourraient être des marqueurs sensibles de progression. Ces résultats collaborent ceux des études montrant que des déficits en fluence sémantique (Papp et al., 2016; R. M. Vaughan, Coen, Kenny, & Lawlor, 2018) et par rapport aux tâches visuospatiales (Salimi et al., 2018) augmentent le risque de progression vers la démence.

La performance en mémoire épisodique suit une trajectoire quadratique par rapport au temps estimé au diagnostic : une période stable suivie d'un déclin accéléré. Cette trajectoire, similaire à celle observée pour la mémoire épisodique dans le type sporadique (étude 2), est compatible avec la littérature, indiquant que des déficits en mémoire verbale représentent un prédicteur significatif de conversion vers la MA et apparaissent précocement dans l'évolution de la maladie (Belleville, Fouquet, et al., 2014; Mortamais et al., 2017). DIAN a rapporté des déficits dans ce domaine environ 10 ans avant le temps estimé au diagnostic (Bateman et al., 2012). Dans la cohorte de cette troisième étude empirique, le déclin par rapport au rappel différé en mémoire commence à partir de 16 ans avec le temps estimé au diagnostic. On peut émettre l'hypothèse que les déficits progressent graduellement dans les années précédant le moment où ils peuvent être détectés par des tâches neuropsychologiques.

Enfin, la quatrième étude empirique avait pour but de présenter les données d'imagerie préliminaires de la cohorte canadienne avec mutations PSEN1, avec une série de cas. Chez les porteurs de mutation, l'amyloïde est un marqueur précoce, significatif même chez les individus non symptomatiques. Le marqueur tau est significatif uniquement près de l'âge estimé du diagnostic chez les porteurs et semble être davantage associé aux déficits cognitifs.

Ces résultats préliminaires indiquent qu'un dépôt significatif d'amyloïde peut être détecté de nombreuses années avant le temps estimé au diagnostic chez les porteurs. Ces

résultats sont cohérents avec l'hypothèse amyloïde de la MA et avec le fait que l'accumulation d'Aβ serait l'un des marqueurs les plus précoces, à tout le moins dans la forme familiale de la maladie (Selkoe & Hardy, 2016). De plus, dans la MAf, les mutations PSEN1 affectent la forme et la fonction de la protéine presenilin1, une des sous-unités du complexe γ-Secretase (Kimberly et al., 2003), une enzyme impliquée dans la protéolyse de la protéine précurseure à l'amyloïde en Aβ. Ceci entraîne donc une accumulation de ce peptide tout au long de la vie des porteurs de mutations. L'imagerie amyloïde PET-PIB permet de distinguer la MA d'autres types de démence, d'aider à déterminer si un TCL est bien dû à la MA et pourrait être utile dans la pratique clinique, particulièrement pour les individus avec des déficits légers ou une présentation atypique (Laforce & Rabinovici, 2011).

L'imagerie tau par le ligand [18F]MK6240 est une technique innovatrice qui permet de caractériser, in vivo, l'accumulation des enchevêtrements neurofibrillaires (Betthauser et al., 2019; Hostetler et al., 2016). La présence d'une pathologie tau significative était détectée plus près de l'âge estimé de conversion et était davantage associée aux déficits cognitifs. Ceci est compatible avec le fait que la présence de protéine tau anormalement phosphorylée et d'enchevêtrements neurofibrillaires est fortement corrélée et associée aux déficits cognitifs, ce qui n'est pas nécessairement le cas pour la présence de plaques amyloïde (Boutajangout & Wisniewski, 2014; Pedersen & Sigurdsson, 2015). Certains auteurs argumentent que le point de mire des essais cliniques devrait passer des thérapies ciblant l'amyloïde vers celles ciblant la pathologie tau (Giacobini & Gold, 2013). La prévalence combinée des tauopathies primaires et son importance dans la MA en font une cible de recherche prioritaire (Lebouvier, Pasquier, & Buee, 2017).

Dans les prochaines sections, les résultats des études qui constituent la thèse seront incorporés à la littérature existante dans une discussion intégrative. Seront ensuite présentées les limites de la thèse, pour enfin conclure avec les implications cliniques de ce travail et les perspectives futures.

## 2. Maladie d'Alzheimer sporadique
### Combinaison des marqueurs cognitifs et fonctionnels : un modèle intégratif

Le modèle issu de la figure 2 de l'article 3 est reproduit ici (figure 1) à titre illustratif, puisqu'il s'agit d'un travail intégratif combinant à la fois les résultats de l'étude 2 (trajectoires cognitives) et de l'étude 3 (trajectoires des capacités à réaliser les AVQi) pour le TCL, dans les années précédant un diagnostic clinique de démence. Comme le montre la figure, les marqueurs significatifs sont : la mémoire épisodique, la mémoire de travail, les fonctions exécutives et les AVQi complexes. Pour chacun de ces marqueurs, la figure indique la trajectoire (linéaire ou quadratique) et le moment où le marqueur devient un prédicteur significatif de progression. Lorsqu'un marqueur traverse la zone en gris, ceci indique qu'il est un prédicteur significatif de progression au T0 (p.ex. les déficits pour les fonctions exécutives sont un prédicteur de progression à partir de T-2).
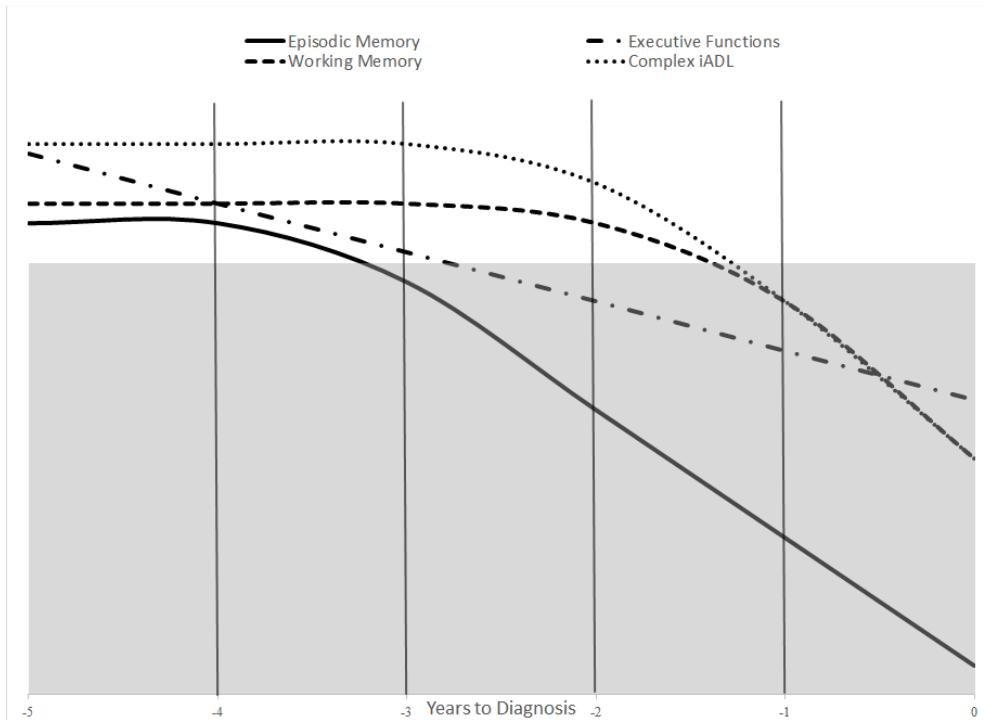
**Figure 1.** Modèle qui combine les trajectoires cognitives et fonctionnelles dans les années précédant un diagnostic clinique de démence, dans le trouble cognitif léger.

La combinaison des résultats des études 2 et 3 nous informe non seulement sur les marqueurs précoces de future progression vers un diagnostic clinique de démence, mais, de façon plus intéressante, sur la forme que prennent les trajectoires de déclin sur ces différents marqueurs. En effet, l'application de modèles statistiques complexes (régressions polynomiales) est un des points innovateurs des travaux de cette thèse. Au-delà de la vitesse de déclin, ces modèles nous permettent de caractériser de manière plus précise la manière dont ce déclin s'opère dans la phase prodromique qu'est le TCL, avec des évidences de plateaux suivis d'une accélération du déclin dans certains domaines. La caractérisation de ces trajectoires complexes est intéressante, non seulement car celles-ci représentent mieux la distribution des données et donc le phénomène observé, mais également, car elles pourraient rendre compte de différents mécanismes, comme la réserve (Barulli & Stern, 2013), la maintenance (Gorbach et al., 2017) et, particulièrement, la compensation (Bondi, Houston, Eyler, & Brown, 2005; Han et al., 2007).

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Ces mécanismes pourraient moduler l'effet de la pathologie sur le tableau clinique/cognitif et expliquer la forme des trajectoires observée.

Un autre aspect innovateur de ces études est le fait qu'il s'agisse d'une cohorte clinique d'individus avec un TCL, qui a permis de séparer les groupes selon qu'ils aient ou non progressé vers un diagnostic de démence. L'évaluation cognitive et fonctionnelle répétée d'une telle cohorte nous a permis de mettre en évidence les marqueurs précoces et les trajectoires associées aux individus qui étaient réellement dans un processus de progression éminente vers la démence (progresseurs). C'est donc l'investigation précise et longitudinale des changements cognitifs et fonctionnels qui offre davantage d'informations sur le pronostic et une meilleure précision diagnostique.

Les marqueurs principaux du modèle seront discutés brièvement dans les prochaines sections.

### 2.1. Mémoire épisodique

Les déficits en mémoire épisodique représentent le marqueur cognitif le plus précoce dans l'étude 2. Ce résultat n'est pas surprenant, étant donné qu'il s'agissait d'une cohorte d'individus avec un TCL amnésique donc, par définition, ils présentaient tous des déficits objectifs dans les tâches de mémoire lors du recrutement dans l'étude. Tel que rapporté dans l'introduction, la mémoire épisodique, qui est associée aux structures médianes des lobes temporaux, est typiquement le premier domaine atteint dans la MA (D. Salmon, 2000). On pouvait donc s'attendre à ce qu'il s'agisse également d'un marqueur précoce (Petersen, Stevens, et al., 2001) et d'un prédicteur significatif de conversion vers la démence (Belleville, Fouquet, et al., 2014; Peters et al., 2014) dans le TCL.

De façon plus intéressante, les résultats indiquent que, bien que présents, les déficits en mémoire épisodique peuvent demeurer relativement stables, même chez les progresseurs, avant de présenter un déclin accéléré dans les 3 années précédant le diagnostic de démence. Cette trajectoire quadratique (plateau suivi d'une chute rapide) est cohérente avec le modèle de déclin non linéaire pour la mémoire épisodique dans les phases précliniques de la MA, proposé par Twamley, Ropacki, and Bondi (2006), sur la base des résultats de quelques études (Backman, Small, & Fratiglioni, 2001; Bunce, Fratiglioni, Small, Winblad, & Backman, 2004; Chen et al., 2001; Lange et al., 2002). Une longue période de stabilité (plateau) pourrait refléter des mécanismes de compensation (Bondi, Houston, Eyler, & Brown, 2005; Bookheimer et al., 2000; Clement & Belleville, 2010, 2012; Dickerson et al., 2005) et le temps du diagnostic correspondrait à un « échec de compensation » face à des dommages cérébraux trop importants (accumulation d'Aβ et de protéine tau anormalement phosphorylée, mort neuronale et synaptique) (Clement & Belleville, 2010, 2012). En d'autres termes, les individus dans les phases précliniques de la maladie pourraient être en mesure de compenser en faisant appel à des ressources/régions alternatives. Toutefois, avec la progression de la maladie, ces ressources alternatives deviennent elles-mêmes compromises et s'ensuit un déclin cognitif accéléré. Les concepts de réserve et de compensation, qui peuvent expliquer en partie les trajectoires complexes de déclin cognitif, seront abordés et discutés dans la section sur les perspectives futures.

## 2.2. Mémoire de travail et fonctions exécutives

La performance en mémoire de travail/vitesse de traitement de l'information suit une trajectoire similaire à celle observée pour la mémoire épisodique, c'est-à-dire une période de stabilité, suivie d'un déclin accéléré. Même si ce déclin (1-2 ans avant l'année de conversion)

survient un peu plus tardivement que celui pour la mémoire épisodique (3-4 ans avant l'année de conversion), la performance dans ce domaine est significativement plus faible chez les progresseurs que les non-progresseurs plusieurs années avant le temps de conversion, indiquant qu'il s'agit d'un marqueur précoce de progression (Kirova, Bays, & Lagalwar, 2015; Saunders & Summers, 2010; Tabert et al., 2006). De plus, considérant la trajectoire quadratique, il est possible qu'il s'agisse, comme pour la mémoire épisodique, d'un domaine cognitif modulé par les mécanismes de réserve et de compensation mentionnés dans la section précédente.

Les fonctions exécutives déclinent de façon graduelle et progressive, mais des déficits dans ce domaine peuvent être détectés précocement dans la progression du TCL à la démence. Ceci est compatible avec des évidences que les déficits par rapport au fonctionnement exécutif seraient, après les déficits en mémoire épisodique, parmi les plus précoces dans la MA (Lefleche & Albert, 1995; Perry & Hodges, 1999; D. P. Salmon & Bondi, 2009) et dans le TCL (Brandt et al., 2009; Clement et al., 2013; Johns et al., 2012; Rainville et al., 2012; Traykov et al., 2007). Parmi les fonctions exécutives, l'inhibition semble être un marqueur plus sensible et des déficits significatifs dans ce domaine sont rapportés dans le TCL (Belanger & Belleville, 2009; Belanger et al., 2010; Johns et al., 2012). Ceci appuie l'importance de bien considérer le choix des outils et des tests cognitifs, particulièrement si ces tests sont regroupés en score composite, puisque l'inclusion d'outils non sensibles pourrait réduire la puissance à détecter des changements subtils qui s'opèrent dans les phases précliniques de la démence (Belleville, Fouquet, et al., 2014; Belleville et al., 2017).

### 2.3. Activités de la vie quotidienne

Les résultats de l'étude 3 indiquent qu'une catégorie d'AVQi, les AVQi complexes, suivent une trajectoire de stabilité, suivie d'un déclin accéléré juste avant le diagnostic clinique

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de démence. Des déficits à réaliser des AVQi faisant partie de cette catégorie avaient été rapportés comme étant des marqueurs précoces de la MA (Barberger-Gateau et al., 1992; Barberger-Gateau et al., 1993; Barberger-Gateau, Fabrigoule, Helmer, et al., 1999; Barberger-Gateau, Fabrigoule, Rouch, Letenneur, & Dartigues, 1999). L'analyse par composante principale semble donc avoir identifié une distinction cliniquement et empiriquement valide par rapport aux AVQi. L'étude des trajectoires de déclin par rapport à cette catégorie spécifique d'AVQi dans le TCL telle que réalisée dans l'étude 3 nous apparaît donc pertinente, puisqu'il s'agit sans doute d'un domaine plus sensible par rapport à la progression vers un diagnostic de démence.

