

An examination of semantic impairment in amnesic MCI and AD: What can we learn from verbal fluency?

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Abstract

Introduction. The Verbal Fluency Test (VF) is commonly used in neuropsychology. Some studies have demonstrated a marked impairment of semantic VF compared to phonemic VF in Alzheimer's disease (AD). Since amnesic Mild Cognitive Impairment (aMCI) is associated with increased risk of conversion to incident AD, it is relevant to examine whether a similar impairment is observed in this population. The objective of the present empirical study is to compare VF performance of aMCI patients to those of AD and elderly controls matched one-to-one for age and education. **Method.** Ninety-six participants divided into three equal groups (N = 32: AD, aMCI and Controls) were included in this study. Participants in each group were, on average, 76 years of age and had 13 years of education. A repeated measures ANOVA with the Group (AD, aMCI, NC) as between-subject factor and the Fluency condition ("P" and "animals") as within-subject factor was performed. T-tests and simple ANOVAs were also

conducted to examine the interaction. **Results.** There was a significant interaction between the groups and the verbal fluency condition. In AD, significantly fewer words were produced in both conditions. In contrast, participants with aMCI demonstrated a pattern similar to controls in the phonemic condition, but generated significantly fewer words in the semantic condition. **Conclusion.** These results indicate a semantic memory impairment in aMCI revealed by a simple, commonly-used neuropsychological test. Future studies are needed to investigate if semantic fluency deficits can help predict future conversion to AD.

Keywords: verbal fluency; aMCI; Alzheimer's disease; semantic memory

Introduction

Alzheimer's disease (AD) represents 50 to 70% of all late-life cases of dementia (Feldman et al., 2014). A recent longitudinal study by Wilson and colleagues (2011) among 2 000 elderly adults revealed that the cognitive decline begins to increase sharply about 6 years before the first diagnosis of AD, and that the semantic memory system is the first to be impaired. These results are supported by other authors who reported an analogous semantic decline even up to 12 years before diagnosis (Amieva et al., 2005; Amieva et al., 2008; Elias et al., 2000; Pakhomov et al., 2014; Raoux et al., 2008; Rubin et al., 1998). In addition, recent evidence suggests that semantic deficits in prodromal AD (i.e. amnesic MCI) are associated with future decline patterns of abnormal functional activation within the semantic cortical network (Pineault et al., 2018) and a reduction in gray matter volume in key regions of the semantic network (Joubert et al., 2010; Barbeau EJ et al., 2012), suggesting that the latter may be compromised early during the course of the disease. Additional evidence also indicates that AD patients demonstrate an abnormal pattern of activation in the default mode network (DMN), more specifically in the posterior cingulate, the prefrontal cortex and the lateral temporoparietal regions, which are also involved in semantic processing (Silverberg et al.,

2011).

Additionally, there is now a strong interest in the identification and development of cognitive tools that could facilitate the diagnosis of prodromal AD, which could in turn lead to the potential development of early targeted intervention strategies. Verbal fluency tests, in which subjects are asked to generate as many words as possible in a limited amount of time, are designed to examine verbal and executive functions based either on a phonemic (words beginning by a specific letter) or a semantic constraint (words that belong to a certain conceptual category) (Teng et al., 2013). These two conditions involve different cognitive demands. Both conditions depend upon processing speed (Greenaway et al., 2009) and executive processes such as organization, retrieval and inhibition. The semantic task, however, requires the search, selection, and generation of items belonging to a specific semantic category, and also relies on the semantic association process (Henry et al., 2004). However, more words are typically generated in the semantic condition than in the phonemic condition because responses are by default clustered in organized semantic mental representations which facilitates generation (Teng et al., 2013). In that regard, a longitudinal normative data study by Vaughan and colleagues (2016) on 5700 older adults demonstrated that healthy controls have a better verbal fluency (VF) performance in the semantic than in the phonemic task, and that this advantage persists over time. Of particular interest, this tool has demonstrated its sensitivity to discriminate AD patients from healthy elderly subjects (Gainotti, Quaranta, Vita, & Marra, 2014). A meta-analysis by Henry and colleagues (2004) revealed that, unlike healthy controls, AD patients are disproportionately more impaired in the semantic than in the phonemic task. Moreover, this impairment in the semantic VF task is highly correlated with temporal lobe cortical thinning and atrophy, which is considered a good indicator of neuronal degeneration (Ahn et al., 2011). In a 10-year follow-up study, Hodges and colleagues (2006) also demonstrated that, in addition to consistent impairment on

episodic memory tests, most of their MCI patients also showed a semantic VF impairment at baseline. No other deficits were identified at this early stage of the disease.

