An examination of semantic performance in MCI progressors and non-progressors

Émilie Delage[a,b], Isabelle Rouleau[c,d], Marc-Antoine Akzam-Ouellette[a,b] Frédérique Roy-Côté[a,d], Sven Joubert[a,b] and the CIMA-Q*

[a] Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal (CRIUGM), Montreal, QC, Canada

[b] Département de Psychologie, Université de Montréal, Montreal, QC, Canada

[c] Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, QC, Canada

[d] Département de Psychologie, Université du Québec à Montréal, Montreal, QC, Canada

Correspondence: Sven Joubert, CRIUGM, 4545 Queen-Mary road, Montreal, Quebec, H3W 1W5, Canada, email: sven.joubert@umontreal.ca

* Data used in the preparation of this article was obtained from the Consortium for Early Identification of Alzheimer's disease - Quebec (CIMA-Q; cima-q.ca). CIMA-Q researchers contributed to the establishment of protocols, implementation of the cohort, obtaining clinical, cognitive and neuroimaging data as well as collection of biological samples. A list of researchers involved in the design of CIMA-Q can be found on the cima-q.ca website.

Acknowledgements
ED received funding in the form of a PhD FRQ-S doctoral award. FRC received funding from the CIMA-Q. SJ and IR were funded by a grant (19-16) from the Alzheimer Society Research Program (Alzheimer Society of Canada).

Authors contribution: SJ, IR, ED were responsible for conception and design of the study. ED, SJ, IR, MAAO and FRC contributed to statistical analyses or data and interpretation. All authors contributed to drafting the manuscript and ED was responsible for drafting the tables and figures. All authors reviewed the manuscript and approved the final version of the manuscript.

Conflict of Interest
none

Abstract

Background. Mild Cognitive Impairment (MCI) is a risk factor for developing Alzheimer's disease (AD), and about half of older people with MCI will progress to AD within the next five years. The aim of the present study was to compare the semantic performance of MCI progressors (MCI-p) and non-progressors (MCI-np). The hypothesis was that MCI-p would present with poorer semantic performance relative to MCI-np at baseline, indicating that semantic deficits may increase the risk of future decline toward AD.

Method. Fifty-six MCI participants (aged 65-89) from the CIMA-Q study were analyzed, with 18 progressing and 38 remaining stable over two years. ANCOVA assessed their initial semantic and non-semantic cognitive performance, and mixed ANOVAs gauged longitudinal patterns of cognitive decline at the 2-year follow-up.

Results. In the semantic domain, MCI-p performed significantly worse than MCI-np at baseline on two semantic tests (category fluency and object decision). In other cognitive domains, MCI-p performed worse than MCI-np on a test of executive functions (cognitive flexibility) but showed similar performance on a test of episodic memory. There were no significant differences between groups in the rates of progression on semantic tests over the 2-year period, but a steeper decline was observed in MCI-p at follow-up on tests of global cognition, episodic memory, and processing speed.

Conclusion. This suggest that MCI patients who present with semantic memory impairment in addition to episodic memory impairment are at greater risk of future progression to AD.

Keywords: MCI; Alzheimer's disease; Semantic memory; neuropsychological predictors.

Key Points summary:

Question: This study investigates the differences in cognition between patients with mild cognitive impairment (MCI) that ultimately progressed, or not, to Alzheimer's disease. **Findings:** Those who progressed displayed heightened deficits in both semantic memory and cognitive flexibility at baseline compared to stable patients, while both groups exhibited similar levels of general cognition and episodic memory. **Importance:** This suggests that older people with MCI who experience deficits in both semantic memory (memory of world facts and common knowledge) and episodic memory (memory of personal life events) are at greater risk of progressing towards Alzheimer's disease than those with deficits solely in episodic memory. **Next steps**: To refine our understanding of the prognostic value of different semantic tests in MCI progression, future studies employing longitudinal designs with larger participant cohorts and a more extensive array of neuropsychological tests would be beneficial.

Introduction

Early diagnosis of Alzheimer's disease (AD) is a major research objective, as pharmacological and non-pharmacological interventions may be more effective in the earliest stages of the disease, prior to clinical diagnosis. Mild cognitive impairment (MCI) is considered by many as a transitional stage between healthy aging and AD (Dubois et al., 2010). Older adults with MCI show mild deficits on neuropsychological tests, without meeting the criteria for dementia. They typically have a memory complaint, which is confirmed by impaired performance on objective memory tests. MCI is a significant risk factor for developing AD: the rate at which MCI patients progress to AD in clinically based studies is 10% to 15% per year (Petersen et al., 1999).

Some MCI patients remain stable over time, however, or even revert to normal at follow-up (Summers & Saunders, 2012). This highlights MCI heterogeneity and the importance of identifying MCI patients who are more likely to progress to AD. Large epidemiological studies have explored the longitudinal trajectories of cognitive and behavioral symptoms in cognitively normal older adults, some of whom developed AD over time. Amieva et al. (2008) followed 3777 cognitively normal older adults over fourteen years. Over the course of the study, 350 of them developed AD. Normal older adults who later developed dementia showed signs of cognitive decline as early as twelve years prior to their diagnosis. In fact, the first identifiable cognitive decline was observed in a category fluency task, a semantic task that requires generating as many exemplars as possible of a conceptual category (e.g., animals) in a limited period of time. A more recent longitudinal study (Payton et al., 2022) followed 1646 individuals for 12 years, and compared the 220 who later developed AD with the other participants. Findings showed that category fluency, along with global cognition and word recall, declined at a higher rate in the time frame from 12 to 6 years prior to diagnosis. Other cognitive domains, such as perceptual speed and executive functions, showed a higher rate of decline only in the time frame from 6 to 0 years prior to diagnosis. Another large epidemiological study conducted by Wilson et al. (2011) followed 1511 cognitively healthy older participants annually for up to 16 years, of whom 217 developed AD. Results indicated that individuals who later developed AD showed an initial decline in semantic memory about 6.3 years prior to diagnosis, and later working memory, perceptual speed, visuospatial skills and episodic memory were affected (respectively 75, 70, 65 and 63 months before diagnosis).

In the past decade or more, a growing number of cross-sectional studies have shown that semantic memory is consistently impaired in MCI (see Joubert et al., 2021 for a recent review and meta-analysis). Semantic memory concerns general knowledge about the world, including language, knowledge about objects, people, places, historical facts or events, scientific knowledge, acquired over a lifetime. Some studies showed that MCI patients were disproportionately impaired in category fluency compared to phonemic fluency, in comparison with healthy controls (Adlam et al., 2006; Chasles et al., 2019; Monsch et al., 1997; Murphy et al., 2006; Vonk et al., 2020; Wright et al., 2022). This

suggests selective deficits in the retrieval or storage of semantic knowledge. In other studies, MCI patients were impaired on picture naming tasks that required naming pictures of common biological and man-made entities. MCI patients provided less spontaneous answers than controls on these tasks (Ahmed et al., 2008; Balthazar et al., 2008; Joubert et al., 2010; Joubert et al., 2008; Salehi et al., 2017; Taler et al., 2020) and made more errors (Gallant et al., 2019), in particular, more semantic errors (Salehi et al., 2017). Similarly, MCI patients provided less spontaneous answers and made more mistakes when they had to name faces and answer questions about famous faces and people (Ahmed et al., 2008; Barbeau et al., 2012; Joubert et al., 2010; Joubert et al., 2008; Rahmani et al., 2019), famous public events (Barbeau et al., 2012; Benoit et al., 2018; Joubert et al., 2008; Langlois et al., 2016) and famous buildings (Ahmed et al., 2008). MCI patients also experienced difficulties when they had to associate words or pictures and answer yes/no semantic questions (Taler et al., 2020). Finally, MCI patients showed reduced semantic priming of famous names despite normal repetition priming (Brambati et al., 2012), suggesting disrupted semantic knowledge in MCI. In summary, these studies showed that semantic deficits have consistently been reported in MCI across a wide range of naming and semantic tasks relative to age and education matched healthy older adults.