Comme le montre le modèle (figure 1), les déficits exécutifs précèdent le déclin dans les capacités à réaliser les AVQi complexes. Ces résultats confortent la relation proposée par plusieurs auteurs entre le fonctionnement exécutif et les habiletés à réaliser les AVQ, dans le continuum du TCL à la démence (Bell-McGinty, Podell, Franzen, Baird, & Williams, 2002; Marshall et al., 2011; Tomaszewski Farias et al., 2009; L. Vaughan & Giovanello, 2010), particulièrement si ces activités sont complexes et requièrent des fonctions cognitives de haut niveau (Jekel et al., 2015).

La mémoire de travail/vitesse de traitement de l'information présente une trajectoire avec un déclin accéléré dans l'année précédant l'entrée dans la démence, de façon concomitante au déclin accéléré par rapport aux capacités à réaliser les AVQ complexes. Ceci est compatible avec le fait qu'il s'agirait d'un domaine cognitif associé à l'impact fonctionnel au quotidien dans le TCL (Aretouli & Brandt, 2010; Brandt et al., 2009). Les résultats de l'étude 3 apportent donc un support au fait que le TCL pourrait être associé à des changements fonctionnels et à l'importance d'intégrer leur évaluation lors du suivi. Des déficits à réaliser des AVQ complexes

ayant une « charge cognitive élevée », pourraient même précéder le TCL (Reppermund et al., 2013) et constituent donc des marqueurs précoces de la MA, que l'on peut détecter plusieurs années avant le diagnostic (Peres et al., 2008).

### 2.4. Prédiction

Au-delà de la forme des trajectoires, le modèle illustré à la figure 1 offre des informations par rapport aux prédicteurs significatifs de progression vers la démence. Les participants de la cohorte étant catégorisés comme ayant un TCL amnésique, ils présentaient tous une performance plus faible de ce qui serait attendu pour l'âge et le niveau d'éducation en mémoire épisodique lors de l'entrée dans l'étude. Toutefois, une performance significativement plus déficitaire lors du rappel différé en mémoire est un prédicteur significatif jusqu'à trois ans précédant l'année de conversion. Ces déficits en mémoire sont accompagnés de déficits pour les fonctions exécutives, qui sont un prédicteur de progression future deux ans précédant le diagnostic clinique de la MA. Enfin, l'année juste avant celle de conversion vers la démence, la performance pour la mémoire de travail/vitesse de traitement de l'information et les habiletés autorapportées à réaliser des AVQi complexes s'ajoutent à ces déficits mnésiques et exécutifs en tant que prédicteurs significatifs de conversion. Bref, en combinant les prédicteurs fonctionnels de progression future vers une démence aux prédicteurs cognitifs, nous obtenons un modèle avec une excellente précision diagnostique, une à deux années précédant la conversion vers la MA.

En somme, l'ensemble de ces résultats nous offre un portrait clair et cohérent par rapport à l'histoire naturelle de progression dans le TCL : un déficit en mémoire épisodique est présent très tôt et reste stable longtemps avant de décliner rapidement 3 à 4 avant le diagnostic de démence. Il est suivi par → une atteinte du fonctionnement exécutif, qui a progressé

graduellement jusqu'à devenir déficitaire proche du diagnostic de démence, puis par → un déclin significatif en mémoire de travail/vitesse de traitement de l'information, qui accompagne un déclin sur les capacités à réaliser des AVQi complexes l'année précédant le moment où les individus rencontrent les critères diagnostiques cliniques pour la démence.

## 3. Maladie d'Alzheimer de type familial

### 3.1. Comparaison des trajectoires observées dans le type familial et le type sporadique

L'objectif des études 2 et 5 était semblable: caractériser les trajectoires de déclin cognitif dans les phases précliniques et précoces de la MA, par l'étude du TCL dans la MA sporadique pour l'étude 2 et par l'étude du phénotype cognitif d'individus porteurs de mutations autosomiques dominantes dans la MAf pour l'étude 5. L'emploi d'une batterie cognitive similaire et de modèles mixtes/régressions polynomiales dans les deux études a permis d'identifier des trajectoires complexes selon le domaine cognitif et de comparer ces trajectoires dans les deux formes de la MA. Le tableau 1 présente un résumé comparatif des trajectoires observées dans l'étude 2 et celles relevées dans l'étude 5.

**Tableau 1.** Comparaison des trajectoires significatives dans le type sporadique (étude 2) et le type familial (étude 5).

| Trajectoire | Type sporadique (étude 2) | Type familial (étude 5) |
|---|---|---|
| Quadratique (stabilité suivie d'un déclin accéléré) | Rappel différé en mémoire | Rappel différé en mémoire |
| | Mémoire de travail/Vitesse de traitement de l'information | Reconnaissance en mémoire |
| Linéaire (déclin graduel) | Rappel immédiat en mémoire | Rappel immédiat en mémoire |
| | Fonctions exécutives (inhibition) | Fonctions exécutives (fluence verbale) |

| | Habiletés visuospatiales | Habiletés visuospatiales |
|---|---|---|
| | | |

Comme le montre le tableau, malgré une méthodologie différente et des cohortes de participants distinctes, on relève un patron très similaire par rapport aux trajectoires de changements cognitifs entre les 2 études. Le rappel différé en mémoire épisodique suit une trajectoire quadratique, alors que le rappel immédiat en mémoire, les fonctions exécutives et les habiletés visuospatiales/visuo-contructives ont présenté une trajectoire linéaire, donc plus graduelle et progressive. Cette grande similitude indique que ces domaines cognitifs et leur trajectoire à travers le temps sont des marqueurs sensibles et spécifiques de la MA. Ceci apporte également un support au fait que les résultats issus de l'étude de la forme génétique autosomique dominante de la MA pourraient être transférables à notre compréhension de la forme sporadique, beaucoup plus commune (Bateman et al., 2011; Dubois et al., 2016). Ceci est encourageant, puisque l'étude de la forme familiale offre un avantage majeur pour détecter des marqueurs très précoces de la maladie : il est possible d'identifier, parmi des individus asymptomatiques, ceux qui progresseront vers un diagnostic clinique de démence et l'âge de conversion estimé. L'étude des phases précliniques dans le type familial nous permettra donc d'identifier les marqueurs précoces, que ce soient les biomarqueurs ou le profil de déficits cognitifs subtils, et de vérifier la valeur diagnostique prédictive de la présence de tels marqueurs chez des individus asymptomatiques dans le type sporadique.

## 4. Limites de ce travail

Cette thèse comporte certaines limites qu'il est important de mentionner. Tout d'abord, concernant les études d'histoire naturelle du TCL dans la MA sporadique (études 2 et 3), nous n'avions pas de groupe contrôle de personnes âgées saines pour comparer les trajectoires de

déclin dans les différents domaines cognitifs à travers le temps. Par conséquent, il n'est pas possible de savoir si les non-progresseurs, au-delà des déficits en mémoire, présentaient un profil cognitif distinct de personnes âgées dans un processus de vieillissement normal. Toutefois, il faut rappeler que l'objectif de ces études était de bien caractériser les trajectoires de déclin d'une cohorte clinique (TCL). Le devis longitudinal rétrospectif est une force, puisqu'il permet d'identifier les individus qui étaient effectivement dans un processus de déclin vers un diagnostic clinique de démence et de comparer ces individus à ceux qui sont demeurés stables sur leur cognition. Cependant, cette approche est accompagnée de défis méthodologiques. Pour les non-progresseurs, le dernier point de données correspond à la dernière évaluation dans l'étude. Ce point dans le temps varie d'un participant à l'autre, selon le moment d'entrée dans l'étude. Étant donné que le temps entre cette entrée dans l'étude et l'année du diagnostic (ou le dernier point de données) varie entre les participants, le nombre de participants inclus dans les analyses diminue plus le temps au diagnostic augmente.

Concernant ces études, nous n'avions pas d'informations par rapport aux biomarqueurs chez les participants. Or, selon les critères plus récents du TCL (Albert et al., 2011) et la définition biologique de la MA (Jack et al., 2018), la présence de biomarqueurs, confirmés par imagerie ou autres techniques, comme une analyse des marqueurs du liquide céphalo-rachidien, est nécessaire pour confirmer l'étiologie des symptômes, ou du moins recommandée pour les critères d'inclusion en recherche.

Ensuite, concernant les études portant sur une cohorte d'individus avec mutations associées à la MAf (études 5 et 6), le nombre de participants était relativement petit, ce qui a pu avoir un impact sur la puissance statistique lors des analyses. Considérant la rareté de cette forme de la maladie, il s'agissait tout de même d'un nombre significatif de participants ayant un

bilan neuropsychologique complet. Les groupes des porteurs de mutations et de non-porteurs étaient équivalents sur l'ensemble des données démographiques, ce qui a permis la comparaison des trajectoires du temps estimé au diagnostic, selon le statut génétique. Ces études ont permis de caractériser des familles canadiennes avec des mutations PSEN1, qui n'étaient pas représentées dans la littérature.

Toujours par rapport à ces études, une bonne partie des participants étaient symptomatiques ou près du temps estimé au diagnostic, ce qui limite la capacité à étudier les trajectoires de changements subtils dans la phase silencieuse de la MA. Ces difficultés à recruter des personnes asymptomatiques pourraient refléter des facteurs humains : il est possible que les jeunes individus issus de familles avec un historique de démence précoce soient appréhensifs à participer à des projets de recherche les confrontant à la possibilité qu'ils soient porteurs de mutations causatives pour la MA. Il pourrait également s'agir d'un sujet de conversation difficile pour les parents porteurs symptomatiques faisant partie des études à aborder auprès de leurs enfants pour les encourager à participer aux projets de recherche. Il s'agit donc de facteurs à considérer dans les études portant sur des maladies génétiques, particulièrement à transmission autosomique dominante et l'inclusion d'une expertise en conseil génétique est essentielle. Il faut noter néanmoins que, malgré ces difficultés concernant le recrutement et un petit échantillon, les résultats par rapport aux trajectoires cognitives sont très cohérents avec ceux observés dans une cohorte avec un nombre de participants plus significatif, soit la cohorte d'individus avec TCL dans le type sporadique (étude 2).

Enfin, il importe de souligner que plusieurs facteurs peuvent contribuer aux déficits cognitifs et n'ont pas pu être pris en compte, comme les facteurs de risque vasculaire, les symptômes anxiodépressifs, les problèmes de sommeil et la réserve cognitive. Il serait important

dans de futures études de les inclure comme variables modératrices des trajectoires de déclin.

De plus, d'autres pathologies souvent associées à la MA, comme la pathologie à corps de Lewy, les lésions de la matière blanche et la neuroinflammation n'ont pas été examinées dans le cadre des travaux de cette thèse. Toutefois, il faut rappeler que l'objectif principal était d'identifier les marqueurs neuropsychologiques précoces de la MA, en étudiant les différentes trajectoires cognitives dans les années précédant le diagnostic clinique de la maladie.

## 5. Implications cliniques de ce travail et perspectives futures

Les travaux de cette thèse ont permis d'identifier des marqueurs neuropsychologiques précoces de future progression vers la démence. Une investigation incorporant les marqueurs du liquide céphalo-rachidien et/ou l'imagerie cérébrale permet d'atteindre une meilleure précision diagnostique (Hansson et al., 2018; Olsson et al., 2016; Palmqvist et al., 2015; Vlassenko et al., 2016). Toutefois, il s'agit de techniques coûteuses. Les résultats des études comprises dans la thèse ont démontré que l'évaluation répétée utilisant des outils simples (tâches cognitives et questionnaire sur les capacités à réaliser des AVQ) permet de distinguer, parmi les individus à risque, ceux qui progresseront effectivement vers un diagnostic clinique de démence. L'aspect longitudinal est important. En effet, tous les individus avec un TCL amnésique présentent des déficits objectifs en mémoire. Toutefois, une proportion de ces individus peut demeurer stable de nombreuses années, comme c'est le cas pour la cohorte faisant partie des études d'histoire naturelle de cette thèse, ou encore peut revenir à une performance cognitive normale ou presque normale (Canevelli et al., 2016). C'est la comparaison d'une année à l'autre qui permet de déterminer le risque accru de progression. Un déclin significatif sur la performance en mémoire, accompagné de déficits exécutifs et touchant la mémoire de

travail/vitesse de traitement de l'information peut prédire l'apparition d'un impact fonctionnel au quotidien et la progression vers un diagnostic clinique de démence dans les années suivantes. Même s'il n'existe pas actuellement de médication permettant d'arrêter la progression de la maladie, il s'agit quand même d'informations importantes pour les cliniciens, afin de guider l'appui qui peut être offert aux patients et aux membres de leur famille.

De plus, dans l'éventualité qu'un traitement efficace pour arrêter la progression de la MA soit découvert, les résultats de cette thèse joignent ceux de l'ensemble des études ayant pour objectifs d'identifier des marqueurs précoces, qui permettent de distinguer les individus à risque de progression, et ce, avant qu'ils manifestent les symptômes cliniques de la maladie, moment qui pourrait être trop tard pour l'administration d'un tel traitement.

Dans la MA sporadique, contrairement à la MA autosomique dominante, il n'existe pas de test ayant une prédiction parfaite d'un diagnostic clinique futur de démence chez des individus asymptomatiques. Le TCL étant une phase clinique intermédiaire entre les changements cognitifs observés dans le vieillissement normal et les déficits relevés dans les premiers stades de la démence (Petersen, 2009), l'étude des marqueurs neuropsychologiques et biomarqueurs dans cette phase prodromique, et leurs trajectoires de changements à travers le temps, a constitué une approche valide pour caractériser les phases précoces de la MA. Toutefois, même le TCL pourrait être considéré comme étant tardif dans le continuum de la maladie, puisque des déficits cognitifs objectifs sont présents. Le concept de trouble subjectif de la cognition a été proposé comme étant une phase encore plus précoce, qui pourrait constituer une des premières manifestations symptomatiques de la MA (Jessen, Amariglio, et al., 2014).