A growing number of studies have focused on investigating the nature of semantic impairment in aMCI (e.g. Duong et al., 2006; Hodges et al., 2006; Ahmed et al., 2008; Joubert et al., 2010; Brambati et al. 2012; Langlois et al., 2016; Benoit et al., 2017). For instance, Joubert and colleagues (2010) reported that naming and knowledge of famous people and objects were significantly impaired in aMCI in both verbal and visual modalities compared to healthy controls, which supports the idea of a central semantic breakdown in aMCI. However, studies comparing VF performance in aMCI, AD and healthy older subjects showed mixed results. While a meta-analysis by Henry and coworkers (2004) reported more impaired semantic than phonemic VF in the early stages of AD, a more recent meta-analysis by Laws and colleagues (2010) revealed that this semantic-phonemic discrepancy did not differ from healthy controls. According to these authors, it would rather be an exaggerated normal tendency because their analysis revealed that the mean discrepancy effect size for their AD patients was almost identical to that of their HC group. Along the same line, other studies reported that both semantic and phonemic VF are impaired in aMCI (Nutter-Upham et al., 2008). In contrast, some studies reported a similar VF profile in aMCI and AD with greater impairment in semantic than in phonemic verbal fluency compared to healthy controls (Lonie et al., 2009; Murphy et al., 2006). Finally, some authors observed a similar profile in participants with aMCI and normal elderly controls, with a better performance in semantic VF than in phonemic VF (Brandt & Manning, 2009; Rinehardt et al., 2014). These conflicting results could be explained by a number of factors, such as the operationalization of the aMCI construct itself (cut-off scores and inclusion criteria), the instructions given and the scoring rules of the VF tests (Brandt & Manning, 2009), the severity of cognitive decline, the presence of cognitive deficits in other domains as well as the differences in demographic

characteristics such as age and education (Kawano et al., 2010). Indeed, while age and level of education have been shown to have a strong impact on both semantic and phonemic verbal fluency performance (Gladsjo et al., 1999; Kawano et al., 2010; Loonstra et al., 2001; Troyer, 2000), some of the previously cited studies simply did not control for level of education (e.g. Lonie et al., 2009). Among the studies that took these variables into account, there are several weaknesses. Some (e.g. Teng et al., 2013) researchers observed significant differences between groups and statistically controlled for these variables only a posteriori. Regarding studies that paired groups a priori for age and level of education (Murphy et al., 2006; Nutter-Upham et al., 2008; Brandt & Manning 2009; Rinehardt et al., 2014), most did not observe the semantic deficit specific to AD in aMCI patients. Instead, their profile closely resembled that of healthy controls. Finally, no study used an a priori individual matching method with equal groups. This technique involves controlling for confounding variables when setting up groups by matching each individual participant, one-to-one, to an individual in another group who possesses the same characteristic (i.e. age, level of education). This method, however, is much more challenging to apply because it requires a large potential participant pool and is more rigorous but allows researchers to maximally neutralize potentially confounding variables.

The objective of the present study is to examine and compare verbal fluency performance of aMCI and mild AD patients to those of healthy elderly subjects carefully matched individually for age and education. The present study aims to examine in more detail the usefulness of VF tests in distinguishing normal aging from aMCI and AD, as well as the clinical relevance of such tests in terms of improving diagnostic accuracy of AD and aMCI patients. Given that aMCI is considered to be a prodromal phase of AD and that most aMCI patients convert to dementia within a decade, we hypothesized that our aMCI group would exhibit a similar pattern of VF decline as our AD group, i.e. greater impairment in semantic

VF than in phonemic VF, when compared to a matched control group. This discrepancy between semantic and phonemic VF would reflect the early semantic memory impairment that occurs in the disease. In the current study, participants across groups were strictly controlled for on a one-to-one basis, on two important variables (age and education). This procedure yielded three groups identical in terms of these parameters, which represents a significant advantage compared to previous studies and may shed some light on the debate.

Methods

Participants

A total of ninety-six participants (N= 96) divided into three equal groups (N= 32: AD, MCI and NC) were included in the study. Ninety-six was the maximum number of participants whose characteristics allowed to achieve the individual matching. Participants from each group were matched one-to-one for age and education, so that the groups did not differ in terms of these variables known to impact cognitive test performance. For instance, each MCI participant was matched to a control participant and to an AD participant who had the same age (± 1 year) and same level of education (± 1 year). Participants were initially involved in larger studies examining semantic and prospective memory functioning at the Centre de recherche de l'Institut Universitaire de Gériatrie de Montréal (CRIUGM) and the Centre de recherche de l'Hôpital Notre-Dame (CRCHUM). To be included in the present study, participants were required to have French as their first language. Exclusion criteria were the same for the three groups. Participants were excluded from the study if they had a history of any systemic or neurological disease (except for the aMCI and AD groups), traumatic brain injury, psychiatric illness, history of alcoholism or drug abuse, untreated metabolic condition, or general anesthesia in the past six months.