These studies were all cross-sectional, however, and cannot inform us on the causal relationship between semantic deficits and risk of progression to AD. In fact, not all MCI patients present with semantic deficits. For instance, one study reported that only about half of MCI patients showed impaired performance on semantic tests (Joubert et al., 2008). Thus, longitudinal studies are needed to determine if the presence of semantic deficits in MCI patients may increase the risk of future progression to AD. Episodic memory impairment is one of the core clinical criteria of MCI, however it is non-specific and may be present in a range of other health conditions, accounting in part for MCI heterogeneity. Therefore, an important question to address is whether MCI patients with episodic and semantic memory deficits have a greater risk of progression to AD than MCI patients without semantic deficits. To our knowledge, only a few recent longitudinal studies have studied the prognostic value of semantic impairment. Gallucci et al. (2018) studied a group of patients with MCI at baseline, who progressed or not to AD at a two-year follow-up. They found that performance within the normal range on the category fluency test and on RAVLT delayed recall was protective against the onset of dementia. Similar results were found by Sutin et al. (2019), showing that better performance on the category fluency test was associated with a lower risk of conversion from MCI to dementia over the 6-year follow-up period. Garcia et al. (2021) showed that MCI patients who developed AD were significantly impaired at baseline on a task that involved naming famous faces compared to those who did not progress. A meta-analysis (Prado et al., 2019) reviewed 24 studies published between 1997 and 2018 that evaluated progression from MCI to AD, based on neuropsychological test results. Findings showed that MCI progressors performed worse than non-progressors in many cognitive domains, including expressive language (evaluated

with semantic tests such as picture naming and category fluency). Another meta-analysis (Belleville et al., 2017) showed that semantic memory tests have high sensitivity and specificity required to predict progression from MCI to AD. Longitudinal studies using a variety of semantic tests are needed to support the idea that semantic deficits may help improve prognosis in MCI.

The primary aim of the current study was to investigate performance on different semantic tests in MCI progressors and MCI non-progressors. Our hypothesis was that, at a 2-year follow-up, MCI progressors would be significantly impaired on semantic tests at baseline, relative to MCI patients who remained stable. A secondary aim of the study was to compare both groups in other cognitive domains such as episodic memory and executive functions. Our hypothesis was that MCI progressors would be significantly impaired at baseline on an episodic memory (learning) test relative to MCI patients who remained stable. To this end, we compared the performance at baseline of MCI participants who declined at follow-up (MCI progressors) versus those who remained stable (MCI non-progressors) at a 2-year follow-up.

Methods

2.1 Design

The data used in this article was obtained from the *Consortium pour l'identification précoce de la Maladie d'Alzheimer – Québec* (CIMA-Q) (Belleville et al., 2019), a research group founded in 2013 with an initial grant from the Fonds de Recherche du Québec – Pfizer. The long term research effort of CIMA-Q was to build a cohort of elderly men and women characterized in terms of clinical outcomes, cognition, neuroimaging, and biological samples with the following objectives: (1) to establish early diagnosis of Alzheimer's disease; (2) to provide the scientific community with a well-characterized cohort; and (3) to identify new therapeutic targets allowing to prevent or slow down the cognitive decline and Alzheimer's disease (4) via subsequent clinical studies. CIMA-Q represents a common effort by several researchers from Québec affiliated with Université Laval, McGill University, Université de Montréal, and Université de Sherbrooke, led by principal investigator and director Dr. Sylvie Belleville from the Centre de recherche de l'Institut universitaire de gériatrie de Montréal, affiliated with the CIUSSS Centre-sud-de-l'ile-de-Montréal. Since 2014, CIMA-Q has recruited 350 cognitively healthy participants with subjective cognitive impairment, mild cognitive impairment, or Alzheimer's disease. Volunteers were recruited from memory clinics, through advertisements posted in the community, and from among participants in the NuAge population study (Gaudreau et al., 2007). The present study was approved by the research ethics board of the IUGM (CER-VN-IUGM) and by CIMA-Q. Further details on the CIMA-Q study can be found in the reference paper by Belleville and collaborators (2019) .

The CIMA-Q study methodology included a neuropsychological assessment, standardized neuroimaging, and biological sampling of participants, carried out at different time points. Prior to participation, a telephone pre-screening interview was conducted with each participant, during which the project was explained, informed verbal consent was obtained and the presence of a memory complaint with or without concerns was documented. At the first visit (baseline), a standardized clinical evaluation and questionnaires to measure health, lifestyle, cognitive complaints, clinical expression, functional impact, and emotional and behavioral symptoms were administered. Participants then came back for a second visit, during which blood samples were obtained, and a standardized neuropsychological and neuropsychiatric evaluation was conducted by a CIMA-Q-certified psychometrician. At that same visit, participants who agreed to the optional procedures underwent an MRI and/or PET scan and/or lumbar puncture for cerebrospinal fluid (CSF) collection. The CSF collection was done by a neurologist who obtained 10-15 mL of fluid, per the recommendations per the Alzheimer's disease neuroimaging initiative (Darby et al., 2015). CSF analyses were carried out to determine the levels of amyloid-beta 38, 40 and 42 peptide and total tau protein, see Belleville et al. (2019) for details.

Because one of the goals of CIMA-Q is to detect individuals at risk of developing AD, the participants of the CIMA-Q cohort had a follow-up full assessment every two years after the initial baseline assessment (2, 4 and 6-year follow-ups). The follow-ups included the clinical, neuropsychological, and neuropsychiatric evaluations, blood samples, and neuroimaging when applicable.

In the current study, we performed a retrospective analysis of longitudinal data in MCI participants and healthy older control participants at baseline and at the 2-year follow-up. We did not include data from later follow-ups in the CIMA-Q study, due to attrition of participants, insufficient sample sizes for the purpose of the present project (explained in part by the COVID-19 pandemic), and the fact that not all participants were seen at all time points.

2.2 Participants

The present study included 2 groups of participants from the CIMA-Q cohort who were assessed both at baseline and after 2 years. The two groups included 18 MCI progressors and 38 MCI non-progressors (N=56 MCI participants). The participants were at least 65 years old and were native French or English speakers.

All MCI participants met the criteria for MCI at baseline, as assessed by the CIMA-Q team and based on the National Institute on Aging and the Alzheimer’s Association (NIA-AA) clinical criteria for MCI (Albert et al., 2011). These criteria included: (a) a reported memory decline; (b) an objective memory impairment based on the WMS-III Logical Memory II score, adjusted for education; (c) a score between 20 and 26 on the MoCA; and (d) a score of 0.5 on the Clinical Dementia Rating Scale. As the criteria is

based on the memory impairment, all MCI patients are amnestic MCI. All MCI patients were subdivided into early and late stages based on their MoCA score and the AD Neuroimaging Initiative criteria (Albert et al., 2011). The group of MCI progressors (MCI-p) included 18 MCI participants (8 females and 10 males) and included both early-MCI (N = 12) and late-MCI participants (N = 6). The CIMA-Q team classified patients at different points in time, independently from the researchers who conducted the present study. MCI participants were classified as progressors when they progressed from early-MCI to late-MCI (N = 8) or from MCI to AD (N = 10) between baseline and the 2-year follow-up assessment. The criteria for AD was based on the NIA/AA criteria (McKhann et al., 2011), which include cognitive symptoms that interfere with the ability to function at usual activities, has an insidious onset and an history of worsening of cognition by report or observations, and has most prominent cognitive deficits in the amnestic presentation . Also, AD patients had to score between 13 and 25 on the MoCA test.

The group of MCI non-progressors (MCI-np) included 38 participants (20 females, 18 males). MCI participants were classified as non-progressors if their MCI status remained stable at the 2-year follow-up (N=26), if they reverted from late-MCI to early-MCI within that time frame (N=4) or if they reverted from MCI to normal cognition (N=8). More specific inclusion and exclusion criteria for groups can be found in the supplementary material of the article describing the CIMA-Q project (Belleville et al., 2019).

2.3 Cognitive Assessment

Semantic memory was assessed based on results from a) the category fluency test, in which participants must produce as many names of animals as possible in one minute; b) the Vocabulary subtest of the WAIS-IV, in which participants are required to define words; and (c) the Object Decision Subtest of the BORB, where participants must decide if line drawings are real or chimera.

Other cognitive domains were also assessed in the present study: 1) **General cognition** was assessed with the MoCA test, a short cognitive screening test (Nasreddine et al., 2005); 2) **Episodic memory** was assessed with delayed recall of the RAVLT test; 3) **Executive functions** were assessed with the Trail Making Test B/A ratio (cognitive flexibility), the Coding subtest of the WAIS-IV (processing speed), and the Letter Fluency test; 4) **Visuospatial skills** were assessed with the Line Orientation subtest of the BORB.