Le trouble subjectif de la cognition est défini par une impression subjective d'un déclin cognitif, mais qui n'est pas encore détectable par des tests neuropsychologiques, c'est-à-dire

que la performance aux tâches se trouve dans les normes pour l'âge et le niveau d'éducation (Molinuevo et al., 2017). Plusieurs études semblent montrer que les individus avec un trouble subjectif de la cognition sont plus à risque de progresser vers un TCL ou une démence (Buckley et al., 2016; Mitchell, Beaumont, Ferguson, Yadegarfar, & Stubbs, 2014; Snitz et al., 2018), particulièrement ceux chez qui cette impression de déclin les inquiète (Jessen, Wolfsgruber, et al., 2014). Davantage de plaintes cognitives subjectives seraient associées à des taux de déclin plus rapide en mémoire verbale (Hohman, Beason-Held, Lamar, & Resnick, 2011) et la combinaison des critères du trouble subjectif de la cognition et de la présence de biomarqueurs pathophysiologiques de la MA, comme les marqueurs amyloïde et tau du liquide céphalo-rachidien, prédirait un déclin significatif dans les domaines comme la mémoire et les fonctions exécutives (van Harten et al., 2013).

Toutefois, le décours temporel des changements cognitifs dans le trouble subjectif de la cognition est peu connu. Il serait intéressant d'appliquer la méthodologie et les statistiques utilisées dans le cadre des travaux de cette thèse lors d'une étude longitudinale d'une cohorte de personnes avec un trouble subjectif de la cognition. Il est possible que des changements cognitifs subtils s'opèrent dans cette phase et que ceux-ci suivent une trajectoire complexe, avec la présence de plateaux et d'accélération du déclin. De façon intéressante, des études ont montré que le trouble subjectif de la cognition était précédé par un déclin en mémoire épisodique verbale (Koppara et al., 2015) et en mémoire de travail/vitesse de traitement de l'information (Reisberg, Shulman, Torossian, Leng, & Zhu, 2010). Comme il s'agit des domaines cognitifs ayant présenté des trajectoires plus complexes avec une accélération précédant le diagnostic de démence dans l'étude 2 de la thèse, ceci apporte un support supplémentaire au fait que des

changements dans ces domaines cognitifs constituent des marqueurs neuropsychologiques très précoces dans la MA.

Il serait également intéressant de moduler les modèles/trajectoires par différents facteurs témoignant de différences individuelles. Des facteurs proxy de réserve, comme l'éducation, la participation à des activités au cours de la vie, un travail cognitivement stimulant, etc., pourraient moduler les trajectoires, soit en termes de vitesse (déclin plus ou moins rapide) ou en termes de forme (graduelle ou présence de plateau et de phase d'accélération du déclin). La réserve est un concept heuristique pour expliquer les différences individuelles face aux changements dans le vieillissement normal ou en présence de maladies, comme les maladies neurodégénératives (Y. Stern et al., 2018). Il s'agit d'une amélioration cumulative, due à des facteurs génétiques, environnementaux ou de ressources neuronales, qui atténue les effets du déclin cognitif normal ou pathologique (Cabeza et al., 2018). La réserve fait partie, avec la maintenance et la compensation, des mécanismes interactifs pouvant médier en partie le lien entre les interactions gènes-environnement (épigénétique) et les différences individuelles observées par rapport au vieillissement cognitif (Cabeza et al., 2018). Il sera important de considérer les facteurs de vie et les différences interindividuelles pouvant influencer les trajectoires de déclin dans la démence, non seulement pour mieux comprendre le décours de la maladie, mais aussi pour adapter les interventions, comme les entraînements cognitifs (Simon, Yokomizo, & Bottino, 2012). Dans le TCL par exemple, des études d'imagerie ont montré des évidences de neuroplasticité suivant de tels entraînements, mais que la réponse aux interventions dépendrait non seulement du degré de sévérité de la maladie, mais aussi des modalités des interventions et de facteurs personnels, comme le niveau de réserve cognitive (Belleville, Boller, & Prieto del Val, 2016).

Par ailleurs, la réserve et les autres facteurs environnementaux peuvent avoir une influence sur l'âge d'apparition des symptômes, même dans des maladies génétiques autosomiques dominantes, comme dans la MAf (Mejia, Giraldo, Pineda, Ardila, & Lopera, 2003). Dans l'étude 5, nous avons rapporté que la mutation F175L (PSEN1) présentait une grande variabilité dans les familles par rapport à l'âge de conversion vers la démence. Comme c'est le cas pour d'autres mutations (Thordardottir et al., 2018), la pénétrance réduite ou l'hétérogénéité de l'âge du diagnostic clinique pourrait être dus à d'autres facteurs génétiques (des mutations non identifiées), à des facteurs épigénétiques (i.e. des modifications de l'expression génétique (Liu, Jiao, & Shen, 2018), p.ex. méthylation de l'ADN (Qazi, Quan, Mir, & Qing, 2018), acétylation/désacétylation des histones (Esposito & Sherr, 2019), etc ) et à des facteurs environnementaux, dans lesquels s'inscrivent les facteurs proxy de réserve. Une étude récente appliquant des modèles similaires à ceux utilisés dans les travaux de cette thèse (modèles mixtes et régressions polynomiales) a trouvé une interaction significative entre la connectivité d'un centre dans le cortex frontal gauche (corrélée à l'éducation, un facteur proxy de réserve) et le temps estimé au diagnostic dans la MAf (Franzmeier et al., 2018). À un niveau de connectivité plus élevé, la pente du temps estimé au diagnostic était plus petite pour la cognition globale et la mémoire, montrant un « déclin » ralenti. Ces résultats indiquent que l'environnement peut avoir un impact, même dans des maladies génétiques dont le pronostic est certain et que les interventions visant à modifier les facteurs de vie pourraient être bénéfiques chez cette population (le diagnostic clinique est presque certain, mais l'âge de ce diagnostic et la vitesse du déclin pourraient varier).

En somme, il serait intéressant dans des études futures de combiner les domaines de recherche sur les facteurs de réserve/compensation, les facteurs épigénétiques, les biomarqueurs

et les analyses longitudinales complexes permettant de caractériser les trajectoires de changements cognitifs et fonctionnels dans la MA, non pas de manière indépendante, mais dans un modèle intégratif et interactif.

# Références

Abner, E. L., Kryscio, R. J., Cooper, G. E., Fardo, D. W., Jicha, G. A., Mendiondo, M. S., . . . Schmitt, F. A. (2012). Mild cognitive impairment: statistical models of transition using longitudinal clinical data. *Int J Alzheimers Dis, 2012*, 291920. doi:10.1155/2012/291920

Ahmed, S., Mitchell, J., Arnold, R., Nestor, P. J., & Hodges, J. R. (2008). Predicting rapid clinical progression in amnestic mild cognitive impairment. *Dement Geriatr Cogn Disord, 25*(2), 170-177. doi:10.1159/000113014

Ahn, I. S., Kim, J. H., Kim, S., Chung, J. W., Kim, H., Kang, H. S., & Kim, D. K. (2009). Impairment of instrumental activities of daily living in patients with mild cognitive impairment. *Psychiatry Investig, 6*(3), 180-184. doi:10.4306/pi.2009.6.3.180

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., . . . Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 270-279. doi:10.1016/j.jalz.2011.03.008

American Psychiatric Association., & American Psychiatric Association. DSM-5 Task Force. (2013). *Diagnostic and statistical manual of mental disorders : DSM-5* (5th ed.). Arlington, Va.: American Psychiatric Association.

American Psychiatric Association., & American Psychiatric Association. Task Force on DSM-IV. (2000). *Diagnostic and statistical manual of mental disorders : DSM-IV-TR* (4th ed.). Washington, DC: American Psychiatric Association.

Amieva, H., Jacqmin-Gadda, H., Orgogozo, J. M., Le Carret, N., Helmer, C., Letenneur, L., . . . Dartigues, J. F. (2005). The 9 year cognitive decline before dementia of the Alzheimer type: a prospective population-based study. *Brain, 128*(Pt 5), 1093-1101. doi:10.1093/brain/awh451

Ardila, A., Lopera, F., Rosselli, M., Moreno, S., Madrigal, L., Arango-Lasprilla, J. C., . . . Kosik, K. S. (2000). Neuropsychological profile of a large kindred with familial Alzheimer's disease caused by the E280A single presenilin-1 mutation. *Arch Clin Neuropsychol, 15*(6), 515-528.

Aretouli, E., & Brandt, J. (2010). Everyday functioning in mild cognitive impairment and its relationship with executive cognition. *Int J Geriatr Psychiatry, 25*(3), 224-233. doi:10.1002/gps.2325

Backman, L., Small, B. J., & Fratiglioni, L. (2001). Stability of the preclinical episodic memory deficit in Alzheimer's disease. *Brain, 124*(Pt 1), 96-102.

Ballard, C., Gauthier, S., Corbett, A., Brayne, C., Aarsland, D., & Jones, E. (2011). Alzheimer's disease. *Lancet, 377*(9770), 1019-1031. doi:10.1016/S0140-6736(10)61349-9

Barberger-Gateau, P., Commenges, D., Gagnon, M., Letenneur, L., Sauvel, C., & Dartigues, J. F. (1992). Instrumental activities of daily living as a screening tool for cognitive impairment and dementia in elderly community dwellers. *J Am Geriatr Soc, 40*(11), 1129-1134.

Barberger-Gateau, P., Dartigues, J. F., & Letenneur, L. (1993). Four Instrumental Activities of Daily Living Score as a predictor of one-year incident dementia. *Age Ageing, 22*(6), 457-463.

Barberger-Gateau, P., Fabrigoule, C., Helmer, C., Rouch, I., & Dartigues, J. F. (1999). Functional impairment in instrumental activities of daily living: an early clinical sign of dementia? *J Am Geriatr Soc, 47*(4), 456-462.

Barberger-Gateau, P., Fabrigoule, C., Rouch, I., Letenneur, L., & Dartigues, J. F. (1999). Neuropsychological correlates of self-reported performance in instrumental activities of daily living and prediction of dementia. *J Gerontol B Psychol Sci Soc Sci, 54*(5), P293-303.

Bateman, R. J., Aisen, P. S., De Strooper, B., Fox, N. C., Lemere, C. A., Ringman, J. M., . . . Xiong, C. (2011). Autosomal-dominant Alzheimer's disease: a review and proposal for the prevention of Alzheimer's disease. *Alzheimers Res Ther, 3*(1), 1. doi:10.1186/alzrt59

Bateman, R. J., Xiong, C., Benzinger, T. L., Fagan, A. M., Goate, A., Fox, N. C., . . . Dominantly Inherited Alzheimer, N. (2012). Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med, 367*(9), 795-804. doi:10.1056/NEJMoa1202753

Bekris, L. M., Yu, C. E., Bird, T. D., & Tsuang, D. W. (2010). Genetics of Alzheimer disease. *J Geriatr Psychiatry Neurol, 23*(4), 213-227. doi:10.1177/0891988710383571

Belanger, S., & Belleville, S. (2009). Semantic inhibition impairment in mild cognitive impairment: a distinctive feature of upcoming cognitive decline? *Neuropsychology, 23*(5), 592-606. doi:10.1037/a0016152

Belanger, S., Belleville, S., & Gauthier, S. (2010). Inhibition impairments in Alzheimer's disease, mild cognitive impairment and healthy aging: effect of congruency proportion in a Stroop task. *Neuropsychologia, 48*(2), 581-590. doi:10.1016/j.neuropsychologia.2009.10.021

Bell-McGinty, S., Podell, K., Franzen, M., Baird, A. D., & Williams, M. J. (2002). Standard measures of executive function in predicting instrumental activities of daily living in older adults. *Int J Geriatr Psychiatry, 17*(9), 828-834. doi:10.1002/gps.646

Belleville, S., Boller, B., & Prieto del Val, L. (2016). Cognitive Training in Mild Cognitive Impairment. In T. Strobach & J. Karbach (Eds.), *Cognitive Training: An overview of Features and Applications* (pp. 187-197). Switzerland: Springer.

Belleville, S., Chertkow, H., & Gauthier, S. (2007). Working memory and control of attention in persons with Alzheimer's disease and mild cognitive impairment. *Neuropsychology, 21*(4), 458-469. doi:10.1037/0894-4105.21.4.458

Belleville, S., Fouquet, C., Duchesne, S., Collins, D. L., & Hudon, C. (2014). Detecting Early Preclinical Alzheimer's Disease via Cognition, Neuropsychiatry, and Neuroimaging: Qualitative Review and Recommendations for Testing. *J Alzheimers Dis, 42*(0), S375-382. doi:10.3233/JAD-141470

Belleville, S., Fouquet, C., Hudon, C., Zomahoun, H. T. V., Croteau, J., & Consortium for the Early Identification of Alzheimer's, d.-Q. (2017). Neuropsychological Measures that Predict Progression from Mild Cognitive Impairment to Alzheimer's type dementia in Older Adults: a Systematic Review and Meta-Analysis. *Neuropsychol Rev, 27*(4), 328-353. doi:10.1007/s11065-017-9361-5

Belleville, S., Gauthier, S., Lepage, E., Kergoat, M. J., & Gilbert, B. (2014). Predicting decline in mild cognitive impairment: a prospective cognitive study. *Neuropsychology, 28*(4), 643-652. doi:10.1037/neu0000063

Bennett, D. A., Wilson, R. S., Schneider, J. A., Evans, D. A., Beckett, L. A., Aggarwal, N. T., . . . Bach, J. (2002). Natural history of mild cognitive impairment in older persons. *Neurology, 59*(2), 198-205. doi:10.1212/wnl.59.2.198

Bettens, K., Sleegers, K., & Van Broeckhoven, C. (2013). Genetic insights in Alzheimer's disease. *Lancet Neurol, 12*(1), 92-104. doi:10.1016/S1474-4422(12)70259-4

Betthauser, T. J., Cody, K. A., Zammit, M. D., Murali, D., Converse, A. K., Barnhart, T. E., . . . Christian, B. T. (2019). In Vivo Characterization and Quantification of Neurofibrillary Tau PET Radioligand (18)F-MK-6240 in Humans from Alzheimer Disease Dementia to Young Controls. *J Nucl Med, 60*(1), 93-99. doi:10.2967/jnumed.118.209650

Beyreuther, K., & Masters, C. L. (1991). Amyloid precursor protein (APP) and beta A4 amyloid in the etiology of Alzheimer's disease: precursor-product relationships in the derangement of neuronal function. *Brain Pathol, 1*(4), 241-251.

Biomarkers Definitions Working, G. (2001). Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther, 69*(3), 89-95. doi:10.1067/mcp.2001.113989

Bird, T. D. (2012). Early-Onset Familial Alzheimer Disease. In R. A. Pagon, M. P. Adam, H. H. Ardinger, T. D. Bird, C. R. Dolan, C. T. Fong, R. J. H. Smith, & K. Stephens (Eds.), *GeneReviews(R)*. Seattle (WA).