Amnesic Mild Cognitive Impairment Group

Thirty-two patients (n=32) aged from 61 to 88 years old were included. These patients, from an outpatient cognition clinic, were diagnosed as having amnesic Mild Cognitive Impairment according to the most recent MCI clinical criteria (Albert et al., 2011; Petersen, 2004) because they demonstrated the following characteristics : (1) a cognitive concern reflecting a change in memory over time, (2) this complaint is corroborated by objective evidence of a memory impairment (> 1.5 standard deviation below the mean for age and education on at least two tests of anterograde memory), (3) no interference of the cognitive decline in daily living activities as assessed during a clinical interview, (4) failure to meet diagnostic criteria for dementia. Since no biomarker screening took place, our aMCI group corresponded to Albert's (2011) 3rd level of certainty of their symptoms being due to an underlying AD; the *MCI-core clinical criteria* diagnostic category.

Alzheimer's Disease Group

Thirty-two patients (n=32) aged from 61 to 88 years old were selected. These patients, from an outpatient cognition clinic, were diagnosed as having a probable AD according to the recommendations of the NIA-AA because they met the following criteria: (1) Met criteria for dementia, (2) presented insidious onset of symptoms including (3) typical initially predominant amnesic presentation, and (4) a clear-cut history of cognitive decline (McKhann et al., 2011). Moreover, a consensus regarding diagnosis was established by the neurologist and a team of mental health professionals, supported by the results of a comprehensive neuropsychological assessment.

Normal Control Group

Thirty-two healthy older adults (n=32) aged from 62 to 88 years old were included.

Candidates were selected using the CRIUGM voluntary participant pool. Selected participants had to perform within normal limits for age and education on the MMSE cognitive screening test (MMSE \geq 26) described in the Measures section below, and normal cognitive functioning was confirmed based on the results of a detailed neuropsychological assessment.

Measures and Procedure

Evaluations took place at the research center of the Institut Universitaire de Gériatrie de Montréal (CRIUGM) or in Notre-Dame Hospital (CHUM). Participants were tested individually by experienced research assistants and PhD students in neuropsychology who were supervised by a licenced neuropsychologist. The research protocol was approved by the Research Ethics Board of IUGM and CHUM and written informed consent was obtained before participation. At the time of referral, aMCI and AD patients had received a diagnosis from their referring neurologist, geriatrician, and/or from a team of health professionals. This diagnosis was then confirmed based on the administration of a 2.5-hour comprehensive neuropsychological assessment described below. Only patients whose prior diagnosis was confirmed by the neuropsychological battery were included in the study and were administered the verbal fluency test. Tests were all administered in French.

Neuropsychological Assessment

First, all participants underwent a cognitive screening test. The Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) was used to evaluate the general cognitive abilities of the participants. The MMSE is a paper-pencil test, which takes five to ten minutes to complete. A score of fewer than 26 out of 30 points is considered to reflect a cognitive impairment (Monsch et al., 1995). Then, multiple neuropsychological tests to

evaluate language, attention, executive functions, visuoconstructional abilities, working memory and episodic memory were administered.

Language was assessed by a 30-item version of the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983). Selective visual attention was evaluated with a cancellation task, the Bells Test (Gauthier, Dehaut, & Joanne, 1989). Executive functions were assessed with the Trail Making Test (Reitan, 1955) and the color-word interference subtest of the D-KEFS (Delis, Kaplan, & Kramer, 2001). Working memory was evaluated with the forward and backward digit span subtests of the WAIS-III (Wechsler, 2000). Visuoconstructional abilities were assessed by the Clock Drawing test (Rouleau, Salmon, Butters, Kennedy, & McGuire, 1992) and the copy of the Rey-Osterrieth complex figure (Rey, 1959). Finally, verbal episodic memory was evaluated with the Logical Memory subtest of the Wechsler Memory Scale (WMS-III; Wechsler, 2001) and the Rey Auditory Verbal Learning Test (Rey, 1964), while visual episodic memory was assessed with the DMS-48 (Barbeau et al., 2004), and recall of the Rey-Osterrieth complex figure (Rey, 1959).