2.4 Statistical Analysis

2.4.1 General dataset

Our data were analyzed using the Statistical Package for the Social Sciences (IBM SPSS 28.0), with an alpha significance level set at $p<0.05$. The normality of the distribution was confirmed by analyzing the skewness and kurtosis of each variable for each group, using the cut-off recommended by Curran et al. (1996) of respectively +/-2 and +/-7. Q-Q plots for each variable were also examined. Preliminary analysis showed that not more than 5%

of data was missing for each variable used in the analysis. Independent samples t-tests were carried out to determine if there were significant differences between the 2 MCI groups (MCI-p, MCI-np) in terms of demographic characteristics. In case of non-normal distribution, Mann-Whitney U-tests were carried out.

2.4.2 Cognitive tests

The main goal of this study was to determine if MCI participants who had declined from baseline at a 2-year follow-up had shown significantly greater difficulties on semantic tests than MCI non-progressors. The secondary goal was to compare the performance of both MCI groups in other cognitive domains, including episodic memory. For the semantic domain, univariate ANCOVA (covariates: age, education and sex) were carried out for the three semantic tests (category fluency test, object decision and vocabulary) to determine if there were significant differences between MCI progressors and non-progressors at baseline, and nonparametric Mann-Whitney U-tests in case of non-normal distribution. For the category fluency test, the letter fluency score was also added as a covariate. This allows to statistically control for the executive component of verbal fluency and isolate semantic processing (Papp et al., 2016).

The same analysis (ANCOVA with age, education, and sex as covariates) was applied for the other cognitive domains, including episodic memory, executive functions and visuospatial skills. Bonferroni corrections were applied for multiple comparisons within each cognitive domain, when necessary. In order to assess the diagnosis performance of our variables, we conducted Receiver Operating Characteristic (ROC) curves. For variables where the area under the curve (AUC) was significant, we determined the optimal classification threshold using the Youden's Index, which calculates the cut-off value that optimizes both sensitivity and specificity of the model. Although there is no consensus in the literature about the labelling of AUC (de Hond et al., 2022), we used the common criteria and considered that AUC below .7 was low, between .7 and .8 was acceptable, between .8 and .9 was good and over .9 was excellent.

Finally, to explore if there were different patterns of longitudinal decline in MCI groups, mixed ANOVAs were performed for the cognitive tests that enabled differentiating MCI progressors from non-progressors at baseline, with Group (MCI-p and MCI-np) as the between-group factor and Time (Baseline and 2-year Follow-up) as the within-subject factor.

2.5 Transparency and openness

Materials and data for this study are not available without the CIMA-Q authorization. In adherence to transparent reporting guidelines (Nosek et al., 2015), additional information regarding sample size, data exclusions (if applicable), manipulations, and the measures employed can be provided upon reasonable request. Note that this study was not pre-registered.

Results

Demographic data. Results of the two groups of participants (MCI-p and MCI-np) are presented in Table 1. There were no significant differences between MCI progressors and MCI non-progressors on any of the variables. Results indicate that the 2 groups did not differ significantly in terms of age ($t(54)=1.62$, $p=0.11$), education ($t(53)=-1.22$, $p=0.23$), memory complaint score ($t(54)=-0.10$, $p=0.92$), depressive symptoms ($t(54)=0.03$, $p=0.98$), anxiety symptoms ($t(54)=-0.84$, $p=0.40$), insomnia ($t(54)=-0.67$, $p=0.51$), daily sleepiness ($t(53)=0.90$, $p=0.37$), vascular health ($t(52)=0.50$, $p=0.62$), csf-Aβ42 levels ($t(10)=-1.54$, $p=0.15$) and csf-tau levels ($t(10)=0.58$, $p=0.58$). Finally, chi-square analysis did not reveal a significant difference in the proportion of males and females ($\chi 2=0.33$, $p=0.57$) or in the proportion of ApoE4 carriers ($\chi 2=0.73$, $p=0.39$) between MCI groups.

Neuropsychological tests

Semantic tests. Results of MCI-p and MCI-np participants on the neuropsychological tests are summarized in Table 2. Our first analysis compared the performance of MCI-p and MCI-np groups on semantic tests (category fluency, object decision and vocabulary) at baseline, when controlling for age, education and sex. Results showed a significant difference between progressors and non-progressors on the category fluency test ($F(1,48)=4.39$, $p=0.04$ $\eta^2 = 0.08$), with progressors producing on average 3 fewer names of animals than non-progressors in one minute ($\bar{X}$ MCI-p=14.8 words, sd=3.82; $\bar{X}$ MCI-np=17.7 words, sd=3.89). Results also showed that MCI progressors were impaired relative to non-progressors on the object decision subtest ($F(1,49)=4.82$, $p=0.03$ $\eta^2= 0.09$), but not on the Vocabulary subtest ($F(1,49)=0.25$, $p=0.62$). These results remained significant after Bonferonni corrections for multiple comparisons.

Also, because category fluency (animals) was significantly impaired in the MCI-p group relative to the MCI-np group, further exploratory analyses were carried out in regard to semantic productions to explore if there were between-group differences in mean cluster size (number of exemplars in a cluster) and number of switches between subcategories (a subcategory corresponds to a category of animals: domestic animals, wild animals, etc.), based on a previously published method (Troyer et al., 1997). The present study also analyzed the mean number of different subcategories mentioned, an aspect of word production not addressed in the previous reference. Since Troyer et al. (2000; 1997; 1998) used 22 subcategories for their analysis, it was possible to extract an index based on these subcategories. All responses for the three indexes (mean cluster size, number of switches, number of subcategories) were extracted with an algorithm in Python that went through the list of animal names produced by each participant and then grouped each animal to its corresponding subcategory, while also measuring the number of switches simultaneously. In the end, the number of subcategories for which there was a response represented the number of different subcategories mentioned. A MANOVA was performed to examine the

multivariate pattern of responses of MCI-p compared to MCI-np (number of switches: MCI-p $\bar{X}(sd)$=6.83 (2.43); MCI-np $\bar{X}(sd)$=8.47 (2.46); number of subcategories: MCI-p $\bar{X}(sd)$=10.5 (2.04); MCI-np $\bar{X}(sd)$=11.7 (1.30); mean cluster size: MCI-p $\bar{X}(sd)$=2.28 (0.41); MCI-np $\bar{X}(sd)$= 2.45 (0.42)). The results show a significantly different pattern of responses for the MCI-p group compared to the MCI-np group (Wilk's Δ = 0,832, F [3] = 3,502, p < 0,05, T^2 = 0,17). The canonical variable is 0.41, which indicates a moderate relationship between group membership and the three variables (Tabachnick et al., 2013). Saturations of the three dependent variables are 0.74 for the number of switches, 0.81 for the number of different subcategories mentioned and 0.48 for the mean cluster size, which indicates that both the number of switches and the number of different subcategories are most associated with differences between the two groups.

Executive functions. In the executive functions domain, groups did not differ on the Coding subtest (processing speed) (F(1,49)=0.78, p=0.38) or on the letter fluency test (F(1,49)=1.23, p=0.27). However, groups differed significantly on the TMTB/A ratio (cognitive flexibility) (F(1,46)=8.76, p=0.005 η^2= 0.16).

Other cognitive domains. Regarding non-semantic cognitive domains at baseline, MCI-p and MCI-np groups did not differ on the MoCA (general cognition; F(1,30)=1.55, p=0.22) and on the Line orientation test (visuospatial domain; F(1,49)=0.08, p=0.78). Finally, in the episodic memory domain, MCI-p and MCI-np groups did not differ on the RAVLT delayed recall (F(1,50)=0.15, p=0.70).

ROC analysis. In terms of predictive accuracy, the ROC curve result indicates a fair ability in distinguishing between MCI-p and MCI-np with the category fluency score (AUC= 0.75, p<0.01). The optimal classification threshold, determined by maximizing the Youden's Index, was 15.5 words. ROC analysis also showed significant results for Object Decision (AUC= 0.73, p<0.01), with an optimal cutoff score of 28.5, and for the TMT Ratio B/A (AUC=0.73, p<0.01), with an optimal cutoff of 2.36. ROC analysis did not show a significant ability to distinguish between MCI-p and MCI-np for other variables in our study, in particular for general cognition (MoCA; AUC=0.63, p=0.14), phonemic fluency (AUC=0.64, p=0.11), and episodic memory (RAVLT delayed recall; AUC = 0.58, p=0.35). Results of the ROC analyses are presented in Table 3 and ROC curves are shown in Figure 2.