Blennow, K., Hampel, H., & Zetterberg, H. (2014). Biomarkers in amyloid-beta immunotherapy trials in Alzheimer's disease. *Neuropsychopharmacology, 39*(1), 189-201. doi:10.1038/npp.2013.154

Blennow, K., Mattsson, N., Scholl, M., Hansson, O., & Zetterberg, H. (2015). Amyloid biomarkers in Alzheimer's disease. *Trends Pharmacol Sci, 36*(5), 297-309. doi:10.1016/j.tips.2015.03.002

Bondi, M. W., Houston, W. S., Eyler, L. T., & Brown, G. G. (2005). fMRI evidence of compensatory mechanisms in older adults at genetic risk for Alzheimer disease. *Neurology, 64*(3), 501-508. doi:10.1212/01.WNL.0000150885.00929.7E

Bookheimer, S. Y., Strojwas, M. H., Cohen, M. S., Saunders, A. M., Pericak-Vance, M. A., Mazziotta, J. C., & Small, G. W. (2000). Patterns of brain activation in people at risk for Alzheimer's disease. *N Engl J Med, 343*(7), 450-456. doi:10.1056/NEJM200008173430701

Boutajangout, A., & Wisniewski, T. (2014). Tau-based therapeutic approaches for Alzheimer's disease - a mini-review. *Gerontology, 60*(5), 381-385. doi:10.1159/000358875

Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol, 82*(4), 239-259.

Brandt, J., Aretouli, E., Neijstrom, E., Samek, J., Manning, K., Albert, M. S., & Bandeen-Roche, K. (2009). Selectivity of executive function deficits in mild cognitive impairment. *Neuropsychology, 23*(5), 607-618. doi:10.1037/a0015851

Buckley, R. F., Maruff, P., Ames, D., Bourgeat, P., Martins, R. N., Masters, C. L., . . . study, A. (2016). Subjective memory decline predicts greater rates of clinical progression in preclinical Alzheimer's disease. *Alzheimers Dement, 12*(7), 796-804. doi:10.1016/j.jalz.2015.12.013

Bunce, D., Fratiglioni, L., Small, B. J., Winblad, B., & Backman, L. (2004). APOE and cognitive decline in preclinical Alzheimer disease and non-demented aging. *Neurology, 63*(5), 816-821. doi:10.1212/01.wnl.0000137041.86153.42

Barulli, D., & Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. *Trends Cogn Sci, 17*(10), 502-509. doi:10.1016/j.tics.2013.08.012

Burns, A., Jacoby, R., & Levy, R. (1991). Progression of cognitive impairment in Alzheimer's disease. *J Am Geriatr Soc, 39*(1), 39-45.

Busse, A., Hensel, A., Guhne, U., Angermeyer, M. C., & Riedel-Heller, S. G. (2006). Mild cognitive impairment: long-term course of four clinical subtypes. *Neurology, 67*(12), 2176-2185. doi:10.1212/01.wnl.0000249117.23318.e1

Cabeza, R., Albert, M., Belleville, S., Craik, F. I. M., Duarte, A., Grady, C. L., . . . Rajah, M. N. (2018). Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. *Nat Rev Neurosci, 19*(11), 701-710. doi:10.1038/s41583-018-0068-2

Cahn-Weiner, D. A., Boyle, P. A., & Malloy, P. F. (2002). Tests of executive function predict instrumental activities of daily living in community-dwelling older individuals. *Appl Neuropsychol, 9*(3), 187-191. doi:10.1207/S15324826AN0903_8

Campion, D., Dumanchin, C., Hannequin, D., Dubois, B., Belliard, S., Puel, M., . . . Frebourg, T. (1999). Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum. *Am J Hum Genet, 65*(3), 664-670. doi:10.1086/302553

Canevelli, M., Grande, G., Lacorte, E., Quarchioni, E., Cesari, M., Mariani, C., . . . Vanacore, N. (2016). Spontaneous Reversion of Mild Cognitive Impairment to Normal Cognition: A Systematic Review of Literature and Meta-Analysis. *J Am Med Dir Assoc, 17*(10), 943-948. doi:10.1016/j.jamda.2016.06.020

Cavedo, E., Lista, S., Khachaturian, Z., Aisen, P., Amouyel, P., Herholz, K., . . . Hampel, H. (2014). The Road Ahead to Cure Alzheimer's Disease: Developmentof Biological Markers and Neuroimaging Methods for Prevention Trials Across all Stages and Target Populations. *The Journal of Prevention of Alzheimer's Disease, 1*(3), 181-202.

Chan, A., Salmon, D., Nordin, S., Murphy, C., & Razani, J. (1998). Abnormality of semantic network in patients with Alzheimer's disease. Evidence from verbal, perceptual, and olfactory domains. *Ann N Y Acad Sci, 855*, 681-685. doi:10.1111/j.1749-6632.1998.tb10645.x

Chen, P., Ratcliff, G., Belle, S. H., Cauley, J. A., DeKosky, S. T., & Ganguli, M. (2001). Patterns of cognitive decline in presymptomatic Alzheimer disease: a prospective community study. *Arch Gen Psychiatry, 58*(9), 853-858. doi:10.1001/archpsyc.58.9.853

Citron, M., Oltersdorf, T., Haass, C., McConlogue, L., Hung, A. Y., Seubert, P., . . . Selkoe, D. J. (1992). Mutation of the beta-amyloid precursor protein in familial Alzheimer's disease increases beta-protein production. *Nature, 360*(6405), 672-674. doi:10.1038/360672a0

Clement, F., & Belleville, S. (2010). Compensation and disease severity on the memory-related activations in mild cognitive impairment. *Biol Psychiatry, 68*(10), 894-902. doi:10.1016/j.biopsych.2010.02.004

Clement, F., & Belleville, S. (2012). Effect of disease severity on neural compensation of item and associative recognition in mild cognitive impairment. *J Alzheimers Dis, 29*(1), 109-123. doi:10.3233/JAD-2012-110426

Clement, F., Gauthier, S., & Belleville, S. (2013). Executive functions in mild cognitive impairment: emergence and breakdown of neural plasticity. *Cortex, 49*(5), 1268-1279. doi:10.1016/j.cortex.2012.06.004

de Frias, C. M., Dixon, R. A., & Strauss, E. (2009). Characterizing executive functioning in older special populations: from cognitively elite to cognitively impaired. *Neuropsychology, 23*(6), 778-791. doi:10.1037/a0016743

Dickerson, B. C., Salat, D. H., Greve, D. N., Chua, E. F., Rand-Giovannetti, E., Rentz, D. M., . . . Sperling, R. A. (2005). Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. *Neurology, 65*(3), 404-411. doi:10.1212/01.wnl.0000171450.97464.49

Doody, R. S., Farlow, M., Aisen, P. S., Alzheimer's Disease Cooperative Study Data, A., & Publication, C. (2014). Phase 3 trials of solanezumab and bapineuzumab for Alzheimer's disease. *N Engl J Med, 370*(15), 1460. doi:10.1056/NEJMc1402193

Doody, R. S., Thomas, R. G., Farlow, M., Iwatsubo, T., Vellas, B., Joffe, S., . . . Solanezumab Study, G. (2014). Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N Engl J Med, 370*(4), 311-321. doi:10.1056/NEJMoa1312889

Doraiswamy, P. M., Leon, J., Cummings, J. L., Marin, D., & Neumann, P. J. (2002). Prevalence and impact of medical comorbidity in Alzheimer's disease. *J Gerontol A Biol Sci Med Sci, 57*(3), M173-177.

Dubois, B., Hampel, H., Feldman, H. H., Scheltens, P., Aisen, P., Andrieu, S., . . . Washington Dc, U. S. A. (2016). Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. *Alzheimers Dement, 12*(3), 292-323. doi:10.1016/j.jalz.2016.02.002

Esposito, M., & Sherr, G. L. (2019). Epigenetic Modifications in Alzheimer's Neuropathology and Therapeutics. *Front Neurosci, 13*, 476. doi:10.3389/fnins.2019.00476

Fellows, L., Bergman, H., Wolfson, C., & Chertkow, H. (2008). Can clinical data predict progression to dementia in amnestic mild cognitive impairment? *Can J Neurol Sci, 35*(3), 314-322.

Ferri, C. P., Prince, M., Brayne, C., Brodaty, H., Fratiglioni, L., Ganguli, M., . . . Alzheimer's Disease, I. (2005). Global prevalence of dementia: a Delphi consensus study. *Lancet, 366*(9503), 2112-2117. doi:10.1016/S0140-6736(05)67889-0

Fiest, K. M., Roberts, J. I., Maxwell, C. J., Hogan, D. B., Smith, E. E., Frolkis, A., . . . Jette, N. (2016). The Prevalence and Incidence of Dementia Due to Alzheimer's Disease: a Systematic Review and Meta-Analysis. *Can J Neurol Sci, 43 Suppl 1*, S51-82. doi:10.1017/cjn.2016.36

Flicker, C., Ferris, S. H., & Reisberg, B. (1991). Mild cognitive impairment in the elderly: predictors of dementia. *Neurology, 41*(7), 1006-1009.

Fox, N. C., Warrington, E. K., Seiffer, A. L., Agnew, S. K., & Rossor, M. N. (1998). Presymptomatic cognitive deficits in individuals at risk of familial Alzheimer's disease. A longitudinal prospective study. *Brain, 121 ( Pt 9)*, 1631-1639.

Franzmeier, N., Duzel, E., Jessen, F., Buerger, K., Levin, J., Duering, M., . . . Ewers, M. (2018). Left frontal hub connectivity delays cognitive impairment in autosomal-dominant and sporadic Alzheimer's disease. *Brain, 141*(4), 1186-1200. doi:10.1093/brain/awy008

Gardini, S., Cuetos, F., Fasano, F., Pellegrini, F. F., Marchi, M., Venneri, A., & Caffarra, P. (2013). Brain structural substrates of semantic memory decline in mild cognitive impairment. *Curr Alzheimer Res, 10*(4), 373-389.

Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R. C., Ritchie, K., Broich, K., . . . International Psychogeriatric Association Expert Conference on mild cognitive, i. (2006). Mild cognitive impairment. *Lancet, 367*(9518), 1262-1270. doi:10.1016/S0140-6736(06)68542-5

Gauthier, S., Zhang, H., Ng, K. P., Pascoal, T. A., & Rosa-Neto, P. (2018). Impact of the biological definition of Alzheimer's disease using amyloid, tau and neurodegeneration (ATN): what about the role of vascular changes, inflammation, Lewy body pathology? *Transl Neurodegener, 7*, 12. doi:10.1186/s40035-018-0117-9

Gerstenecker, A., & Mast, B. (2014). Mild cognitive impairment: a history and the state of current diagnostic criteria. *Int Psychogeriatr*, 1-13. doi:10.1017/S1041610214002270

Giacobini, E., & Gold, G. (2013). Alzheimer disease therapy--moving from amyloid-beta to tau. *Nat Rev Neurol, 9*(12), 677-686. doi:10.1038/nrneurol.2013.223

Gorbach, T., Pudas, S., Lundquist, A., Oradd, G., Josefsson, M., Salami, A., . . . Nyberg, L. (2017). Longitudinal association between hippocampus atrophy and episodic-memory decline. *Neurobiol Aging, 51*, 167-176. doi:10.1016/j.neurobiolaging.2016.12.002

Godbolt, A. K., Cipolotti, L., Watt, H., Fox, N. C., Janssen, J. C., & Rossor, M. N. (2004). The natural history of Alzheimer disease: a longitudinal presymptomatic and symptomatic study of a familial cohort. *Arch Neurol, 61*(11), 1743-1748. doi:10.1001/archneur.61.11.1743

Gold, D. A. (2012). An examination of instrumental activities of daily living assessment in older adults and mild cognitive impairment. *J Clin Exp Neuropsychol, 34*(1), 11-34. doi:10.1080/13803395.2011.614598

Goldman, J. S. (2015). Chapter 7: Alzheimer's Disease. *Genetic Counseling for Adult Neurogenetic Disease*, 97-107. doi:10.1007/978-1-4899-7482-2_7

Gotz, J., Chen, F., van Dorpe, J., & Nitsch, R. M. (2001). Formation of neurofibrillary tangles in P301l tau transgenic mice induced by Abeta 42 fibrils. *Science, 293*(5534), 1491-1495. doi:10.1126/science.1062097

Han, S. D., Houston, W. S., Jak, A. J., Eyler, L. T., Nagel, B. J., Fleisher, A. S., . . . Bondi, M. W. (2007). Verbal paired-associate learning by APOE genotype in non-demented older adults: fMRI evidence of a right hemispheric compensatory response. *Neurobiol Aging, 28*(2), 238-247. doi:10.1016/j.neurobiolaging.2005.12.013

Hansson, O., Seibyl, J., Stomrud, E., Zetterberg, H., Trojanowski, J. Q., Bittner, T., . . . Alzheimer's Disease Neuroimaging, I. (2018). CSF biomarkers of Alzheimer's disease concord with amyloid-beta PET and predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts. *Alzheimers Dement, 14*(11), 1470-1481. doi:10.1016/j.jalz.2018.01.010

Hardy, J. (2009). The amyloid hypothesis for Alzheimer's disease: a critical reappraisal. *J Neurochem, 110*(4), 1129-1134. doi:10.1111/j.1471-4159.2009.06181.x

Hardy, J., & Allsop, D. (1991). Amyloid deposition as the central event in the aetiology of Alzheimer's disease. *Trends Pharmacol Sci, 12*(10), 383-388.