Verbal fluency test

All participants (NC, aMCI, AD) performed the verbal fluency test using the same procedure. Instructions used for the phonemic and semantic verbal fluency tasks have been published previously (St-Hilaire et al., 2016). First, phonemic verbal fluency was assessed by asking the participant to generate as many words as possible beginning with the letter "P" in 90 seconds, excluding proper names (places, people, etc.), words of the same family that are morphologically similar to another word previously generated (e.g. prince and princess), repetitions and non-words. Administration of the letter P only (instead of PFL or TNP) is a common administration procedure in Quebec. It has been demonstrated that Letter P is the one for which the largest number of words are generated, probably due to the number of

words available in French ($P = 12,616$; $T = 6,759$; $F = 5,890$; $L = 3,296$). In fact, it also have been demonstrated that performance for letter P strongly correlates with performance for TNP ($r = .866, p < .001$) and PFL ($r = .884, p < .001$), and that participants who have a Z-score greater than or equal to -1.00 for letter P also tend to have (about 95% of the time) a Z-score greater than or equal to -1.00 for TNP or PFL (Saint-Hilaire et al., 2016). Ninety seconds instead of 60 is also commonly used, as the last 30 seconds are considered more sensitive in tapping effortful retrieval processes. The semantic verbal fluency task was administered immediately after. Participants were instructed to generate as many names of animals as possible in 90 seconds. If the participant generated a subcategory (mammal, bird, fish, etc.), it was accepted as long as it was not followed by an item belonging to that subcategory. For example, if the participant generated: insect, spider, butterfly, etc. Only the words spider and butterfly would have been counted. All words generated by the examinee were written verbatim by the examiner on the scoring sheet. The total number of correct responses generated for each verbal fluency task was computed and served as the dependent variable.

Statistical Analysis

Our data were analyzed using the Statistical Package of Social Science (IBM SPSS 22) with an alpha significance level set at $p < 0.05$. Preliminary analysis showed that the assumptions for normality of the distribution, homogeneity of variances and sphericity were satisfied, and that there was no missing data. Demographic characteristics were analysed with one-way ANOVA (age, education) and chi-square (gender). We performed a mixed ANOVA (3x2) on the number of words generated, using the group (3 levels: NC, aMCI, AD) as the between-group factor, and the verbal fluency condition (2 levels: phonemic and semantic) as the within-subject factor. One-way ANOVAs, Tukey post hoc analyses and paired sample t-tests

were conducted to examine the interaction and the difference between phonemic and semantic fluency in each group.

Results

As expected, there was no difference between groups in terms of age, $F(2, 93) = 0.107$, $p = .899$, n.s., and education, $F(2, 93) = 0.651$, $p = .524$, n.s. Moreover, a chi-square test was conducted and revealed no significant gender difference between groups ($\chi^2(2) = 0.720$, n.s.). Demographic information for NC, aMCI and AD participants are presented in Table 1. All participants presented previously were included in the statistical analysis, and there was no missing data for each variable of interest.

Results of the mixed ANOVA revealed a main effect of Group, $F(2, 93) = 35.477$, $p < .001$, $\eta^2 = 0.433$, a main effect of Condition, $F(1, 93) = 17.687$, $p < .001$, $\eta^2 = 0.160$ and a significant Group X Condition interaction, $F(2, 93) = 4.758$, $p = .011$, $\eta^2 = 0.093$.

To examine the interaction, two one-way ANOVAs were conducted to study the effect of Group separately for each verbal fluency condition (phonemic and semantic). Homogeneity of variances was confirmed by Levene's test in each ANOVA. Results of the first ANOVA showed a significant effect of Group on phonemic verbal fluency condition, $F(2, 93) = 14.441$, $p < .001$, $\eta^2 = 0.237$. Tukey post hoc comparisons revealed that the AD group generated significantly fewer words than aMCI ($p = .001$) and NC ($p < .001$), but there was no significant difference in phonemic verbal fluency between aMCI and NC ($p = .160$) (AD < aMCI = NC). The second ANOVA showed a significant effect of Group on semantic verbal fluency condition, $F(2, 93) = 38.135$, $p < .001$, $\eta^2 = 0.451$. Tukey post hoc comparisons revealed that the AD group generated significantly fewer words than the aMCI ($p < .001$), and the latter group generated significantly fewer words than the NC ($p = .001$) (AD < aMCI < NC).

Finally, paired sample t-tests were conducted in each group to compare phonemic and semantic verbal fluency performance. Results showed a significant semantic-phonemic difference in the NC group ($p < .001$), but not in the aMCI ($p = .078$) or AD ($p = 0.462$, n.s) groups. As seen in Figure 1, the advantage of semantic over phonemic fluency in NC is sufficiently attenuated to be non-significant in the aMCI group and virtually absent in the AD group.

[Insert Figure 1 here]

Discussion

The present study aimed to examine and compare verbal fluency performance of aMCI and mild AD patients to those of healthy elderly subjects carefully matched for age and education. More specifically, since aMCI is considered as prodromal AD, we aimed to determine if aMCI patients presented a similar semantic VF impairment to that found in AD, thereby revealing early semantic memory deterioration.