Longitudinal analysis. In terms of longitudinal progression, a mixed ANOVA showed a significant interaction between the moment of testing (baseline vs follow-up) and the participant group (MCI-p vs MCI-np) for general cognition (MoCA test; (F(1,54)=17.89, p<.001, η2=.25)), processing speed (coding subtest; (F(1,34)=4.58, p=.04, η2= .12)), and episodic memory (RAVLT; (F(1,36)=10.46, p=.003, η2=.23)). This means that for these three tests, the pattern of decline between baseline and the follow-up evaluation was different for the MCI-p and MCI-np, with MCI-p showing a more severe decline in performance than MCI-np. The patterns of decline were not different between the two groups for the other tests (category fluency (F(1,37)=0.12, p=0.73), object decision

(F(1,36)=2.05, p=0.16), TMT ratio (F(1,33)=0.03, p=0.87) and line orientation (F(1,36)=1.70, p=0.2), indicating that MCI-p and MCI-np progress at the same rate over time. See Table 3 and Figure 1a-g.

Discussion

Semantic impairment is a consistent feature of MCI (Joubert et al., 2021). However, nearly all previous studies assessing semantic memory in MCI were cross-sectional and thus it was not possible to determine if semantic impairment in MCI actually increased the risk of future progression to AD. The current study addressed this question by examining longitudinal neuropsychological data in MCI progressors and non-progressors in the CIMA-Q cohort. The semantic performance of MCI progressors and non-progressors was compared at baseline and at follow-up 2 years later.

In the first place, results showed that the MCI groups did not differ at baseline in terms of different variables such as age, education, sex, memory complaint, anxiety, depression, vascular health, insomnia, and daily sleepiness. The fact that the two groups did not differ significantly on any of these variables is important, because some, such as depression, anxiety, older age, and female gender, have been reported to impact cognitive performance and heighten the risk of conversion from MCI to AD (Li et al., 2016). Thus, in our study, differences in cognitive performance observed seem independent of these factors. More surprisingly, however, MCI groups did not differ significantly in terms of biomarkers such as csf-Aβ42 and csf-Tau levels, but this is likely because only a small subset of these patients had lumbar puncture and that biomarker results do not accurately reflect the groups. Similarly, there was a non-significant difference in APOE4 status between MCI progressors and non progressors. This result is unexpected, since APOE4 is the primary genetic risk factor for sporadic AD (Emrani et al., 2020), however similar results have been reported previously where APOE4 was associated with both stable and progressive MCI (Ganguli et al., 2019). Again, results of the current study regarding APOE4 need to be interpreted with caution due to the modest sample size.

Semantic memory. Results showed that MCI progressors performed significantly worse than non-progressors at baseline on two of the three semantic tests (category fluency and object decision). Regarding category fluency, our findings are consistent with earlier studies that demonstrated impaired category fluency in individuals with MCI (Chasles et al., 2019; Monsch et al., 1997; Murphy et al., 2006). However, most studies adopted a cross-sectional approach, comparing individuals with MCI to normal controls. Our study is one of the few that uses a longitudinal approach comparing patients who will eventually progress toward AD and those who will not (Vaughan et al., 2018; Vonk et al., 2020; Wright et al., 2022).

Category fluency has been widely used as a measure of semantic memory, although it also involves elements of processing speed and executive function (Belleville et al., 2017; Chertkow & Bub, 1990), as well as language skills (Whiteside et al., 2016). This is why it

is recommended to use both category fluency and phonemic (letter) fluency tasks (Henry & Crawford, 2004). Both tasks place similar demands on executive functions—such as the ability to generate specific words with organized efficiency, efficient retrieval of words, and inhibition of inappropriate words. However, category fluency introduces an additional component related to semantic memory. In our study, our results indicate that only category fluency, and not phonemic fluency, exhibited a significant difference between the MCI-p and MCI-np groups at baseline. It is worth pointing out that phonemic fluency was included as a covariate in the category fluency analysis, allowing to better extract the semantic component, akin to the approach taken by Papp et al. (2016). Our finding of reduced category fluency but not letter fluency performance in MCI progressors relative to non-progressors thus point to the underlying semantic nature of deficit. It is also worth pointing out that other methods, such as a phonemic/category discrepancy score, have proven useful in distinguishing semantic from executive components of verbal fluency (Marra et al., 2021; Wright et al., 2023), and may be more operational in clinical practice.

Further analysis of the category fluency task results showed that there is a significant difference between the MCI progressors' and non-progressors' responses across three variables (i.e., number of switches, number of different subcategories and mean cluster size), with a moderate effect size (Steyn Jr & Ellis, 2009). We found that the number of different subcategories and the number of switches, respectively, are most associated with group differences. Since optimal category fluency performance involves generating words within a subcategory until exhaustion and then switching to a new subcategory (Troyer, 2000), a better performance is associated with more switching, generating more subcategories, and larger cluster sizes. In this study, MCI-np demonstrated better performance than MCI-p across all three variables. The pattern of performance in the MCI-p group, which is disproportionately affected in the category fluency test compared to the phonemic fluency test, and also produces fewer words per category, smaller clusters and fewer switches between subcategories, is similar to the performance of Alzheimer's patients, as documented by Troyer et al. (1998).

The other semantic test for which the MCI-p group was significantly impaired relative to the MCI-np group was the BORB object decision test. This test assesses knowledge of visual representations of objects and (mainly) animals and requires discriminating between real and non-real line drawings. Results on this test have previously been shown to be impaired both in AD and in the semantic variant of primary progressive aphasia (svPPA) (St-Hilaire et al., 2018), but to our knowledge, this is the first study to report significantly worse performance in MCI progressors. Like the category fluency test, the object decision test is simple and brief to administer and our results suggest that it may be useful in a clinical setting in the assessment of older adults with mild neurocognitive impairment. It is important to point out that the object decision test is non-executive in nature, contrary to category fluency. Therefore, our results do not support the idea that semantic deficits in MCIp are purely executive in nature. Finally, performance of MCI

progressors and non-progressors did not differ on the Vocabulary test, which indicates that vocabulary may remain stable over the course of AD progression, or at least during the prodromal stage of the disease.

The ROC analysis in our study highlights the good discriminating ability of the category fluency and object decision tests, both allowing to distinguish between MCI-p and MCI-np at a fair level. In category fluency, using a cut-off of 15 words would distinguish which patients are in the MCI-p group with a sensitivity of 0.68 and a specificity of 0.77. Similarly, in the object decision test, using a cut-off score of 29 allows to identify patients in the MCI-p group with a sensitivity of 0.71 and a specificity of 0.77. These results enhances the clinical utility of semantic memory assessments among older patients.

Other cognitive domains

At baseline, the MCI progressor and non-progressor groups also had similar global cognitive status, as measured with the MoCA cognitive screening test. This suggests that the differences reported between the two MCI groups do not reflect differences in severity of the disease, and rule out the possibility that MCI progressors were at a more advanced stage of cognitive decline at baseline.

In terms of episodic memory, all MCI patients by definition have episodic memory deficits, since they are part of the core diagnostic features of MCI (Albert et al., 2011). However, performance on the verbal learning test (RAVLT delayed recall) did not enable differentiation of MCI progressors from non-progressors at baseline in this study. It is worth mentioning that MCI inclusion was based on performance on another episodic memory test, the logical memory test, and that the RAVLT was not used as a screening tool for MCI. Therefore, in our view it cannot be argued that similar episodic memory performance in MCI groups is related to the screening procedure.

An interesting finding of this study is the significant difference observed between the two groups in the TMT ratio B/A, which is a measure of cognitive flexibility and executive function (Arbuthnott & Frank, 2000). This result implies that decline in cognitive flexibility could potentially serve as a predictor of progression toward AD in MCI, in addition to and independently of semantic memory. Our result aligns with prior research which has also identified certain measures of executive function allowing to distinguish non-demented older adults who subsequently experience global cognitive decline from those who maintain cognitive stability (Clark et al., 2012; Junquera et al., 2020). However, a decline in executive function is not specific to AD, as it can also occur in other neurodegenerative conditions such as Parkinson's disease (Levy et al., 2002), frontotemporal dementia (Hornberger et al., 2008), as well as in non-degenerative conditions such as depression (Nuño et al., 2021), anxiety (Shields et al., 2016) and even COVID-19 (Ariza et al., 2023).

Longitudinal analyses

Longitudinal performance on semantic tests showed that while MCI-p and MCI-np groups differed at baseline on category fluency and object decision tests, semantic performance remained stable in the two groups over the course of two years. In contrast, the MCIp group declined significantly more at follow-up on the MoCA (global cognition) and on the delayed recall of the RAVLT (episodic memory), even though the two groups did not differ on these measures at baseline.