Hardy, J., & Selkoe, D. J. (2002). The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science, 297*(5580), 353-356. doi:10.1126/science.1072994

Hohman, T. J., Beason-Held, L. L., Lamar, M., & Resnick, S. M. (2011). Subjective cognitive complaints and longitudinal changes in memory and brain function. *Neuropsychology, 25*(1), 125-130. doi:10.1037/a0020859

Hostetler, E. D., Walji, A. M., Zeng, Z., Miller, P., Bennacef, I., Salinas, C., . . . Evelhoch, J. L. (2016). Preclinical Characterization of 18F-MK-6240, a Promising PET Tracer for In Vivo Quantification of Human Neurofibrillary Tangles. *J Nucl Med, 57*(10), 1599-1606. doi:10.2967/jnumed.115.171678

Ittner, L. M., & Gotz, J. (2011). Amyloid-beta and tau--a toxic pas de deux in Alzheimer's disease. *Nat Rev Neurosci, 12*(2), 65-72. doi:10.1038/nrn2967

Jack, C. R., Jr., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., . . . Contributors. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement, 14*(4), 535-562. doi:10.1016/j.jalz.2018.02.018

Jack, C. R., Jr., Bennett, D. A., Blennow, K., Carrillo, M. C., Feldman, H. H., Frisoni, G. B., . . . Dubois, B. (2016). A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers. *Neurology, 87*(5), 539-547. doi:10.1212/WNL.0000000000002923

Jack, C. R., Jr., Knopman, D. S., Jagust, W. J., Shaw, L. M., Aisen, P. S., Weiner, M. W., . . . Trojanowski, J. Q. (2010). Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol, 9*(1), 119-128. doi:10.1016/S1474-4422(09)70299-6

James, O. G., Doraiswamy, P. M., & Borges-Neto, S. (2015). PET Imaging of Tau Pathology in Alzheimer's Disease and Tauopathies. *Front Neurol, 6*, 38. doi:10.3389/fneur.2015.00038

Jefferson, A. L., Paul, R. H., Ozonoff, A., & Cohen, R. A. (2006). Evaluating elements of executive functioning as predictors of instrumental activities of daily living (IADLs). *Arch Clin Neuropsychol, 21*(4), 311-320. doi:10.1016/j.acn.2006.03.007

Jekel, K., Damian, M., Wattmo, C., Hausner, L., Bullock, R., Connelly, P. J., . . . Frolich, L. (2015). Mild cognitive impairment and deficits in instrumental activities of daily living: a systematic review. *Alzheimers Res Ther, 7*(1), 17. doi:10.1186/s13195-015-0099-0

Jessen, F., Amariglio, R. E., van Boxtel, M., Breteler, M., Ceccaldi, M., Chetelat, G., . . . Subjective Cognitive Decline Initiative Working, G. (2014). A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers Dement, 10*(6), 844-852. doi:10.1016/j.jalz.2014.01.001

Jessen, F., Wolfsgruber, S., Wiese, B., Bickel, H., Mosch, E., Kaduszkiewicz, H., . . . Dementia in Primary Care, P. (2014). AD dementia risk in late MCI, in early MCI, and in subjective memory impairment. *Alzheimers Dement, 10*(1), 76-83. doi:10.1016/j.jalz.2012.09.017

Jia, J., Wei, C., Chen, S., Li, F., Tang, Y., Qin, W., . . . Gauthier, S. (2018). The cost of Alzheimer's disease in China and re-estimation of costs worldwide. *Alzheimers Dement, 14*(4), 483-491. doi:10.1016/j.jalz.2017.12.006

Johns, E. K., Phillips, N. A., Belleville, S., Goupil, D., Babins, L., Kelner, N., . . . Chertkow, H. (2012). The profile of executive functioning in amnestic mild cognitive impairment: disproportionate deficits in inhibitory control. *J Int Neuropsychol Soc, 18*(3), 541-555. doi:10.1017/S1355617712000069

Joshi, A., Ringman, J. M., Lee, A. S., Juarez, K. O., & Mendez, M. F. (2012). Comparison of clinical characteristics between familial and non-familial early onset Alzheimer's disease. *J Neurol, 259*(10), 2182-2188. doi:10.1007/s00415-012-6481-y

Kimberly, W. T., LaVoie, M. J., Ostaszewski, B. L., Ye, W., Wolfe, M. S., & Selkoe, D. J. (2003). Gamma-secretase is a membrane protein complex comprised of presenilin,

nicastrin, Aph-1, and Pen-2. *Proc Natl Acad Sci U S A, 100*(11), 6382-6387. doi:10.1073/pnas.1037392100

Kirova, A. M., Bays, R. B., & Lagalwar, S. (2015). Working memory and executive function decline across normal aging, mild cognitive impairment, and Alzheimer's disease. *Biomed Res Int, 2015*, 748212. doi:10.1155/2015/748212

Koppara, A., Wagner, M., Lange, C., Ernst, A., Wiese, B., Konig, H. H., . . . Jessen, F. (2015). Cognitive performance before and after the onset of subjective cognitive decline in old age. *Alzheimers Dement (Amst), 1*(2), 194-205. doi:10.1016/j.dadm.2015.02.005

Kröger, E., Rochette, L., Bocti, C., Laforce, R., Pelletier, É., & Émond, V. (2014). Building a cohort of Alzheimer disease and dementia cases from administrative data. *Presented at Journées de la Recherche du Réseau Québecois de recherche sur le vieillissement, 12th edition*(October 6-8).

Laforce, R., Jr., & Rabinovici, G. D. (2011). Amyloid imaging in the differential diagnosis of dementia: review and potential clinical applications. *Alzheimers Res Ther, 3*(6), 31. doi:10.1186/alzrt93

Lange, K. L., Bondi, M. W., Salmon, D. P., Galasko, D., Delis, D. C., Thomas, R. G., & Thal, L. J. (2002). Decline in verbal memory during preclinical Alzheimer's disease: examination of the effect of APOE genotype. *J Int Neuropsychol Soc, 8*(7), 943-955.

Lebouvier, T., Pasquier, F., & Buee, L. (2017). Update on tauopathies. *Curr Opin Neurol, 30*(6), 589-598. doi:10.1097/WCO.0000000000000502

Lefleche, G., & Albert, M. S. (1995). Executive function deficits in mild Alzheimer's disease. *Neuropsychology, 9*, 313-320.

Liang, Y., Pertzov, Y., Nicholas, J. M., Henley, S. M. D., Crutch, S., Woodward, F., . . . Husain, M. (2016). Visual short-term memory binding deficit in familial Alzheimer's disease. *Cortex, 78*, 150-164. doi:10.1016/j.cortex.2016.01.015

Liu, X., Jiao, B., & Shen, L. (2018). The Epigenetics of Alzheimer's Disease: Factors and Therapeutic Implications. *Front Genet, 9*, 579. doi:10.3389/fgene.2018.00579

Lleo, A., Blesa, R., Queralt, R., Ezquerra, M., Molinuevo, J. L., Pena-Casanova, J., . . . Oliva, R. (2002). Frequency of mutations in the presenilin and amyloid precursor protein genes in early-onset Alzheimer disease in Spain. *Arch Neurol, 59*(11), 1759-1763.

Marshall, G. A., Rentz, D. M., Frey, M. T., Locascio, J. J., Johnson, K. A., Sperling, R. A., & Alzheimer's Disease Neuroimaging, I. (2011). Executive function and instrumental activities of daily living in mild cognitive impairment and Alzheimer's disease. *Alzheimers Dement, 7*(3), 300-308. doi:10.1016/j.jalz.2010.04.005

Martyr, A., & Clare, L. (2012). Executive function and activities of daily living in Alzheimer's disease: a correlational meta-analysis. *Dement Geriatr Cogn Disord, 33*(2-3), 189-203. doi:10.1159/000338233

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr., Kawas, C. H., . . . Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 263-269. doi:10.1016/j.jalz.2011.03.005

Mejia, S., Giraldo, M., Pineda, D., Ardila, A., & Lopera, F. (2003). Nongenetic factors as modifiers of the age of onset of familial Alzheimer's disease. *Int Psychogeriatr, 15*(4), 337-349.

Mitchell, A. J., Beaumont, H., Ferguson, D., Yadegarfar, M., & Stubbs, B. (2014). Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: meta-analysis. *Acta Psychiatr Scand, 130*(6), 439-451. doi:10.1111/acps.12336

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. *Cogn Psychol, 41*(1), 49-100. doi:10.1006/cogp.1999.0734

Molinuevo, J. L., Rabin, L. A., Amariglio, R., Buckley, R., Dubois, B., Ellis, K. A., . . . Subjective Cognitive Decline Initiative Working, G. (2017). Implementation of subjective cognitive decline criteria in research studies. *Alzheimers Dement, 13*(3), 296-311. doi:10.1016/j.jalz.2016.09.012

Morris, J. C., Aisen, P. S., Bateman, R. J., Benzinger, T. L., Cairns, N. J., Fagan, A. M., . . . Buckles, V. D. (2012). Developing an international network for Alzheimer research: The Dominantly Inherited Alzheimer Network. *Clin Investig (Lond), 2*(10), 975-984. doi:10.4155/cli.12.93

Mortamais, M., Ash, J. A., Harrison, J., Kaye, J., Kramer, J., Randolph, C., . . . Ritchie, K. (2017). Detecting cognitive changes in preclinical Alzheimer's disease: A review of its feasibility. *Alzheimers Dement, 13*(4), 468-492. doi:10.1016/j.jalz.2016.06.2365

Mullan, M., Scibelli, P., Duara, R., Fallin, D., Gold, M., Schinka, J., . . . Crawford, F. (1996). Familial and population-based studies of apolipoprotein E and Alzheimer's disease. *Ann N Y Acad Sci, 802*, 16-26.

Mura, T., Proust-Lima, C., Jacqmin-Gadda, H., Akbaraly, T. N., Touchon, J., Dubois, B., & Berr, C. (2014). Measuring cognitive change in subjects with prodromal Alzheimer's disease. *J Neurol Neurosurg Psychiatry, 85*(4), 363-370. doi:10.1136/jnnp-2013-305078

Newman, S. K., Warrington, E. K., Kennedy, A. M., & Rossor, M. N. (1994). The earliest cognitive change in a person with familial Alzheimer's disease: presymptomatic neuropsychological features in a pedigree with familial Alzheimer's disease confirmed at necropsy. *J Neurol Neurosurg Psychiatry, 57*(8), 967-972.

Olsson, B., Lautner, R., Andreasson, U., Ohrfelt, A., Portelius, E., Bjerke, M., . . . Zetterberg, H. (2016). CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *Lancet Neurol, 15*(7), 673-684. doi:10.1016/S1474-4422(16)00070-3

Palmqvist, S., Zetterberg, H., Mattsson, N., Johansson, P., Alzheimer's Disease Neuroimaging, I., Minthon, L., . . . Swedish Bio, F. S. G. (2015). Detailed comparison of amyloid PET and CSF biomarkers for identifying early Alzheimer disease. *Neurology, 85*(14), 1240-1249. doi:10.1212/WNL.0000000000001991

Papp, K. V., Mormino, E. C., Amariglio, R. E., Munro, C., Dagley, A., Schultz, A. P., . . . Rentz, D. M. (2016). Biomarker validation of a decline in semantic processing in preclinical Alzheimer's disease. *Neuropsychology, 30*(5), 624-630. doi:10.1037/neu0000246

Parra, M. A., Abrahams, S., Logie, R. H., & Della Sala, S. (2010). Visual short-term memory binding in Alzheimer's disease and depression. *J Neurol, 257*(7), 1160-1169. doi:10.1007/s00415-010-5484-9

Parra, M. A., Saarimaki, H., Bastin, M. E., Londono, A. C., Pettit, L., Lopera, F., . . . Abrahams, S. (2015). Memory binding and white matter integrity in familial Alzheimer's disease. *Brain, 138*(Pt 5), 1355-1369. doi:10.1093/brain/awv048

Pedersen, J. T., & Sigurdsson, E. M. (2015). Tau immunotherapy for Alzheimer's disease. *Trends Mol Med, 21*(6), 394-402. doi:10.1016/j.molmed.2015.03.003

Pedretti, L. W., Pendleton, H. M., & Schultz-Krohn, W. (2006). *Pedretti's occupational therapy : practice skills for physical dysfunction* (6th ed.). St. Louis, Mo.: Mosby/Elsevier.

Peres, K., Helmer, C., Amieva, H., Orgogozo, J. M., Rouch, I., Dartigues, J. F., & Barberger-Gateau, P. (2008). Natural history of decline in instrumental activities of daily living performance over the 10 years preceding the clinical diagnosis of dementia: a prospective population-based study. *J Am Geriatr Soc, 56*(1), 37-44. doi:10.1111/j.1532-5415.2007.01499.x

Perry, R. J., & Hodges, J. R. (1999). Attention and executive deficits in Alzheimer's disease. A critical review. *Brain, 122 ( Pt 3)*, 383-404.

Peters, F., Villeneuve, S., & Belleville, S. (2014). Predicting progression to dementia in elderly subjects with mild cognitive impairment using both cognitive and neuroimaging predictors. *J Alzheimers Dis, 38*(2), 307-318. doi:10.3233/JAD-130842

Petersen, R. C. (2009). Early diagnosis of Alzheimer's disease: is MCI too late? *Curr Alzheimer Res, 6*(4), 324-330.

Petersen, R. C., Doody, R., Kurz, A., Mohs, R. C., Morris, J. C., Rabins, P. V., . . . Winblad, B. (2001). Current concepts in mild cognitive impairment. *Arch Neurol, 58*(12), 1985-1992.

Petersen, R. C., Stevens, J. C., Ganguli, M., Tangalos, E. G., Cummings, J. L., & DeKosky, S. T. (2001). Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology, 56*(9), 1133-1142.