As predicted, our results suggest a significant difference in the verbal fluency generation pattern between NC, aMCI and AD participants. Overall, planned comparisons revealed that the AD group generated fewer words than aMCI and NC in the two verbal fluency conditions. More interestingly, aMCI participants exhibited a similar verbal fluency performance to the NC in the phonemic task, but significantly poorer performance in the semantic task, with performance falling midway between that of NC and AD groups. Furthermore, paired sample t-tests conducted in each group showed that NC seemed to be significantly better at the semantic than the phonemic verbal fluency task, an advantage that was present neither in AD nor in aMCI participants. We generally expect elderly individuals to generate more words in the semantic than in the phonemic task because responses are already clustered in organized mental representations (Teng et al., 2013). Thus, the

participant refers to his animal-oriented mental schemas (farm, domestics, birds, etc.) to support his research process and solve the task. However, unlike our healthy control group, aMCI patients did not perform significantly better at the semantic than the phonemic task, and they generated significantly fewer words than HC.

Taken together, these results support the notion that semantic memory deficits in aMCI resemble those observed in AD, although they are milder, since aMCI participants performed significantly better than those affected by AD. The present results also support the idea of a pathologic continuum between these two diagnostic entities. In fact, there seems to be a linear trend whereby the semantic-phonemic advantage observed in healthy individuals tends to disappear as the disease progresses. These results are consistent with those of other authors who have previously reported on VF patterns in aMCI and AD (Henry et al., 2004; Lonie et al., 2009; Murphy et al., 2006; Teng et al., 2013), and in contrast to those who found a similar VF pattern in aMCI and controls (Brandt & Manning, 2009; Rinehardt et al., 2014). Furthermore, unlike Nutter-Upham and colleagues (2008), we did not observe a significant difference between the phonemic VF performance in aMCI versus controls. Some would argue that the selective deficit in the semantic task in aMCI could be explained by its greater cognitive demands, which actively require a search for items belonging to a subordinate conceptual category, above and beyond the executive functions the phonemic task requires (Gauthier et al., 2006). However, as previously mentioned, performance in the semantic condition is generally better because responses are already clustered in organized semantic mental representations which facilitates generation. The more restrictive rules in the phonemic condition, such as the exclusion of proper nouns and morphological variants of words already generated, require greater executive control, which also contributes to this task being more difficult (Teng et al., 2013). Thus, since the phonemic VF performance of our aMCI group was normal, the difficulties presented in the semantic task can only be explained

by an underlying semantic deficit, which prevents patients from benefiting from the advantage that semantic associations provide in control subjects. Finally, several studies on verbal fluency have observed that AD patients have a reverse profile, in which semantic VF is significantly more impaired than phonemic VF (Henry et al., 2004; Murphy et al., 2006; Teng et al., 2013). The fact that we did not observe such a pattern may be because our AD participants were in a very early stage of the disease, as indicated by their performance on the MMSE screening test. Indeed, our AD participants may have been less impaired than those in previous studies. In sum, our study demonstrated marked differences between the NC, aMCI and AD groups, which supports the idea that semantic deficits are present very early on and that semantic memory declines rather rapidly over the course of AD. These results are also consistent with longitudinal studies revealing that the semantic memory system seems to be the first impaired in the preclinical stage of the disease (Amieva et al., 2005; Gainotti et al., 2014; Wilson et al., 2011).

Impaired semantic VF performance typically found in AD has been suggested to be due to neurodegenerative changes in regions involved in the default mode network (DMN), including the MTL, posterior cingulate, prefrontal cortex and lateral temporoparietal regions implicated in semantic processing (Silverberg et al., 2011). The resemblance between VF patterns observed in our aMCI and AD groups suggests similar patterns of underlying neurological damage in these groups. As proposed by other studies, early neuropathological processes of AD, including A β and Tau pathology, may extend beyond the hippocampus and include cortical areas supporting semantic association processes even before the onset of dementia (Barbeau et al., 2012; Murphy et al., 2006; Pineault et al., 2017). Our findings support previous research which suggests that the VF test is a relevant tool to identify early semantic memory breakdown in prodromal stages of AD, and the idea that semantic VF

impairment is a neuropsychological hallmark of AD found prior to the onset of dementia (Kawano et al., 2010).

Age and education were shown to have a strong influence on verbal fluency performance, especially on semantic VF (Kawano et al., 2010). Compared to other studies, a major strength of our study is that participants were carefully matched (one-to-one) for age and education so that the differences observed between our groups could not be explained in terms of these variables. Yet, the fact that all our groups were relatively well educated may be a relative weakness of our study because it limits the generalization of our results to the entire population. Indeed, a good educational background has been shown to be a protective factor against cognitive decline, as proposed by the cognitive reserve hypothesis (Meng & D'Arcy, 2012). This hypothesis also states that, among AD patients, greater brain pathology occurs before the clinical symptoms of disease becomes manifest, and that the disease progression of people with a higher educational level follows distinct pathological and clinical paths (Meng & D'Arcy, 2012). Therefore, it can be questioned whether we would have obtained the same results with less educated participants. Furthermore, it is possible that this higher educational level, and the presence of a greater cognitive reserve, may partially explain why our AD group did not present a reversed VF pattern. Moreover, as part of this study, we mainly focused on the quantitative aspect of verbal fluency at the expense of qualitative elements such as clustering and switching that have recently been proved useful to distinguish aMCI and healthy elderly, as well as in identifying prodromal AD (Mueller et al., 2015; Weakley & Schmitter-Edgecombe, 2014). In line with our results supporting a semantic deterioration in aMCI, a recent study revealed that individuals with aMCI show performance decrements in total words and switching production on both VF conditions, whereas those naMCI produce fewer words and switches only on the phonemic condition (Weakley et al., 2013). Finally, future longitudinal studies would be required to assess the