Taken together, results of the current study appear to support our hypothesis that semantic deficits may precede episodic deficits in MCI progression to AD. MCI progressors showed worse semantic performance at baseline, along with poorer cognitive flexibility, followed by a significant decline in episodic memory and global cognition at the follow-up. This view is in line with epidemiological studies which have shown that semantic memory declines first among other domains in older adults who go on to develop Alzheimer's disease (Wilson et al., 2011). It is also in line with studies showing that baseline semantic verbal fluency performance is predictive of future conversion to dementia (Sutin et al., 2019; Garcia et al., 2021). Although further studies are needed to confirm this hypothesis, the idea that semantic impairment may serve as a useful marker allowing to detect those MCI individuals who are more prone to conversion to AD is key, because: all MCI patients have episodic memory impairment; semantic decline may be more specific to AD (as opposed to executive dysfunction for instance); semantic memory is preserved in normal aging (Park et al., 2002); and semantic tests are easily accessible, as opposed to biomarkers which are costly and not necessarily associated with clinical outcome (Pang et al., 2023). Therefore, a cognitive approach to the early identification of AD may be useful compared to a purely biological approach to the identification of AD.

Limitations

Several limitations are worth acknowledging in our study. Firstly, the number of participants was relatively modest, hence early- and late-stage MCI participants were combined in a single group. Secondly, only a small subset of participants had lumbar puncture, potentially accounting for the absence of significant difference between the two groups concerning csf-Aβ42 and csf-Tau levels. Additionnaly, it must be pointed out that the CIMA-Q study did not use detailed semantic testing, such as tests for instance that require naming and providing semantic information about famous faces or famous places, which are more sensitive in detecting semantic impairment in MCI and AD (Joubert et al., 2021; Montembeault et al., 2017). Therefore, more longitudinal studies are needed to compare the prognotic value of different semantic tests in MCI progression.

Conclusion

This is one of the first longitudinal studies to investigate semantic performance at different time points in MCI patients. Our results indicate that performance on category fluency and object decision semantic tests was worse at baseline in MCI progressors relative to non-progressors. Semantic tests such as these may thus be helpful in identifying MCI patients who are more likely to progress to AD and may be useful in routine clinical practice, especially when we consider that semantic knowledge remains stable during normal aging (Park et al., 2002). In addition, MCI progressors were significantly impaired on a measure of cognitive flexibility at baseline relative to non-progressors, indicating that executive dysfunction may also contribute to improving prognosis. There were no differences between the two MCI groups in terms of several potentially confounding variables such as age, education, sex, depression, anxiety, sleep, and vascular burden, indicating that these variables could not explain the differences observed. Finally, steeper rates of decline in global cognition, episodic memory, and processing speed at follow-up in the MCI progressor group suggest that decline in these domains may follow shortly after semantic decline. In the longer run, more precise screening of AD-MCI patients may allow them and their families to make better informed decisions in regard to their jobs or lifestyle (Gauthier et al., 2011), plan for the future in order to improve their quality of life (Porsteinsson et al., 2021), and choose to participate in different therapeutic treatments such as cognitive interventions (Jean et al., 2010).

Acknowledgements
[hidden, see title page]

Conflict of Interest

[hidden, see title page]

Table 1. Patient and healthy control characteristics (mean and S.D.).

	MCI progressors (N=18) Mean (S.D.) Range	MCI non-progressors (N=38) Mean (S.D.) Range
Age	77.7 (5.4) 70 - 88	75.1 (5.7) 66 - 86
Education (years)	13.6 (4.0) 7 - 20	14.9 (3.7) 10 - 24
Sex (female / male)	8/10	20/18
Memory complaint (QAM)	22.5 (6.2) 15 - 38	22.7 (8.0) 11 - 40
Depression (GDS-10)	6.4 (4.4) 0 - 15	6.3 (5.7) 0 - 24
Anxiety (GAI)	3.2 (3.4) 0 - 13	4.4 (5.6) 0 - 20
Insomnia (questionnaire)	6.7 (6.2) 0 - 23	7.8 (6.1) 0 - 22
Daily Sleepiness (Epworth scale)	5.6 (1.9) 3 - 10	4.8 (3.5) 0 - 16
Vascular Health (Hachinski)	1.7 (1.7) 0 - 7	1.4 (1.4) 0 - 5
CSF Aβ42	233 [1] (118) 161 - 410	407 [2] (207) 121 - 763
CSF Tau	525 [1] (375) 239 - 1077	412 [2] (290) 199 - 1097
ApoE4 carriers (1 allele/2 alleles)	3/4	9/2

§ $p<0.05$ between MCI progressors and non-progressors (there were no significant differences on any of the variables between the 2 groups)

[1] Data available for N=4 participants in this group

[2] Data available for N=8 participants in this group

Table 2. Cognitive performance of MCI progressors and non-progressors at baseline.

	MCI progressors (N=18) Mean (S.D.) Range	**MCI non-progressors** (N=38) Mean (S.D.) Range
Semantic Memory		
Category Fluency (1 min) †	14.8 (3.8) 9 - 22	17.7 (3.9) 12 - 29
Object Decision (BORB) †	26.8 (3.4) 17 - 32	29.2 (2.2) 24 - 32
Vocabulary (WAIS-IV)	42.1 (17.4) 3 - 62	45.6 (10.0) 21 - 62
Episodic Memory		
RAVLT delayed recall	6.4 (3.8) 0 - 12	7.6 (3.3) 1 - 14
Executive functions		
TMT B/A ratio* †	2.8 (0.9) 2 - 4	2.2 (0.7) 1 - 5
Coding (WAIS-IV)	51.3 (16.2) 21 - 84	52.0 (13.1) 30 - 76
Letter fluency	11.7 (4.0) 5 - 19	13.6 (4.5) 2 - 23
Visuospatial skills		
Line Orientation	24.8 (3.3) 19 - 29	25.1 (2.4) 14 / 28
Global cognition		
MoCA	24.1 (1.9) 21 - 27	25.0 (2.0) 19 - 30

† $p<0.05$ between MCI progressors and non-progressors.

* A higher TMT B/A ratio indicates more deficits in cognitive flexibility, i.e., a greater trade-off in TMTB vs. TMTA performance.

Note. All analyses included age, education and sex as covariates.

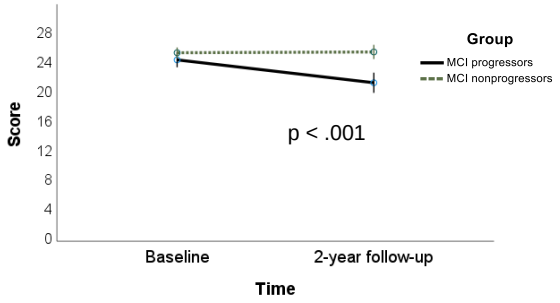
Table 3. ROC analyses at baseline

	AUC (CI 95%) p-value	Optimal threshold (score in test)	Youden's index (sensitivity; specificity)
Semantic Memory			
Category Fluency (1 min)	**0.75** (0.61-0.90) p<0.01	15.5	0.45 (0.68; 0.77)
Object Decision (BORB)	**0.73** (0.57-0.88) p<0.01	28.5	0.48 (0.71; 0.77)
Vocabulary (WAIS-IV)	**0.50** (0.33-0.68) p=0.96		
Episodic Memory			
RAVLT delayed recall	**0.58** (0.41-0.75) p=0.35		
Executive functions			
TMT B/A ratio	**0.73** (0.58-0.88) p<0.01	2.36	0.35 (0.67; 0.69)
Coding (WAIS-IV)	**0.51** (0.34-0.68) p=0.90		
Letter fluency	**0.64** (0.48-0.80) p=0.11		
Visuospatial skills			
Line Orientation	**0.52** (0.33-0.71) p=0.86		
Global cognition			
MoCA	**0.63** (0.46-0.79) p=0.14		

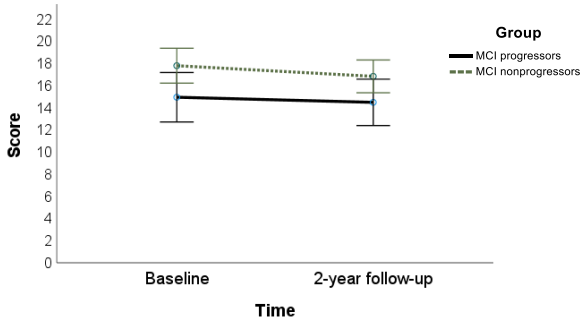
Note. AUC below .7 is low, between .7 and .8 is acceptable, between .8 and .9 is good and over .9 is excellent.