Price, S. E., Kinsella, G. J., Ong, B., Storey, E., Mullaly, E., Phillips, M., . . . Perre, D. (2012). Semantic verbal fluency strategies in amnestic mild cognitive impairment. *Neuropsychology, 26*(4), 490-497. doi:10.1037/a0028567

Qazi, T. J., Quan, Z., Mir, A., & Qing, H. (2018). Epigenetics in Alzheimer's Disease: Perspective of DNA Methylation. *Mol Neurobiol, 55*(2), 1026-1044. doi:10.1007/s12035-016-0357-6

Querfurth, H. W., & LaFerla, F. M. (2010). Alzheimer's disease. *N Engl J Med, 362*(4), 329-344. doi:10.1056/NEJMra0909142

Rainville, C., Lepage, E., Gauthier, S., Kergoat, M. J., & Belleville, S. (2012). Executive function deficits in persons with mild cognitive impairment: a study with a Tower of London task. *J Clin Exp Neuropsychol, 34*(3), 306-324. doi:10.1080/13803395.2011.639298

Rapoport, M., Dawson, H. N., Binder, L. I., Vitek, M. P., & Ferreira, A. (2002). Tau is essential to beta -amyloid-induced neurotoxicity. *Proc Natl Acad Sci U S A, 99*(9), 6364-6369. doi:10.1073/pnas.092136199

Reisberg, B., Shulman, M. B., Torossian, C., Leng, L., & Zhu, W. (2010). Outcome over seven years of healthy adults with and without subjective cognitive impairment. *Alzheimers Dement, 6*(1), 11-24. doi:10.1016/j.jalz.2009.10.002

Reppermund, S., Brodaty, H., Crawford, J. D., Kochan, N. A., Draper, B., Slavin, M. J., . . . Sachdev, P. S. (2013). Impairment in instrumental activities of daily living with high cognitive demand is an early marker of mild cognitive impairment: the Sydney memory and ageing study. *Psychol Med, 43*(11), 2437-2445. doi:10.1017/S003329171200308X

Ringman, J. M., Diaz-Olavarrieta, C., Rodriguez, Y., Chavez, M., Fairbanks, L., Paz, F., . . . Kawas, C. (2005). Neuropsychological function in nondemented carriers of presenilin-1 mutations. *Neurology, 65*(4), 552-558. doi:10.1212/01.wnl.0000172919.50001.d6

Ritchie, L. J., & Tuokko, H. (2010). Patterns of cognitive decline, conversion rates, and predictive validity for 3 models of MCI. *Am J Alzheimers Dis Other Demen, 25*(7), 592-603. doi:10.1177/1533317510382286

Rizk-Jackson, A., Insel, P., Petersen, R., Aisen, P., Jack, C., & Weiner, M. (2013). Early indications of future cognitive decline: stable versus declining controls. *PLoS One, 8*(9), e74062. doi:10.1371/journal.pone.0074062

Roe, C. M., Xiong, C., Miller, J. P., & Morris, J. C. (2007). Education and Alzheimer disease without dementia: support for the cognitive reserve hypothesis. *Neurology, 68*(3), 223-228. doi:10.1212/01.wnl.0000251303.50459.8a

Ryman, D. C., Acosta-Baena, N., Aisen, P. S., Bird, T., Danek, A., Fox, N. C., . . . And the Dominantly Inherited Alzheimer, N. (2014). Symptom onset in autosomal dominant Alzheimer disease: A systematic review and meta-analysis. *Neurology*. doi:10.1212/WNL.0000000000000596

Salimi, S., Irish, M., Foxe, D., Hodges, J. R., Piguet, O., & Burrell, J. R. (2018). Can visuospatial measures improve the diagnosis of Alzheimer's disease? *Alzheimers Dement (Amst), 10*, 66-74. doi:10.1016/j.dadm.2017.10.004

Salloway, S., Sperling, R., Fox, N. C., Blennow, K., Klunk, W., Raskind, M., . . . Clinical Trial, I. (2014). Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *N Engl J Med, 370*(4), 322-333. doi:10.1056/NEJMoa1304839

Salmon, D. (2000). Disorders of memory in Alzheimer's disease. *Handbook of Neuropsychology, 2*, 155-195.

Salmon, D. P., & Bondi, M. W. (2009). Neuropsychological assessment of dementia. *Annu Rev Psychol, 60*, 257-282. doi:10.1146/annurev.psych.57.102904.190024

Saunders, N. L., & Summers, M. J. (2010). Attention and working memory deficits in mild cognitive impairment. *J Clin Exp Neuropsychol, 32*(4), 350-357. doi:10.1080/13803390903042379

Saunders, N. L., & Summers, M. J. (2011). Longitudinal deficits to attention, executive, and working memory in subtypes of mild cognitive impairment. *Neuropsychology, 25*(2), 237-248. doi:10.1037/a0021134

Scarmeas, N., Albert, S. M., Manly, J. J., & Stern, Y. (2006). Education and rates of cognitive decline in incident Alzheimer's disease. *J Neurol Neurosurg Psychiatry, 77*(3), 308-316. doi:10.1136/jnnp.2005.072306

Scholl, M., Lockhart, S. N., Schonhaut, D. R., O'Neil, J. P., Janabi, M., Ossenkoppele, R., . . . Jagust, W. J. (2016). PET Imaging of Tau Deposition in the Aging Human Brain. *Neuron, 89*(5), 971-982. doi:10.1016/j.neuron.2016.01.028

Selkoe, D. J., & Hardy, J. (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol Med, 8*(6), 595-608. doi:10.15252/emmm.201606210

Shepherd, C., McCann, H., & Halliday, G. M. (2009). Variations in the neuropathology of familial Alzheimer's disease. *Acta Neuropathol, 118*(1), 37-52. doi:10.1007/s00401-009-0521-4

Simon, S. S., Yokomizo, J. E., & Bottino, C. M. (2012). Cognitive intervention in amnestic Mild Cognitive Impairment: a systematic review. *Neurosci Biobehav Rev, 36*(4), 1163-1178. doi:10.1016/j.neubiorev.2012.01.007

Small, B. J., Fratiglioni, L., Viitanen, M., Winblad, B., & Backman, L. (2000). The course of cognitive impairment in preclinical Alzheimer disease: three- and 6-year follow-up of a population-based sample. *Arch Neurol, 57*(6), 839-844. doi:10.1001/archneur.57.6.839

Smits, L. L., Pijnenburg, Y. A., Koedam, E. L., van der Vlies, A. E., Reuling, I. E., Koene, T., . . . van der Flier, W. M. (2012). Early onset Alzheimer's disease is associated with a distinct neuropsychological profile. *J Alzheimers Dis, 30*(1), 101-108. doi:10.3233/JAD-2012-111934

Snider, B. J., Norton, J., Coats, M. A., Chakraverty, S., Hou, C. E., Jervis, R., . . . Morris, J. C. (2005). Novel presenilin 1 mutation (S170F) causing Alzheimer disease with Lewy bodies in the third decade of life. *Arch Neurol, 62*(12), 1821-1830. doi:10.1001/archneur.62.12.1821

Snitz, B. E., Wang, T., Cloonan, Y. K., Jacobsen, E., Chang, C. H., Hughes, T. F., . . . Ganguli, M. (2018). Risk of progression from subjective cognitive decline to mild cognitive impairment: The role of study setting. *Alzheimers Dement, 14*(6), 734-742. doi:10.1016/j.jalz.2017.12.003

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., . . . Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement, 7*(3), 280-292. doi:10.1016/j.jalz.2011.03.003

Stern, R. G., Mohs, R. C., Davidson, M., Schmeidler, J., Silverman, J., Kramer-Ginsberg, E., . . . Davis, K. L. (1994). A longitudinal study of Alzheimer's disease: measurement, rate, and predictors of cognitive deterioration. *Am J Psychiatry, 151*(3), 390-396.

Stern, Y., Arenaza-Urquijo, E. M., Bartres-Faz, D., Belleville, S., Cantilon, M., Chetelat, G., . . . Conceptual Frameworks, W. (2018). Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimers Dement*. doi:10.1016/j.jalz.2018.07.219

Storandt, M., Balota, D. A., Aschenbrenner, A. J., & Morris, J. C. (2014). Clinical and psychological characteristics of the initial cohort of the Dominantly Inherited Alzheimer Network (DIAN). *Neuropsychology, 28*(1), 19-29. doi:10.1037/neu0000030

Swearer, J. M., O'Donnell, B. F., Drachman, D. A., & Woodward, B. M. (1992). Neuropsychological features of familial Alzheimer's disease. *Ann Neurol, 32*(5), 687-694. doi:10.1002/ana.410320513

Sweeney, M. D., Montagne, A., Sagare, A. P., Nation, D. A., Schneider, L. S., Chui, H. C., . . . Zlokovic, B. V. (2019). Vascular dysfunction-The disregarded partner of Alzheimer's disease. *Alzheimers Dement, 15*(1), 158-167. doi:10.1016/j.jalz.2018.07.222

Sylvain-Roy, S., Lungu, O., & Belleville, S. (2015). Normal Aging of the Attentional Control Functions That Underlie Working Memory. *J Gerontol B Psychol Sci Soc Sci, 70*(5), 698-708. doi:10.1093/geronb/gbt166

Tabert, M. H., Manly, J. J., Liu, X., Pelton, G. H., Rosenblum, S., Jacobs, M., . . . Devanand, D. P. (2006). Neuropsychological prediction of conversion to Alzheimer disease in patients with mild cognitive impairment. *Arch Gen Psychiatry, 63*(8), 916-924. doi:10.1001/archpsyc.63.8.916

Thies, W., Bleiler, L., & Alzheimer's, A. (2013). 2013 Alzheimer's disease facts and figures. *Alzheimers Dement, 9*(2), 208-245. doi:10.1016/j.jalz.2013.02.003

Thordardottir, S., Rodriguez-Vieitez, E., Almkvist, O., Ferreira, D., Saint-Aubert, L., Kinhult-Stahlbom, A., . . . Graff, C. (2018). Reduced penetrance of the PSEN1 H163Y autosomal dominant Alzheimer mutation: a 22-year follow-up study. *Alzheimers Res Ther, 10*(1), 45. doi:10.1186/s13195-018-0374-y

Tomaszewski Farias, S., Cahn-Weiner, D. A., Harvey, D. J., Reed, B. R., Mungas, D., Kramer, J. H., & Chui, H. (2009). Longitudinal changes in memory and executive functioning are associated with longitudinal change in instrumental activities of daily living in older adults. *Clin Neuropsychol, 23*(3), 446-461. doi:10.1080/13854040802360558

Traykov, L., Raoux, N., Latour, F., Gallo, L., Hanon, O., Baudic, S., . . . Rigaud, A. S. (2007). Executive functions deficit in mild cognitive impairment. *Cogn Behav Neurol, 20*(4), 219-224. doi:10.1097/WNN.0b013e31815e6254

Twamley, E. W., Ropacki, S. A., & Bondi, M. W. (2006). Neuropsychological and neuroimaging changes in preclinical Alzheimer's disease. *J Int Neuropsychol Soc, 12*(5), 707-735. doi:10.1017/S1355617706060863

van Harten, A. C., Smits, L. L., Teunissen, C. E., Visser, P. J., Koene, T., Blankenstein, M. A., . . . van der Flier, W. M. (2013). Preclinical AD predicts decline in memory and executive functions in subjective complaints. *Neurology, 81*(16), 1409-1416. doi:10.1212/WNL.0b013e3182a8418b

Vaughan, L., & Giovanello, K. (2010). Executive function in daily life: Age-related influences of executive processes on instrumental activities of daily living. *Psychol Aging, 25*(2), 343-355. doi:10.1037/a0017729

Vaughan, R. M., Coen, R. F., Kenny, R., & Lawlor, B. A. (2018). Semantic and Phonemic Verbal Fluency Discrepancy in Mild Cognitive Impairment: Potential Predictor of Progression to Alzheimer's Disease. *J Am Geriatr Soc, 66*(4), 755-759. doi:10.1111/jgs.15294

Vlassenko, A. G., McCue, L., Jasielec, M. S., Su, Y., Gordon, B. A., Xiong, C., . . . Fagan, A. M. (2016). Imaging and cerebrospinal fluid biomarkers in early preclinical alzheimer disease. *Ann Neurol, 80*(3), 379-387. doi:10.1002/ana.24719

Wadley, V. G., Okonkwo, O., Crowe, M., & Ross-Meadows, L. A. (2008). Mild cognitive impairment and everyday function: evidence of reduced speed in performing instrumental activities of daily living. *Am J Geriatr Psychiatry, 16*(5), 416-424. doi:10.1097/JGP.0b013e31816b7303

Warrington, E. K., Agnew, S. K., Kennedy, A. M., & Rossor, M. N. (2001). Neuropsychological profiles of familial Alzheimer's disease associated with mutations in the presenilin 1 and amyloid precursor protein genes. *J Neurol, 248*(1), 45-50.

Wilkosz, P. A., Seltman, H. J., Devlin, B., Weamer, E. A., Lopez, O. L., DeKosky, S. T., & Sweet, R. A. (2010). Trajectories of cognitive decline in Alzheimer's disease. *Int Psychogeriatr, 22*(2), 281-290. doi:10.1017/S1041610209991001

Wilson, R. S., Aggarwal, N. T., Barnes, L. L., Mendes de Leon, C. F., Hebert, L. E., & Evans, D. A. (2010). Cognitive decline in incident Alzheimer disease in a community population. *Neurology, 74*(12), 951-955. doi:10.1212/WNL.0b013e3181d64786

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L. O., . . . Petersen, R. C. (2004). Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med, 256*(3), 240-246. doi:10.1111/j.1365-2796.2004.01380.x

Yaffe, K., Petersen, R. C., Lindquist, K., Kramer, J., & Miller, B. (2006). Subtype of mild cognitive impairment and progression to dementia and death. *Dement Geriatr Cogn Disord, 22*(4), 312-319. doi:10.1159/000095427

Yesavage, J. A., Poulsen, S. L., Sheikh, J., & Tanke, E. (1988). Rates of change of common measures of impairment in senile dementia of the Alzheimer's type. *Psychopharmacol Bull, 24*(4), 531-534.

Zheng, D., Dong, X., Sun, H., Xu, Y., Ma, Y., & Wang, X. (2012). The overall impairment of core executive function components in patients with amnestic mild cognitive impairment: a cross-sectional study. *BMC Neurol, 12*, 138. doi:10.1186/1471-2377-12-138

**Annexe 1**

**Description des tests neuropsychologiques**

*Mesures de mémoire*

Le RL/RI est une tâche de rappel sémantique libre et indicé, dans laquelle les participants associent une liste de mots à une catégorie sémantique. Ils doivent ensuite rappeler ces mots immédiatement après la présentation de la liste, et après l'introduction d'un délai. Après chaque rappel libre, un rappel indicé sémantiquement leur est proposé. Ils doivent également faire une tâche de reconnaissance de mots cibles dans une liste dans laquelle on retrouve également des mots proches sémantiquement (distracteurs sémantiques) ou non associés au même domaine sémantique (distracteurs neutres).

Le RAVLT est un test de mémorisation et de rappel de mots. Une première liste (liste A) de 15 mots est lue au participant, au rythme d'un mot par seconde. Il doit rappeler le plus de mots de cette liste, peu importe l'ordre. Cet exercice est répété 4 autres fois. Puis, une seconde liste (liste B) de 15 mots est lue au participant et il doit rappeler le plus de mots de cette seconde liste. On lui demande ensuite de rappeler une nouvelle fois les mots de la liste A. Après l'introduction d'un délai de 20 minutes, le participant doit rappeler une dernière fois les mots de la liste A. Finalement, on administre un test de reconnaissance, c'est-à-dire que le participant doit indiquer si des mots qui lui sont présentés faisaient partie des listes mémorisées ou non (distracteurs). Il est possible de mesurer les erreurs de commissions (un mot qui ne faisait pas partie de la liste est rapporté par le participant), les erreurs d'omission (certains mots ne sont pas rappelés) et les intrusions (le participant dit des mots de la liste B lors du rappel de la liste A). De plus, en répétant plusieurs fois la liste A, cela nous permet de mesurer l'encodage et les effets

d'apprentissage, et le rappel différé de la liste A nous permet d'avoir une indication de la perte d'information avec le temps.