predictive nature of verbal fluency performance to distinguish individuals who are most at risk of conversion to AD. Future studies should also incorporate neuroimaging measures such as PET or fMRI to investigate to what extent VF performance is representative of underlying neurodegenerative changes.

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Conflict of Interest

None declared.

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References

- 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.
- Ahn, H.-J., Seo, S. W., Chin, J., Suh, M. K., Lee, B. H., Kim, S. T., . . . Heilman, K. M. (2011). The cortical neuroanatomy of neuropsychological deficits in mild cognitive impairment and Alzheimer's disease: a surface-based morphometric analysis. *Neuropsychologia*, 49(14), 3931-3945.

- Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., . . . 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., 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(5), 1093-1101.
- Amieva, H., Le Goff, M., Millet, X., Orgogozo, J. M., Pérès, K., Barberger-Gateau, P., . . . Dartigues, J. F. (2008). Prodromal Alzheimer's disease: successive emergence of the clinical symptoms. *Annals of neurology*, 64(5), 492-498.
- Barbeau, E., Didic, M., Tramon, E., Felician, O., Joubert, S., Sontheimer, A., . . . Poncet, M. (2004). Evaluation of visual recognition memory in MCI patients. *Neurology*, 62(8), 1317-1322.
- Barbeau, E. J., Didic, M., Joubert, S., Guedj, E., Koric, L., Felician, O., . . . Ceccaldi, M. (2012). Extent and neural basis of semantic memory impairment in mild cognitive impairment. *Journal of Alzheimer's disease*, 28(4), 823-837.
- Benoit, S., Rouleau, I., Langlois, R., Dostie, V., Kergoat, M., & Joubert, S. (2017). The Impact of Time and Repeated Exposure on Famous Person Knowledge in Amnesic Mild Cognitive Impairment and Alzheimer's Disease. *Neuropsychology*.
- 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.
- Brandt, J., & Manning, K. J. (2009). Patterns of word-list generation in mild cognitive impairment and Alzheimer's disease. *The Clinical Neuropsychologist*, 23(5), 870-879.

- Chan, A. S., Butters, N., Paulsen, J. S., Salmon, D. P., Swenson, M. R., & Maloney, L. T. (1993). An assessment of the semantic network in patients with Alzheimer's disease. *Journal of Cognitive Neuroscience*, 5(2), 254-261.
- Chan, A. S., Butters, N., & Salmon, D. P. (1997). The deterioration of semantic networks in patients with Alzheimer's disease: A cross-sectional study. *Neuropsychologia*, 35(3), 241-248.
- Delis, D. (2001). Delis-Kaplan executive function scale (D-KEFS). *San Antonio: The Psychological Corporation*.
- Duong, A., Whitehead, V., Hanratty, K., & Chertkow, H. (2006). The nature of lexico-semantic processing deficits in mild cognitive impairment. *Neuropsychologia*, 44(10), 1928-1935.
- Elias, M. F., Beiser, A., Wolf, P. A., Au, R., White, R. F., & D'Agostino, R. B. (2000). The preclinical phase of Alzheimer disease: a 22-year prospective study of the Framingham Cohort. *Archives of neurology*, 57(6), 808-813.
- Feldman, H. H., Haas, M., Gandy, S., Schoepp, D. D., Cross, A. J., Mayeux, R., . . . Dougal, S. (2014). Alzheimer's disease research and development: a call for a new research roadmap. *Annals of the New York Academy of Sciences*, 1313(1), 1-16.
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research*, 12(3), 189-198.
- Gainotti, G., Quaranta, D., Vita, M. G., & Marra, C. (2014). Neuropsychological predictors of conversion from mild cognitive impairment to Alzheimer's disease. *Journal of Alzheimer's Disease*, 38(3), 481-495.
- Gauthier, L., Dehaut, F., & Joanette, Y. (1989). The bells test: a quantitative and qualitative test for visual neglect. *International journal of clinical neuropsychology*.

- Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R. C., Ritchie, K., Broich, K., . . . Chertkow, H. (2006). Mild cognitive impairment. *The Lancet*, *367*(9518), 1262-1270.
- Gladsjo, J. A., Schuman, C. C., Evans, J. D., Peavy, G. M., Miller, S. W., & Heaton, R. K. (1999). Norms for letter and category fluency: demographic corrections for age, education, and ethnicity. *Assessment*, *6*(2), 147-178.
- Greenaway, M. C., Smith, G. E., Tangalos, E. G., Geda, Y. E., & Ivnik, R. J. (2009). Mayo older americans normative studies: factor analysis of an expanded neuropsychological battery. *The Clinical Neuropsychologist*, *23*(1), 7-20.
- Henry, J. D., Crawford, J. R., & Phillips, L. H. (2004). Verbal fluency performance in dementia of the Alzheimer's type: a meta-analysis. *Neuropsychologia*, *42*(9), 1212-1222.
- Hodges, J. R., Erzinclioglu, S., & Patterson, K. (2006). Evolution of cognitive deficits and conversion to dementia in patients with mild cognitive impairment: a very-long-term follow-up study. *Dement Geriatr Cogn Disord*, *21*(5-6), 380-391.
doi:10.1159/000092534
- Joubert, S., Brambati, S. M., Ansado, J., Barbeau, E. J., Felician, O., Didic, M., . . . 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.
- Kaplan, E., Goodglass, H., & Weintraub, S. (2001). *Boston naming test*: Pro-ed.
- Kawano, N., Umegaki, H., Suzuki, Y., Yamamoto, S., Mogi, N., & Iguchi, A. (2010). Effects of educational background on verbal fluency task performance in older adults with Alzheimer's disease and mild cognitive impairment. *International Psychogeriatrics*, *22*(06), 995-1002.

- 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.
- Laws, K. R., Duncan, A., & Gale, T. M. (2010). 'Normal' semantic–phonemic fluency discrepancy in Alzheimer's disease? A meta-analytic study. *Cortex, 46*(5), 595-601.
- Lonie, J. A., Herrmann, L. L., Tierney, K. M., Donaghey, C., O'Carroll, R., Lee, A., & Ebmeier, K. P. (2009). Lexical and semantic fluency discrepancy scores in aMCI and early Alzheimer's disease. *Journal of neuropsychology, 3*(1), 79-92.
- Loonstra, A. S., Tarlow, A. R., & Sellers, A. H. (2001). COWAT metanorms across age, education, and gender. *Applied neuropsychology, 8*(3), 161-166.
- McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Kawas, C. H., . . . 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.
- Meng, X., & D'Arcy, C. (2012). Education and dementia in the context of the cognitive reserve hypothesis: a systematic review with meta-analyses and qualitative analyses. *PLoS One, 7*(6), e38268.
- Monsch, A. U., Foldi, N., Ermini-Fünfschillin, D., Berres, M., Taylor, K., Seifritz, E., . . . Spiegel, R. (1995). Improving the diagnostic accuracy of the Mini-Mental State Examination. *Acta Neurologica Scandinavica, 92*(2), 145-150.
- Mueller, K. D., Kosciak, R. L., LaRue, A., Clark, L. R., Hermann, B., Johnson, S. C., & Sager, M. A. (2015). Verbal Fluency and Early Memory Decline: Results from the Wisconsin Registry for Alzheimer's Prevention. *Archives of Clinical Neuropsychology, 30*(5), 448-457.

- Murphy, K. J., Rich, J. B., & Troyer, A. K. (2006). Verbal fluency patterns in amnesic mild cognitive impairment are characteristic of Alzheimer's type dementia. *Journal of the International Neuropsychological Society*, 12(04), 570-574.
- Nutter-Upham, K. E., Saykin, A. J., Rabin, L. A., Roth, R. M., Wishart, H. A., Pare, N., & Flashman, L. A. (2008). Verbal fluency performance in amnesic MCI and older adults with cognitive complaints. *Archives of Clinical Neuropsychology*, 23(3), 229-241.
- Pakhomov, S. V., & Hemmy, L. S. (2014). A computational linguistic measure of clustering behavior on semantic verbal fluency task predicts risk of future dementia in the Nun Study. *Cortex*, 55, 97-106.
- Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of internal medicine*, 256(3), 183-194.
- Pineault, J., Jolicoeur, P., Grimault, S., Bermudez, P., Brambati, S. M., Lacombe, J., . . . Joubert, S. (2018). Functional changes in the cortical semantic network in amnesic mild cognitive impairment. *Neuropsychology*, 32(4), 417.
- Raoux, N., Amieva, H., Le Goff, M., Auriacombe, S., Carcaillon, L., Letenneur, L., & Dartigues, J. F. (2008). Clustering and switching processes in semantic verbal fluency in the course of Alzheimer's disease subjects: Results from the PAQUID longitudinal study. *Cortex*, 44(9), 1188-1196.
- Reitan, R. (1955). The relationship of the Trail Making Test to organic brain damage. *Journal of Consulting Psychology*, 19, 393-394.
- Rey, A. (1964). L'examen clinique en psychologie [The clinical psychological examination]. *Paris: Presses Universitaires de France*.