Figure 1. Patterns of change on different cognitive tests at baseline and follow-up.

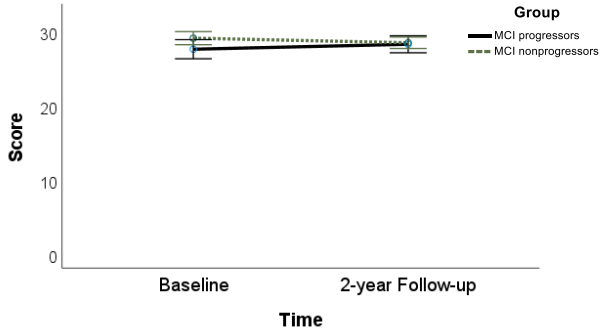
a. General cognition : MoCA



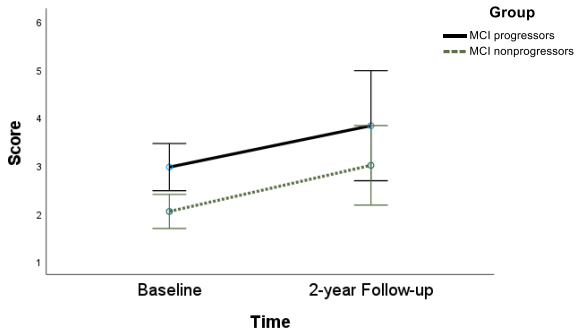
b. Semantic memory: Category Fluency



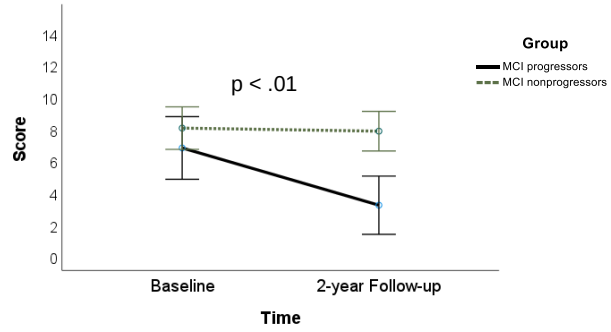
c. Semantic memory: Object decision



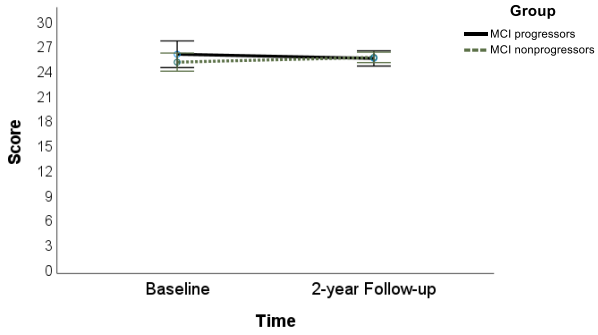
d. Cognitive flexibility: TMT B/A Ratio



e. Episodic memory: RAVLT delayed recall



f. Visuospatial skills: Line Orientation



g. Processing speed: Coding

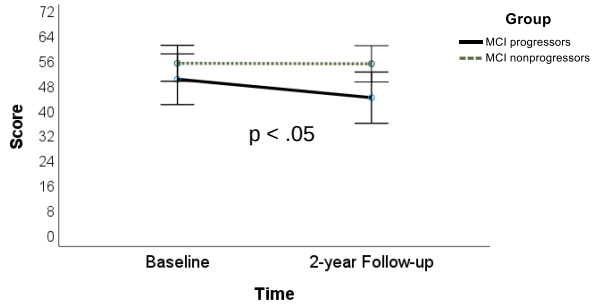
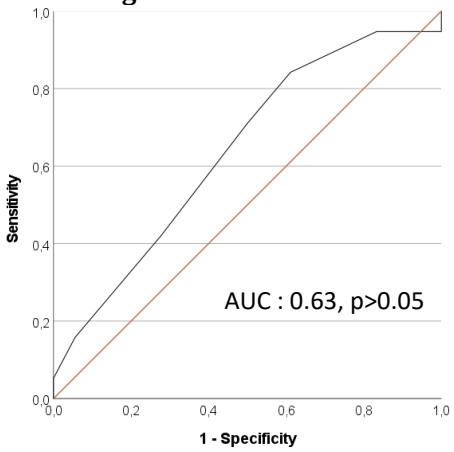
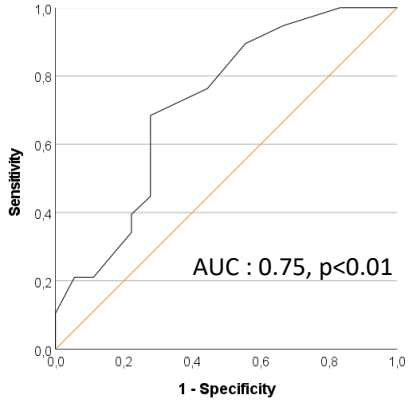


Figure 2. ROC curves

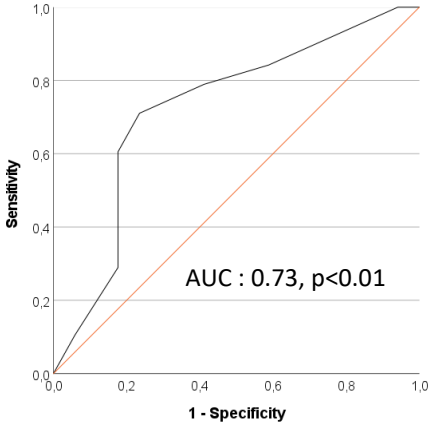
a. General cognition : MoCA



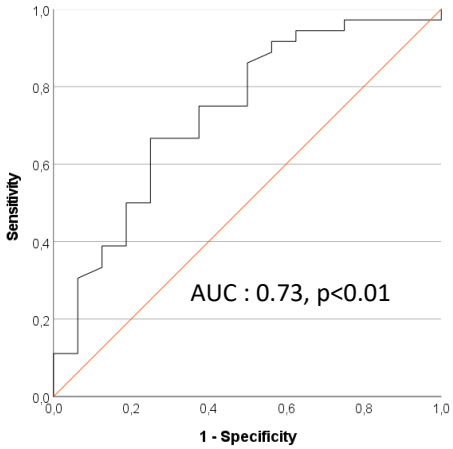
b. Semantic memory: Category Fluency



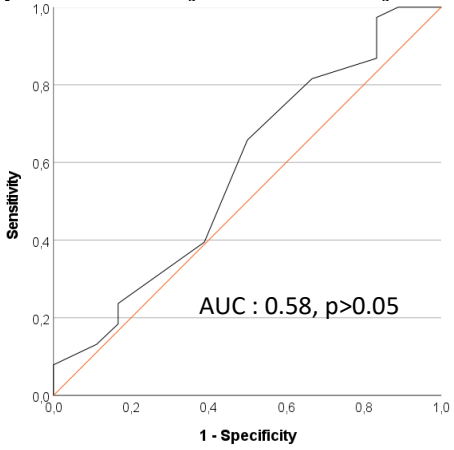
c. Semantic memory: Object decision



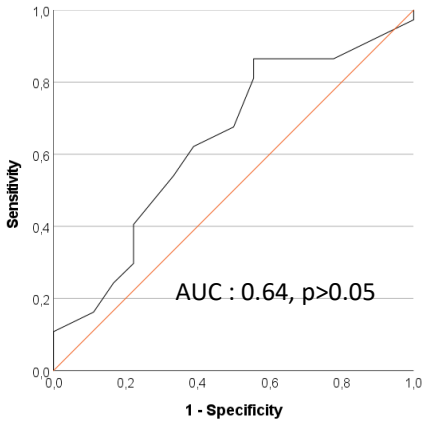
d. Cognitive flexibility: TMT B/A Ratio



e. Episodic memory: RAVLT delayed recall



f. Executive function: Phonemic Fluency



Bibliography

Adlam, A.-L. R., Bozeat, S., Arnold, R., Watson, P., & Hodges, J. R. (2006). Semantic knowledge in mild cognitive impairment and mild Alzheimer's disease. *Cortex*, *42*(5), 675-684.

Ahmed, S., Arnold, R., Thompson, S. A., Graham, K. S., & Hodges, J. R. (2008). Naming of objects, faces and buildings in mild cognitive impairment. *Cortex*, *44*(6), 746-752.

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. (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. *Alzheimer's dementia*, *7*(3), 270-279.