L'épreuve d'histoires logiques est adaptée d'un sous-test de la Wechsler Memory Scale III (WMS-III, MEM-III en français). Une histoire est racontée au participant à qui on demande de la répéter avec le plus de détails possibles. Comme il ne s'agit pas d'un test de mémoire incidente, on lui indique qu'il devra rappeler cette histoire plus tard dans l'évaluation. Suivant un délai de 25 à 35 minutes, on demande au participant de rappeler le plus d'éléments qu'il se souvient de l'histoire. Finalement, une série de questions auxquelles il doit répondre par oui ou non permet d'avoir une mesure de reconnaissance. Pour la cotation, des points sont attribués selon les détails correctement rappelés et si certains thèmes sont présents (par exemple un des thèmes est "indication que le personnage principal est une femme").

Le test de la figure complexe de Rey permet d'évaluer 2 domaines cognitifs: l'organisation spatiale/praxie constructive et la mémoire spatiale. Une figure est présentée au participant à qui on demande de la recopier le plus fidèlement possible. Il s'agit d'un test de mémoire incidente, ce qui signifie que les participants ne sont pas informés durant la copie de la figure qu'ils auront à la dessiner de mémoire, 3 et 20 minutes après la copie. La figure est constituée de 18 éléments et on attribue de 0 à 2 points par élément, selon qu'ils soient bien dessinés et bien placés, pour un score total de 36 points. On mesure le temps que prend la personne à recopier la figure lorsqu'elle l'a sous les yeux et on note la façon dont elle organise son dessin, à l'essai copie, à l'essai de rappel immédiat (3 minutes) et à l'essai de rappel différé (20 minutes).

*Mesures d'attention et de vitesse de traitement*

Le sous-test Code du WAIS-III permet d'avoir une mesure de la mémoire de travail et de la vitesse de traitement des participants. Des symboles sont appariés à chacun des chiffres de 0 à 9. Une série de chiffres aléatoires sous lesquels on retrouve des cases vides sont présentés au participant à qui on demande de dessiner les symboles correspondants, le plus rapidement possible, en essayant de ne pas faire d'erreurs. On arrête le participant après 2 minutes et on note le nombre de symboles correctement dessinés.

L'empan de chiffres à l'endroit et à l'envers du WAIS-III est une mesure d'attention et de mémoire à court terme. Dans cette tâche, les participants répètent des chiffres dits par l'évaluateur, à raison d'un chiffre par seconde. Au départ, les séquences sont courtes (2 chiffres), mais au fur et à mesure de l'avancement de la tâche, les séquences deviennent plus longues, jusqu'à 9 chiffres pour l'empan à l'endroit et jusqu'à 8 chiffres pour l'empan à l'envers.

*Mesures de langage*

Le test de fluence verbale consiste à nommer le plus d'animaux possible dans une période d'une minute. On note le nombre total d'animaux différents rapportés et le nombre par intervalle de 15 secondes.

Le Boston Naming Test est un test durant lequel les participants doivent nommer une série d'images qui leur sont présentées. La version originale comprend 60 items, mais dans le cadre de cette étude, nous allons utiliser la version à 30 items. Si le participant n'arrive pas à identifier une image, un indice sémantique lui est donné. S'il n'y arrive toujours pas, un indice phonétique lui est donné. Par exemple, pour l'image d'un balai, l'indice sémantique est "utilisé pour nettoyer" et l'indice phonétique est "ba...". La performance des participants sera mesurée par le nombre total d'images correctement identifiées sans indices sémantique ou phonétique.

Le test de Stroop est une mesure des fonctions exécutives, en particulier de l'inhibition. Dans un premier temps, les participants lisent des mots, qui sont des noms de couleurs (par exemple: ROUGE VERT BLEU): condition "mots". Dans un 2e temps, il doivent nommer des couleurs (par exemple ■ ■ ■ ): condition "couleurs". Dans un troisième temps, ils doivent nommer la couleur de l'encre, et non le mot qui est écrit (par exemple: **VERT**, dans ce cas-ci, la personne doit lire rouge et non vert): condition interférence. Finalement, dans la dernière condition, les participants doivent alterner entre lire le mot et nommer la couleur, c'est-à-dire que si le mot n'est pas dans un encadré, il faut nommer la couleur de l'encre, alors que s'il est encadré, il faut lire le mot (par exemple: **VERT** **VERT** **ROUGE:** dans ce cas-ci, la bonne réponse serait rouge, vert, bleu): condition alternance. Pour chaque condition, on mesure le temps pris par le participant pour lire ou nommer tous les stimuli. Il est donc possible de faire des contrastes afin d'avoir des mesures plus pures d'interférence, en contrôlant pour le temps de lecture (par exemple: interférence - (mots + couleurs)).

Le Trail Making Test est une épreuve de flexibilité mentale. Une première tâche consiste à relier avec des traits, dans l'ordre, des cercles numérotés de 1 à 25. La seconde tâche consiste aussi à relier avec des traits des cercles, mais en alternant entre des chiffres et des lettres. Donc le participant doit commencer par relier le 1 au A et ensuite relier le A au 2 et le 2 au B, etc. Étant donné qu'en Chine, l'alphabet romain n'est pas d'usage, une version dans laquelle les participants doivent alterner entre des chiffres et des couleurs sera utilisée à la place: le Color Trails Test.

Le test de Hayling est une tâche d'inhibition sémantique. Les participants doivent lire des phrases dont il manque le dernier mot. Dans la condition automatique, ils ajoutent le mot

selon le contexte de la phrase (par exemple: " Les prisonniers se sont évadés de la _____ (prison)", ils doivent dire le mot "prison"). Dans la condition d'inhibition, ils ne doivent pas compléter la phrase selon le contexte (par exemple: "Quand ils se sont rencontrés, ce fut le coup de _____", ils doivent inhiber la réponse automatique qu'est de dire le mot "foudre" et dire un autre mot à la place).

*Mesures de perception et d'habiletés visuospatiales*

Les habiletés visuospatiales seront estimées à partir de la performance des sujets à un test de jugement d'orientation de lignes (*Benton Judgment of Line Orientation*). La figure de référence est une série de 11 lignes, de même longueur, mais d'orientations différentes, séparées entre elles par un angle de 20º. Elles couvrent donc un cadran de 180º auquel le participant doit se référer lorsqu'on lui présente deux lignes seules d'une certaine orientation qui correspondent à 2 des lignes de référence. En d'autres termes, le sujet doit juger de l'orientation des lignes présentées et indiquer à quelles lignes de références elles correspondent.

Pour mesurer la perception et les habiletés visuospatiales, un sous-test de la BORB (*Birmingham Object Recognition Battery*) a été administré: l'épreuve de jugement d'orientation de lignes (*Orientation Match Task*). Des paires de lignes sont présentées aux participants et ils doivent indiquer si elles sont parallèles. Il y a 3 niveaux de difficultés: grandes différences d'orientation entre les 2 lignes, différences intermédiaires et petites différences.

Le Block Design Test est un sous-test de la WAIS-III et permet d'évaluer la planification spatiale et les habiletés perceptives. On demande aux participants de reproduire avec des blocs le plus rapidement possible des modèles présentés en images. Tous les blocs sont identiques: ils ont 2 côtés rouges, 2 côtés blancs et 2 côtés moitié-rouge, moitié-blanc. Les premiers modèles sont simples: ils peuvent être reproduits avec 4 blocs. Le niveau de difficulté augmente avec les

items et les derniers modèles sont plus difficiles: ils sont construits avec 9 blocs. À chaque item, on note si le modèle est bien reproduit et le temps d'exécution.

Le score de copie du RCFT sera également utilisé comme mesure des habiletés visuospatiales.

*Mesures de réserve cognitive*

Le sous-test vocabulaire de la WAIS-III peut être utilisé comme mesure proxy de réserve, étant donné qu'il s'agit d'une épreuve qui permet de bien estimer l'efficience intellectuelle pré-morbide.

# Annexe 2

*Case Study: Comparing the Cognitive Profiles and MRI Markers of Two Individuals with Non-Amnestic Mild Cognitive Impairment (naMCI)*

**Annexe 2: Case Study: Comparing the Cognitive Profiles and MRI Markers of Two Individuals with Non-Amnestic Mild Cognitive Impairment (naMCI)**

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Mild cognitive impairment (MCI) is a term used to describe individuals whose performance on neuropsychological tests is deemed abnormal for their age and education level, but not impaired enough to notably interfere with activities of daily living and justify a diagnosis of dementia (Gauthier et al., 2006). Meeting criteria for MCI significantly increases the risk of progression to dementia and thus, many of these patients stand in the prodromal phase of Alzheimer's disease (AD) or a related disorder (Belleville, Cloutier, & Corriveau-Lecavalier, 2016). MCI subtypes have been identified based on their cognitive profiles. One major distinction contrasts patients with episodic memory difficulties, who are identified as individuals with amnestic MCI (aMCI), to those with cognitive deficits in other domains, who are identified as non-amnestic MCI (naMCI) patients.

Most studies have focused on aMCI because these patients have a large likelihood of progressing to dementia (Jungwirth, Zehetmayer, Hinterberger, Tragl, & Fischer, 2012). However, the non-amnestic subtype (naMCI) is interesting both clinically and scientifically. First, the naMCI subtype is quite prevalent: single-domain naMCI in older adults ranges from 3 to 15 % (Jak et al., 2009), compared to about 0.5 to 8% for single-domain aMCI patients. Second, a characteristic profile is starting to emerge for individuals with naMCI that suggests that people with this type of MCI are not only phenomenologically cohesive, but that they may share some etiological and/or clinical commonalities. For instance, studies have suggested that persons classified with naMCI are more likely to develop non-AD dementia (Busse, Hensel, Guhne, Angermeyer, & Riedel-Heller, 2006) and that persons with naMCI have a higher frequency of cardiovascular risk factors, higher Hachinski ischemic scores, and more white matter lesions on magnetic resonance imaging (MRI) (Mariani et al., 2007). The attentional-executive domain seems to be the most commonly impaired in single-domain

naMCI, followed by the semantic and the visuospatial cognitive domains (Alladi, Arnold, Mitchell, Nestor, & Hodges, 2006).

In this chapter, the clinical history, neuropsychological profile and imaging markers of two individuals with naMCI at entry are presented.

**CLINICAL CASES**

**Patient 1 (JPN)**

*History and clinical examination*

JPN is a 73 year-old French-speaking, right-handed man. He completed thirteen years of education, was an accountant and retired 10 years ago. He lives at home with his wife and has 2 children and 5 grandchildren.

Upon his first assessment, JPN reported having difficulty recalling recent events over the last two years. He mentioned being less reliable for appointments and having some difficulties with calculation. There were no reported difficulties regarding language or personal hygiene. He reported no problem with budget making and is able to pay his bills on time. He drives well but noted hesitation for directions in less familiar areas. His wife reported that JPN often forgets personal items (i.e., keys, tools) and that he leaves cabinet doors and drawers open.

The clinical history revealed hyperopia and prostatic surgery for cancer in June 2001. He has had atrial fibrillation since 1999 and high blood pressure (hypertension) since he was 42 years old, with one episode of numbness in his left hand, which led to a hospitalization in 1987. There is no diabetes. Other vascular risk factors include hyperlipedemia and smoking. He obtained a score of 10 on the Hachinski scale, which is above the recommended cutoff

(7). He takes the following medication: synthroid, anastore, diltiazem, citalopram. JPN reported no family history of dementia.

Clinical examination indicated a blood pressure (BP) of 160/85. The pulse (72) was regular. General neurological exam was normal. The result on the Boston Naming Test was 14/15 and the clock was well drawn. Functional autonomy was preserved based on both the patient's and the spouse's interview.

### *Neuropsychological examination*

Results from the neuropsychological testing are shown in Table 1. Errors on the third inhibition plate of the Stroop test are indicative of difficulties with executive functions, particularly with inhibition. When asked to copy the Rey figure, JPN showed construction apraxia (see figure 1). The neuropsychological profile was also characterized by psychomotor slowing (Coding and reading/naming plates of the Stroop test). He showed no major verbal memory problems.

**Table 1.** JPN's results on the neuropsychological tests

| | At entry | | 18-month follow-up | |
|---|---|---|---|---|
| | raw score | z score | raw score | z score |
| **Global Cognition** | | | | |
| Mattis | 132 | -3.63* | 103 | -15.7* |
| MMSE | 27 | | 27 | |
| **Processing Speed and Executive Functions** | | | | |
| Coding | 20 | -2.0* | NA** | |
| Stroop Victoria, color | 27.53 | 2.47* | 47.59 | 6.4* |
| Stroop Victoria, word | 28.59 | 1.87 | 52.66 | 6.6* |
| Stroop Victoria, inhibition | 72.91 | 2.56* | 119.07 | 6.0* |
| Stroop Victoria, errors | 2 | 1.22 | 1 | ,3 |
| **Verbal Memory** | | | | |
| RL/RI, immediate recall | 14 | -1.62 | 13 | -2.9* |
| RL/RI, delayed recall | 11 | -,18 | 4 | -3.7* |
| **Language** | | | | |
| Boston Naming Test | 10 | -1.5 | 7 | -3.1* |
| **Visuo-Perceptual Functions** | | | | |
| Benton, line orientation | 19 | -1.33 | NA** | |
| **Constructional Functions** | | | | |
| Rey complex figure test, copy | 13,5 | -5.14* | NA** | |

*Notes:* *Indicates that the patient is impaired.
**Indicates that the patient is unable to do the task.
RL/RI: *Rappel libre/Rappel indicé* (French for Free Recall/Cued Recall)
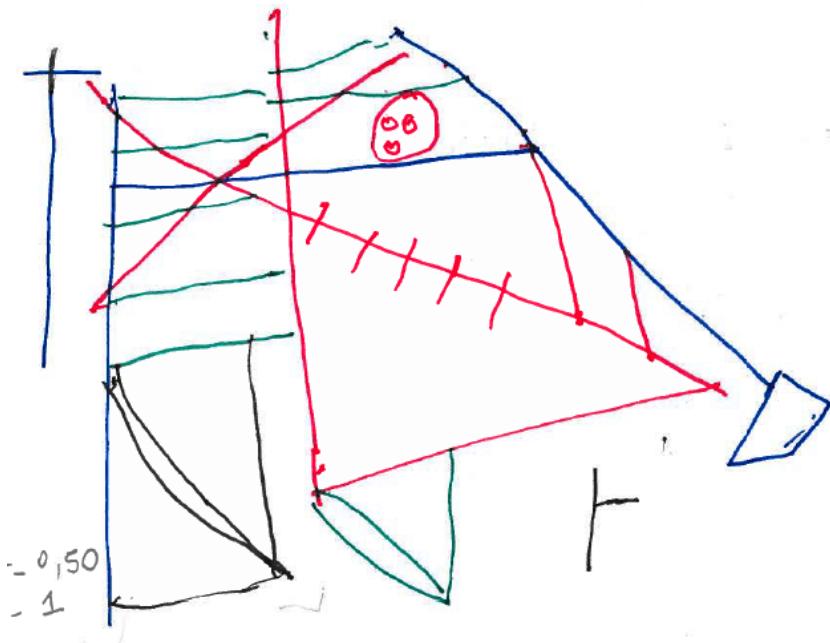
*Figure 1*. JPN's Rey Complex Figure, Copy Trial

***Neuroimaging examination***

At entry, the MRI showed diffuse cortical and subcortical atrophy, particularly in the right temporal region with right ventricular ectasia (see figure 2). Slightly higher than average white matter hyperintensities were found based on a sample of healthy older adults who were scanned as part of SB's studies on brain aging (Total White Matter Hyperintensities (TWMH) = $6^2$ (z = 0,73)), with moderate demyelination in the parieto-occipital regions.