- Rinehardt, E., Eichstaedt, K., Schinka, J. A., Loewenstein, D. A., Mattingly, M., Fils, J., . . . Schoenberg, M. R. (2014). Verbal fluency patterns in mild cognitive impairment and Alzheimer's disease. *Dementia and geriatric cognitive disorders*, *38*(1-2), 1-9.
- Rouleau, I., Salmon, D. P., Butters, N., Kennedy, C., & McGuire, K. (1992). Quantitative and qualitative analyses of clock drawings in Alzheimer's and Huntington's disease. *Brain and cognition*, *18*(1), 70-87.
- Rubin, E. H., Storandt, M., Miller, J. P., Kinscherf, D. A., Grant, E. A., Morris, J. C., & Berg, L. (1998). A prospective study of cognitive function and onset of dementia in cognitively healthy elders. *Archives of neurology*, *55*(3), 395-401.
- Silverberg, N. B., Ryan, L. M., Carrillo, M. C., Sperling, R., Petersen, R. C., Posner, H. B., . . . Ferman, T. J. (2011). Assessment of cognition in early dementia. *Alzheimers Dement*, *7*(3), e60-e76. doi:10.1016/j.jalz.2011.05.001
- St-Hilaire, A., Hudon, C., Vallet, G. T., Bherer, L., Lussier, M., Gagnon, J.-F., . . . Rouleau, I. (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. *The Clinical Neuropsychologist*, 1-25.
- Teng, E., Leone-Friedman, J., Lee, G. J., Woo, S., Apostolova, L. G., Harrell, S., . . . Lu, P. H. (2013). Similar verbal fluency patterns in amnesic mild cognitive impairment and Alzheimer's disease. *Archives of clinical neuropsychology*, *28*(5), 400-410.
- Troyer, A. K. (2000). Normative data for clustering and switching on verbal fluency tasks. *Journal of clinical and experimental neuropsychology*, *22*(3), 370-378.
- Vaughan, R., Coen, R., Kenny, R., & Lawlor, B. (2016). Preservation of the Semantic Verbal Fluency Advantage in a Large Population-Based Sample: Normative Data from the TILDA Study. *Journal of the International Neuropsychological Society: JINS*, *22*(5), 570-576.

- Weakley, A., Schmitter-Edgecombe, M., & Anderson, J. (2013). Analysis of verbal fluency ability in amnesic and non-amnesic mild cognitive impairment. *Archives of Clinical Neuropsychology*, 28(7), 721-731.
- Weakley, A., & Schmitter-Edgecombe, M. (2014). Analysis of verbal fluency ability in Alzheimer's disease: the role of clustering, switching and semantic proximities. *Archives of Clinical Neuropsychology*, 29(3), 256-268.
- Wechsler, D. (2000). *Echelle d'intelligence de Wechsler pour adultes*.
- Wechsler, D. (2001). Echelle de mémoire de Wechsler MEM III. *Les éditions du Centre de Psychologie appliquée, Paris*.
- 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.

Table 1. Demographic data for the participant groups.

Figure 1. Total number of words generated in phonemic and semantic verbal fluency conditions for the experimental groups. Error bars represent the standard error of the mean.

VF = Verbal fluency, AD = Alzheimer's disease, aMCI = amnesic Mild Cognitive Impairment, NC = normal control participants.

Table 1. Demographic data for the participant groups

	NC (n=32)	aMCI (n=32)	AD (n=32)
Age (years)	76.81 (7.43)	76.03 (7.35)	76.66 (6.68)
Range	62-88	61-88	61-88
Gender (Women/Men)	20/12	21/11	23/9
Education (years)	13.00 (3.92)	14.00 (3.91)	13.09 (3.79)
MMSE	29.09 (0.93)	27.42 (2.26)*	25.78(2.14)**

Note. Mean score with standard deviations in parentheses; NC = Normal controls; aMCI = amnesic mild cognitive impairment; AD =Alzheimer's disease; MMSE = Mini-Mental Status Exam.

* $p < .05$. aMCI performed significantly more poorly than NC on the MMSE.** $p < .001$. AD performed significantly more poorly than both aMCI and NC, but there was no other significant difference between groups on demographic variables.

FIGURE CAPTION

Figure 1. Total number of words generated in phonemic and semantic verbal fluency conditions for the experimental groups. Error bars represent the standard error of the mean. VF = Verbal fluency, AD = Alzheimer’s disease, aMCI = amnesic Mild Cognitive Impairment, NC = normal control participants.