Amieva, H., Le Goff, M., Millet, X., Orgogozo, J. M., Pérès, K., Barberger-Gateau, P., Jacqmin-Gadda, H., & Dartigues, J. F. (2008). Prodromal Alzheimer's disease: successive emergence of the clinical symptoms. *Annals of Neurology: Official Journal of the American Neurological Association the Child Neurology Society*, *64*(5), 492-498.

Arbuthnott, K., & Frank, J. (2000). Trail making test, part B as a measure of executive control: validation using a set-switching paradigm. *Journal of clinical and experimental neuropsychology*, *22*(4), 518-528.

Ariza, M., Cano, N., Segura, B., Adan, A., Bargalló, N., Caldú, X., Campabadal, A., Jurado, M. A., Mataró, M., & Pueyo, R. (2023). COVID-19 severity is related to poor executive function in people with post-COVID conditions. *Journal of Neurology*, *270*(5), 2392-2408.

Balthazar, M. L. F., Cendes, F., & Damasceno, B. P. (2008). Semantic error patterns on the Boston Naming Test in normal aging, amnestic mild cognitive impairment, and mild Alzheimer's disease: is there semantic disruption? *Neuropsychology*, *22*(6), 703.

Barbeau, E. J., Didic, M., Joubert, S., Guedj, E., Koric, L., Felician, O., Ranjeva, J.-P., Cozzone, P., & Ceccaldi, M. (2012). Extent and neural basis of semantic memory impairment in mild cognitive impairment. *Journal of Alzheimer's disease*, *28*(4), 823-837.

Belleville, S., Fouquet, C., Hudon, C., Zomahoun, H. T. V., Croteau, J., & Disease-Quebec, C. f. t. E. I. o. A. s. (2017). Neuropsychological measures that predict progression from mild cognitive impairment to Alzheimer's type dementia in older adults: a systematic review and meta-analysis. *Neuropsychology Review*, *27*, 328-353.

Belleville, S., LeBlanc, A. C., Kergoat, M. J., Calon, F., Gaudreau, P., Hébert, S. S., Hudon, C., Leclerc, N., Mechawar, N., & Duchesne, S. (2019). The Consortium for the early identification of Alzheimer's disease–Quebec (CIMA-Q). *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *11*(1), 787-796.

Benoit, S., Rouleau, I., Langlois, R., Dostie, V., & Joubert, S. (2018). Le POP-40: un nouvel outil d'évaluation de la mémoire sémantique liée aux personnes célèbres. *Revue de neuropsychologie*, *10*(1), 91-103.

Brambati, S. M., Peters, F., Belleville, S., & Joubert, S. (2012). Lack of semantic priming effects in famous person recognition in Mild Cognitive Impairment. *Cortex*, *48*(4), 414-420.

Chasles, M.-J., Tremblay, A., Escudier, F., Lajeunesse, A., Benoit, S., Langlois, R., Joubert, S., & Rouleau, I. (2019). An Examination of Semantic Impairment in Amnestic MCI and AD: What Can We Learn From Verbal Fluency? *Archives of Clinical Neuropsychology*.

Chertkow, H., & Bub, D. (1990). Semantic memory loss in dementia of Alzheimer's type: What do various measures measure? *Brain*, *113*(2), 397-417.

Clark, L. R., Schiehser, D. M., Weissberger, G. H., Salmon, D. P., Delis, D. C., & Bondi, M. W. (2012). Specific measures of executive function predict cognitive decline in older adults. *Journal of the International Neuropsychological Society*, *18*(1), 118-127.

Curran, P. J., West, S. G., & Finch, J. F. (1996). The robustness of test statistics to nonnormality and specification error in confirmatory factor analysis. *Psychological methods*, *1*(1), 16.

Darby, R., Brickhouse, M., Wolk, D., & Dickerson, B. (2015). Semantic Memory, but not Episodic Memory, is Modulated by Cognitive Reserve in Patients with MCI and AD *Neurology*, *84*(14 Supplement), P2.168.

de Hond, A. A., Steyerberg, E. W., & van Calster, B. (2022). Interpreting area under the receiver operating characteristic curve. *The Lancet Digital Health*, *4*(12), e853-e855.

Dubois, B., Feldman, H. H., Jacova, C., Cummings, J. L., DeKosky, S. T., Barberger-Gateau, P., Delacourte, A., Frisoni, G., Fox, N. C., & Galasko, D. (2010). Revising the definition of Alzheimer's disease: a new lexicon. *The Lancet Neurology*, *9*(11), 1118-1127.

Emrani, S., Arain, H. A., DeMarshall, C., & Nuriel, T. (2020). APOE4 is associated with cognitive and pathological heterogeneity in patients with Alzheimer’s disease: a systematic review. *Alzheimer's Research & Therapy*, *12*, 1-19.

Gallant, M., Lavoie, M., Hudon, C., & Monetta, L. (2019). Analysis of Naming Errors in Healthy Aging, Mild Cognitive Impairment, and Alzheimer’s Disease. *Canadian Journal of Speech-Language Pathology and Audiology*, *43*(2), 95-108.

Gallucci, M., Di Battista, M. E., Battistella, G., Falcone, C., Bisiacchi, P. S., & Di Giorgi, E. (2018). Neuropsychological tools to predict conversion from amnestic mild cognitive impairment to dementia. The TREDEM Registry. *Aging, Neuropsychology, and Cognition*, *25*(4), 550-560.

Ganguli, M., Jia, Y., Hughes, T. F., Snitz, B. E., Chang, C. C. H., Berman, S. B., Sullivan, K. J., & Kamboh, M. I. (2019). Mild cognitive impairment that does not progress to dementia: a population-based study. *Journal of the American Geriatrics Society*, *67*(2), 232-238.

García, S., Cuetos, F., Novelli, A., & Martínez, C. (2021). Famous faces naming test predicts conversion from mild cognitive impairment to Alzheimer’s disease. *Acta Neurologica Belgica*, *121*(6), 1721-1727.

Gaudreau, P., Morais, J. A., Shatenstein, B., Gray-Donald, K., Khalil, A., Dionne, I., Ferland, G., Fülöp, T., Jacques, D., & Kergoat, M.-J. (2007). Nutrition as a determinant of successful aging: description of the Quebec longitudinal study