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[2] The presence of white matter lesions was assessed by T2- weighted MRimaging examination with fluid-attenuated inversionrecovery (FLAIR). White matter lesions were assessed by an independent experienced neuroradiologist and were quantified using the rating scale for age-related white matter changes (ARWMC) criteria proposed by Wahlund et al. (2001), a four-point scale (0: no lesion, 1: focal lesions, 2: beginning confluence of lesions, 3: diffuse involvement of entire region) rated on five brain areas (frontal, parieto-occipital, temporal, infratentorial/cerebellum and basal ganglia) (Villeneuve, Massoud, Bocti, Gauthier, & Belleville, 2011). TWMH is the sum for all four regions.

Corrected hippocampal volume is higher than average (Left (L): 0,21[3] of total intra-cranial

volume (ICV) z = 2.5; Right (R): 0.18 ICV z = 0.5).

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[3] Hippocampal volumes were normalized to head size using the formula: (Hippocampal volume/ICV). All volumes were measured by a single experienced rater, blind to participant diagnosis (Peters, Villeneuve, & Belleville, 2014). Intracranial volume (ICV) was measured following the procedure of Eritaia et al. (2000).

**AT ENTRY**          **18 MONTHS LATER**

JPN
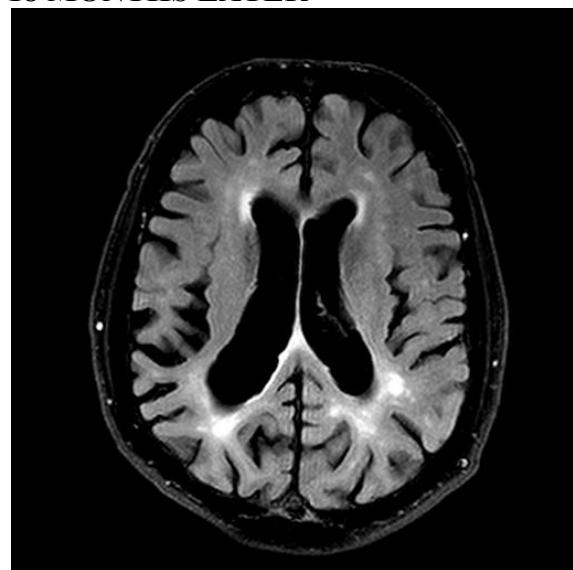
CM
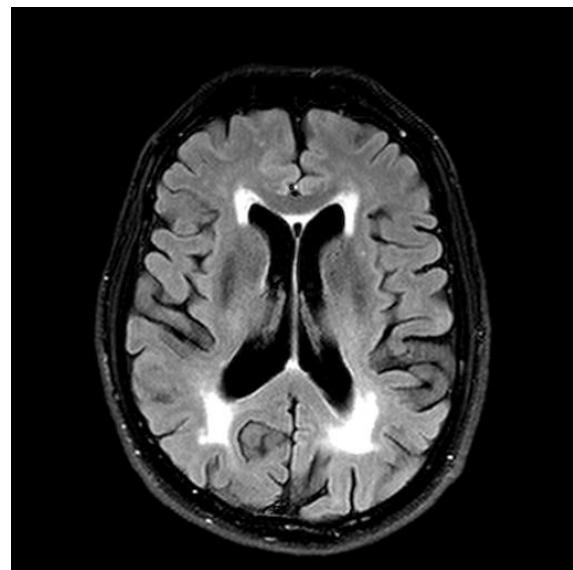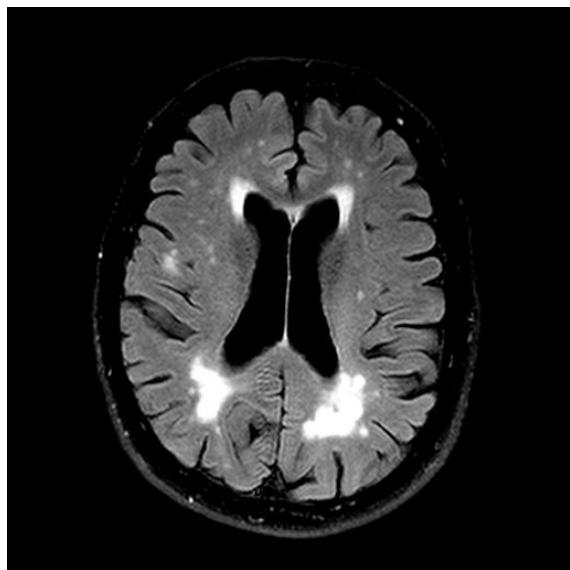
*Figure 2.* MRI scans of patients 1 (JPN) and 2 (CM) at entry (left column) and at follow-up (right column), 18 months later.

### *Diagnostic impression at initial assessment*

Multiple-domain naMCI.

*18-month follow-up examination*

The examination was repeated 18 months following the initial assessment. The clinical examination showed a progression of symptoms, with a significant cognitive decline. The score on the MoCA was 24/30, and JPN failed the clock-drawing task. Furthermore, functional autonomy was significantly affected at this point. Neuropsychological testing (see table 1) showed that the impairment had increased in severity, and additional domains were found to be impaired. Notably, memory deficits appeared in the cognitive profile, with impairment on both immediate and delayed recall of verbal information. The MRI scan showed an increase in cortical atrophy (see figure 1). Furthermore, the volume of the left and right hippocampus significantly decreased after 18 months compared to the initial scan and is now below average (L: 0.13 ICV $z = -1,5$; R: 0.11 ICV $z = -3$). White matter hyperintensities remained stable ($6 z = 0.73$). The diagnosis at the 18-month follow-up was one of mixed dementia.

**Patient 2 (CM)**

*History and clinical examination*

CM is a 72 year-old French-speaking, right-handed male. He completed seven years of education, was a salesman and retired 10 years ago. He lives at home with his wife and has 3 children.

Upon the initial assessment, CM reported progressive difficulties with recall over the last two years. He mentioned hesitating when trying to remember words and names and losing things around the house. He pays his bills on time, drives well, but reported hesitation for directions in less familiar routes. No impairments in self-care activities were reported.

CM takes the following medication: aspen (80 mg), quinine (300 mg), apo-trazodone (50 mg), zocor. His vascular risk factors include hypercholesterolemia, heart murmur (clogged artery leading to right carotid endarterectomy in 2002), and transient ischemic attack. He obtained a Hachinski score of 6, just below the cutoff (7). CM reported no family history of dementia, but his father suffered from stroke.

At clinical examination, his BP was 120/70. His pulse (72) was regular with no carotid bruits. CM obtained a perfect score on the MMSE (30/30). The result on the Boston Naming Test was 15/15 and the clock was well drawn.

### *Neuropsychological examination*

On neuropsychological testing, CM showed errors on the third inhibition plate of the Stroop test, which is indicative of difficulties in executive functioning. He also had an impaired score on the Mattis dementia rating scale due to problems in attention, initiation, concepts, and memory.

**Table 2.** CM's results on the neuropsychological tests

| | At entry | | 18 months follow-up | |
|---|---|---|---|---|
| | raw score | z score | raw score | z score |
| **Global Cognition** | | | | |
| Mattis | 130 | -2.4* | 135 | -1.1 |
| MMSE | 30 | | 28 | |
| **Processing speed and Executive Functions** | | | | |
| Coding | 48 | -.3 | 46 | -.3 |
| Stroop Victoria, color | 14,41 | -.1 | 16.80 | .4 |
| Stroop Victoria, word | 19,63 | -.1 | 20.81 | .3 |
| Stroop Victoria, inhibition | 40,10 | .1 | 38.09 | -.1 |
| Stroop Victoria, errors | 4 | 3.1* | 5 | 4.0* |
| **Verbal Memory** | | | | |
| RL/RI, immediate recall | 16 | .9 | 15 | -.4 |
| RL/RI, delayed recall | 9 | -.8 | 13 | .7 |
| **Language** | | | | |
| Boston Naming Test | 11 | -1 | 12 | .5 |
| **Visuo-Perceptual Functions** | | | | |
| Benton, line orientation | 25 | .6 | 26 | .6 |
| **Constructional Functions** | | | | |
| Rey complex figure test, copy | 30 | -.8 | 30 | -.8 |

*Notes:* *Indicates that the patient is impaired.
RL/RI: *Rappel libre/Rappel indicé* (French for Free Recall/Cued Recall)

### *Neuroimaging examination*

The MRI showed white matter changes and small lacunar infarcts (centrum semiovale). There were also significantly higher than normal white matter hyperintensities (TWMH = 12 (z = 2,97)), with moderate demyelination in the frontal and parieto-occipital regions. Hippocampal volume was average (L: 0,16 ICV z = 0; R: 0,18 z = 0,5). There was no significant cortical atrophy.

*Diagnostic impression at initial assessment*

Single domain naMCI with a vascular component.

*18-month follow-up examination*

CM showed a slight decrease on his MMSE score (28/30). Otherwise, CM was stable on all neuropsychological tests (see table 2). His mild executive difficulties remained present but were not more severe than when he was first tested and he did not develop deficits in other domains. The MRI showed no changes in terms of cortical volume. Hippocampal volumes were slightly reduced relative to the previous examination but remained within the average range (L: 0.15 z = -0.5; R: 0.15 z = -1). White matter hyperintensities remained stable (10 z = 2.14). Thus, CM still meets criteria for naMCI with a vascular component, but cognition and neuroimaging markers are stable.

## DISCUSSION

We presented two patients who met criteria for naMCI at entry: both had vascular co-morbidities, and were impaired on the Stroop task, which is indicative of deficits in executive functions. However, they markedly differed in their clinical progression as JPN converted to mixed dementia, whereas CM remained stable at follow-up. Furthermore, there were some striking differences in their MRI and neuropsychological characteristics. JPN's impairment covered multiple domains including processing speed and construction abilities. Thus, compared to CM's cognitive profile, JPN's global cognitive profile can be described as more severely impaired, with subclinical difficulties on multiple domains (language, immediate recall, etc.). Regarding the MRI markers, JPN showed slightly higher than average white matter hyperintensities, but significant cortical atrophy, and a marked reduction in

hippocampal volume from the initial MRI to the follow-up scan. There was a significant amount of white matter hyperintensities in CM, but very little if any cortical and hippocampal atrophy. This pattern is consistent with the notion that the cumulative effect of brain insults (e.g., atrophy + white matter changes) increases vulnerability and is associated with larger cognitive impairment and decline.

## ACKNOWLEDGEMENTS

## References

Alladi, S., Arnold, R., Mitchell, J., Nestor, P.J., & Hodges, J.R. (2006). Mild cognitive impairment: applicability of research criteria in a memory clinic and characterization of cognitive profile. *Psychological Medicine, 36*, 507-515. doi: 10.1017/S0033291705006744

Belleville, S., Cloutier, S., & Corriveau-Lecavalier, N. (2016). Mild Cognitive Impairment. In N. A. Pachana (Ed.), *Encyclopedia of Geropsychology* (pp. 1-11): Springer Singapore.

Busse, A., Hensel, A., Guhne, U., Angermeyer, M. C., & Riedel-Heller, S. G. (2006). Mild cognitive impairment: long-term course of four clinical subtypes. *Neurology, 67*(12), 2176-2185. doi: 10.1212/01.wnl.0000249117.23318.e1

Eritaia, J., Wood, S. J., Stuart, G. W., Bridle, N., Dudgeon, P., Maruff, P., . . . Pantelis, C. (2000). An optimized method for estimating intracranial volume from magnetic resonance images. *Magn Reson Med, 44*(6), 973-977.

Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R. C., Ritchie, K., Broich, K., . . . International Psychogeriatric Association Expert Conference on mild cognitive, impairment. (2006). Mild cognitive impairment. *Lancet, 367*(9518), 1262-1270. doi: 10.1016/S0140-6736(06)68542-5

Jak, A. J., Bangen, K. J., Wierenga, C. E., Delano-Wood, L., Corey-Bloom, J., & Bondi, M. W. (2009). Contributions of neuropsychology and neuroimaging to understanding clinical subtypes of mild cognitive impairment. *Int Rev Neurobiol, 84*, 81-103. doi: 10.1016/S0074-7742(09)00405-X

Jungwirth, S., Zehetmayer, S., Hinterberger, M., Tragl, K. H., & Fischer, P. (2012). The validity of amnestic MCI and non-amnestic MCI at age 75 in the prediction of Alzheimer's dementia and vascular dementia. *Int Psychogeriatr, 24*(6), 959-966. doi: 10.1017/S1041610211002870

Mariani, E., Monastero, R., Ercolani, S., Mangialasche, F., Caputo, M., Feliziani, F. T., . . . Re, GAl Study Group. (2007). Vascular risk factors in mild cognitive impairment subtypes. Findings from the ReGAl project. *Dement Geriatr Cogn Disord, 24*(6), 448-456. doi: 10.1159/000110653

Peters, F., Villeneuve, S., & Belleville, S. (2014). Predicting progression to dementia in elderly subjects with mild cognitive impairment using both cognitive and neuroimaging predictors. *J Alzheimers Dis, 38*(2), 307-318. doi: 10.3233/JAD-130842

Villeneuve, S., Massoud, F., Bocti, C., Gauthier, S., & Belleville, S. (2011). The nature of episodic memory deficits in MCI with and without vascular burden. *Neuropsychologia, 49*(11), 3027-3035. doi: 10.1016/j.neuropsychologia.2011.07.001

Wahlund, L. O., Barkhof, F., Fazekas, F., Bronge, L., Augustin, M., Sjogren, M., . . . European Task Force on Age-Related White Matter, Changes. (2001). A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke, 32*(6), 1318-1322.