Nuage and results from cross-sectional pilot studies. *Rejuvenation Research*, *10*(3), 377-386.
Gauthier, S., Patterson, C., Gordon, M., Soucy, J.-P., Schubert, F., & Leuzy, A. (2011). Commentary on "Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease." A Canadian perspective. *Alzheimer's & Dementia*, *7*(3), 330-332.
Henry, J. D., & Crawford, J. R. (2004). A meta-analytic review of verbal fluency performance following focal cortical lesions. *Neuropsychology*, *18*(2), 284.
Hornberger, M., Piguet, O., Kipps, C., & Hodges, J. R. (2008). Executive function in progressive and nonprogressive behavioral variant frontotemporal dementia. *Neurology*, *71*(19), 1481-1488.
Jean, L., Bergeron, M.-È., Thivierge, S., & Simard, M. (2010). Cognitive intervention programs for individuals with mild cognitive impairment: systematic review of the literature. *The American Journal of Geriatric Psychiatry*, *18*(4), 281-296.
Joubert, S., Brambati, S. M., Ansado, J., Barbeau, E. J., Felician, O., Didic, M., Lacombe, J., Goldstein, R., Chayer, C., & Kergoat, M.-J. (2010). The cognitive and neural expression of semantic memory impairment in mild cognitive impairment and early Alzheimer's disease. *Neuropsychologia*, *48*(4), 978-988.
Joubert, S., Felician, O., Barbeau, E. J., Didic, M., Poncet, M., & Ceccaldi, M. (2008). Patterns of semantic memory impairment in mild cognitive impairment. *Behavioural neurology*, *19*(1, 2), 35-40.
Joubert, S., Gardy, L., Didic, M., Rouleau, I., & Barbeau, E. J. (2021). A meta-analysis of semantic memory in mild cognitive impairment. *Neuropsychology Review*, *31*(2), 221-232.
Junquera, A., García-Zamora, E., Olazarán, J., Parra, M. A., & Fernández-Guinea, S. (2020). Role of executive functions in the conversion from mild cognitive impairment to dementia. *Journal of Alzheimer's disease*, *77*(2), 641-653.
Langlois, R., Joubert, S., Benoit, S., Dostie, V., & Rouleau, I. (2016). Memory for public events in mild cognitive impairment and Alzheimer's disease: The importance of rehearsal. *Journal of Alzheimer's disease*, *50*(4), 1023-1033.
Levy, G., Jacobs, D. M., Tang, M. X., Côté, L. J., Louis, E. D., Alfaro, B., Mejia, H., Stern, Y., & Marder, K. (2002). Memory and executive function impairment predict dementia in Parkinson's disease. *Movement disorders: official journal of the Movement Disorder Society*, *17*(6), 1221-1226.
Li, J.-Q., Tan, L., Wang, H.-F., Tan, M.-S., Tan, L., Xu, W., Zhao, Q.-F., Wang, J., Jiang, T., & Yu, J.-T. (2016). Risk factors for predicting progression from mild cognitive impairment to Alzheimer's disease: a systematic review and meta-analysis of cohort studies. *Neurol Neurosurg Psychiatry*, *87*(5), 476-484.
Marra, C., Piccininni, C., Masone Iacobucci, G., Caprara, A., Gainotti, G., Costantini, E. M., Callea, A., Venneri, A., & Quaranta, D. (2021). Semantic memory as an early cognitive marker of Alzheimer's disease: role of category and phonological verbal fluency tasks. *Journal of Alzheimer's disease*, *81*(2), 619-627.
McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack Jr, C. R., Kawas, C. H., Klunk, W. E., Koroshetz, W. J., Manly, J. J., & Mayeux, R. (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. *Alzheimer's & Dementia*, *7*(3), 263-269.
Monsch, A. U., Seifritz, E., Taylor, K. I., Ermini-Fünfschilling, D., Staehelin, H. B., & Spiegel, R. (1997). Category fluency is also predominantly affected in Swiss Alzheimer's disease patients. *Acta Neurologica Scandinavica*, *95*(2), 81-84.
Montembeault, M., Brambati, S. M., Joubert, S., Boukadi, M., Chapleau, M., Laforce, R. J., Wilson, M. A., Macoir, J., & Rouleau, I. (2017). Naming unique entities in the semantic variant of primary progressive aphasia and Alzheimer's disease: Towards a better understanding of the semantic impairment. *Neuropsychologia*, *95*, 11-20.
Murphy, K. J., Rich, J. B., & Troyer, A. K. (2006). Verbal fluency patterns in amnestic mild cognitive impairment are characteristic of Alzheimer's type dementia. *Journal of the International Neuropsychological Society*, *12*(4), 570-574.
Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695-699.
Nosek, B. A., Alter, G., Banks, G. C., Borsboom, D., Bowman, S. D., Breckler, S. J., Buck, S., Chambers, C. D., Chin, G., & Christensen, G. (2015). Promoting an open research culture. *Science*, *348*(6242), 1422-1425.
Nuño, L., Gómez-Benito, J., Carmona, V. R., & Pino, O. (2021). A systematic review of executive function and information processing speed in major depression disorder. *Brain Sciences*, *11*(2), 147.
Pang, Y., Kukull, W., Sano, M., Albin, R., Shen, C., Zhou, J., & Dodge, H. H. (2023). Predicting Progression from Normal to MCI and from MCI to AD Using Clinical Variables in the National Alzheimer's Coordinating Center Uniform Data Set Version 3: Application of Machine Learning Models and a Probability Calculator. *The journal of prevention of Alzheimer's disease*, *10*(2), 301-313.
Papp, K. V., Mormino, E. C., Amariglio, R. E., Munro, C., Dagley, A., Schultz, A. P., Johnson, K. A., Sperling, R. A., & Rentz, D. M. (2016). Biomarker validation of a decline in semantic processing in preclinical Alzheimer's disease. *Neuropsychology*, *30*(5), 624.
Park, D. C., Lautenschlager, G., Hedden, T., Davidson, N. S., Smith, A. D., & Smith, P. K. (2002). Models of visuospatial and verbal memory across the adult life span. *Psychology aging*, *17*(2), 299.
Payton, N. M., Marseglia, A., Grande, G., Fratiglioni, L., Kivipelto, M., Bäckman, L., & Laukka, E. J. (2022). Trajectories of cognitive decline and dementia development: A 12-year longitudinal study. *Alzheimer's & Dementia*.
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*(3), 303-308.
Porsteinsson, A., Isaacson, R., Knox, S., Sabbagh, M., & Rubino, I. (2021). Diagnosis of early Alzheimer's disease: clinical practice in 2021. *The journal of prevention of Alzheimer's disease*, *8*, 371-386.

Prado, C. E., Watt, S., Treeby, M. S., & Crowe, S. F. (2019). Performance on neuropsychological assessment and progression to dementia: A meta-analysis. *Psychology and aging*, *34*(7), 954.

Rahmani, F., Fathi, M., & Bahadori, E. (2019). Recognition of Famous and Unfamiliar Faces among Patients Suffering from Amnesia Mild Cognitive Impairment (AMCI) and Alzheimer's Disease. *Iranian journal of psychiatry*, *14*(3), 227.

Salehi, M., Reisi, M., & Ghasisin, L. (2017). Lexical retrieval or semantic knowledge which one causes naming errors in patients with mild and moderate alzheimer's disease. *Dementia and geriatric cognitive disorders extra*, *7*(3), 419-429.

Shields, G. S., Moons, W. G., Tewell, C. A., & Yonelinas, A. P. (2016). The effect of negative affect on cognition: Anxiety, not anger, impairs executive function. *Emotion*, *16*(6), 792.

St-Hilaire, A., Blackburn, M.-C., Wilson, M. A., Laforce Jr, R., Hudon, C., & Macoir, J. (2018). 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. *Aging, Neuropsychology, and Cognition*, *25*(3), 427-442.

Steyn Jr, H., & Ellis, S. (2009). Estimating an effect size in one-way multivariate analysis of variance (MANOVA). *Multivariate Behavioral Research*, *44*(1), 106-129.

Summers, M. J., & Saunders, N. L. (2012). Neuropsychological measures predict decline to Alzheimer's dementia from mild cognitive impairment. *Neuropsychology*, *26*(4), 498.

Sutin, A. R., Stephan, Y., & Terracciano, A. (2019). Verbal fluency and risk of dementia. *International journal of geriatric psychiatry*, *34*(6), 863-867.

Tabachnick, B. G., Fidell, L. S., & Ullman, J. B. (2013). *Using multivariate statistics* (Vol. 6). pearson Boston, MA.

Taler, V., Monetta, L., Sheppard, C., & Ohman, A. (2020). Semantic function in mild cognitive impairment. *Frontiers in Psychology*, *10*, 3041.

Troyer, A. K. (2000). Normative data for clustering and switching on verbal fluency tasks. *Journal of clinical and experimental neuropsychology*, *22*(3), 370-378.

Troyer, A. K., Moscovitch, M., & Winocur, G. (1997). Clustering and switching as two components of verbal fluency: evidence from younger and older healthy adults. *Neuropsychology*, *11*(1), 138.

Troyer, A. K., Moscovitch, M., Winocur, G., Alexander, M. P., & Stuss, D. (1998). Clustering and switching on verbal fluency: The effects of focal frontal-and temporal-lobe lesions. *Neuropsychologia*, *36*(6), 499-504.

Troyer, A. K., Moscovitch, M., Winocur, G., Leach, L., & Freedman, M. (1998). Clustering and switching on verbal fluency tests in Alzheimer's and Parkinson's disease. *Journal of the International Neuropsychological Society*, *4*(2), 137-143.

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. *Journal of the American Geriatrics Society*, *66*(4), 755-759.

Vonk, J. M., Bouteloup, V., Mangin, J. F., Dubois, B., Blanc, F., Gabelle, A., Ceccaldi, M., Annweiler, C., Krolak-Salmon, P., & Belin, C. (2020). Semantic loss marks early Alzheimer's disease-related neurodegeneration in older adults without

dementia. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *12*(1), e12066.
Whiteside, D. M., Kealey, T., Semla, M., Luu, H., Rice, L., Basso, M. R., & Roper, B. (2016). Verbal fluency: Language or executive function measure? *Applied Neuropsychology: Adult*, *23*(1), 29-34.
Wilson, R. S., Leurgans, S. E., Boyle, P. A., & Bennett, D. A. (2011). Cognitive decline in prodromal Alzheimer disease and mild cognitive impairment. *Archives of neurology*, *68*(3), 351-356.
Wright, L. M., De Marco, M., & Venneri, A. (2022). Verbal fluency discrepancies as a marker of the prehippocampal stages of Alzheimer's disease. *Neuropsychology*.
Wright, L. M., De Marco, M., & Venneri, A. (2023). Current Understanding of Verbal Fluency in Alzheimer's Disease: Evidence to Date. *Psychology Research and Behavior Management*, 1691-1705.