Vulnerability to Semantic and Phonological Interference in Normal Aging and amnestic Mild Cognitive Impairment (aMCI)

Marie-Joëlle Chasles[1,3], Sven Joubert[2,3], Jessica Cole [1,3], Émilie Delage[2,3] and Isabelle Rouleau[1,4*]

[1]*Psychology department, Université du Québec à Montréal (UQAM), Montréal, Canada;*

[2]*Psychology Department, Université de Montréal (UdeM), Montréal, Canada;*

[3]*Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal (CRIUGM), Canada;*

[4]*Centre Hospitalier de l'Université de Montréal (CHUM) research center, Montréal, Canada*

Author Note

*Correspondence concerning this article should be adressed to Isabelle Rouleau, Ph.D., Psychology Department, Université du Québec à Montréal (UQAM), Montréal, Qc, Canada, H3C 3P8. E-mail: rouleau.isabelle@uqam.ca

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Abstract

Objective: To determine whether the increased vulnerability to semantic interference previously observed in aMCI is specifically associated with semantic material, or if it also affects other types of material, suggesting generalized executive and inhibitory impairment. **Method.** Seventy-two participants divided into two groups (33 aMCI, 39 NC) matched for age and education were included. They completed a comprehensive neuropsychological examination, the French version of the LASSI-L (semantic interference test), and a homologous experimental phonological test, the TIP-A. Independent sample *t*-tests, mixed ANOVA and ANCOVA on memory and interference scores were conducted to compare memory and interference in both conditions for both groups. **Results.** For memory scores, results revealed significant main effects of Group (NC > aMCI) and Condition (semantic > phonological), and significant interactions (poorer performance in the semantic condition for aMCI). aMCI committed more phonological false recognition errors, were disproportionately more vulnerable to retroactive semantic interference and showed a higher percentage of intrusion errors associated with proactive semantic interference than NC. **Conclusions.** To our knowledge, this is the first study to compare vulnerability to interference in aMCI and normal aging with two similarly designed semantic and phonological word list learning tasks. Taken together, our results suggest that aMCI present with broad difficulties in source memory and inhibition, but that impaired deep semantic processing results in additional semantic intrusion errors during proactive interference and impacts their ability to show good recall after an interference list (greater semantic retroactive interference). Results are discussed according to the Level-of-processing and Activation/Monitoring theories.

Keywords: phonological and semantic interference; MCI; semantic memory; verbal learning; LASSI-L

Key points:

- Question: Is the greater vulnerability to semantic memory interference (SI) of aMCI patients specifically attributable to their semantic impairment, or does it also arise from executive factors?
- Findings: Vulnerability to SI in aMCI seems to be explained by both executive factors and an inability to process semantic material as efficiently as controls. aMCI do not perform worse in a semantic than in a phonological context, but rather lose the advantage generally conferred by semantic material.
- Importance: This study provides a better understanding of the mechanisms underlying vulnerability to SI, which has recently emerged as a promising early cognitive marker of aMCI and Dementia of the Alzheimer Type (DAT).
- Next steps: This paradigm allowed assessment of interference effects on a wider range of episodic memory processes than previous paradigms. This phenomenon could be replicated among populations with other conditions or neurodegenerative diseases.

Introduction

Discovering early cognitive markers of Dementia of the Alzheimer Type (DAT) is essential to identify the most at-risk individuals at an early stage, especially since DAT is fundamentally defined by its cognitive symptoms. Furthermore, cognitive tests are non-invasive and often more easily accessible tools than advanced medical imaging techniques and biomarkers. A large body of research has demonstrated that DAT and amnestic Mild Cognitive Impairment (aMCI), considered a prodromal phase of the disease, are associated with deficits in episodic memory as well as early impairment of semantic memory (Amieva et al., 2008; Benoit et al., 2018; Chasles et al., 2020; Joubert et al., 2010; Joubert et al., 2021; Langlois et al., 2015; Marra et al., 2021; Wilson et al., 2011; Chertkow & Bub, 1990), which refers to our general knowledge about the world, its organization and meaning (Tulving, 1972).

More recently, some researchers have investigated vulnerability to semantic interference in memory as an early cognitive marker of DAT. Memory interference occurs when one learned piece of information disrupts the learning or recall of another. Interference is qualified as perceptual when both pieces of information share similar phonological or orthographic features, or as semantic when they share conceptual features (e.g., fall into the same category, such as animals). A distinction is made between proactive interference (PI), which occurs when previous learning interferes with subsequent learning, and retroactive interference (RI), which occurs when new learning interferes with previously learned information (Atkins et al., 2011; Postman & Underwood, 1973).Vulnerability to interference depends on an individual's ability to inhibit irrelevant competing information present in the environment (for example, in another list of words), or salient in memory (e.g. because of priming effect). Indeed, one dual-process theory of memory, the Activation/Monitoring Theory (Gallo & Roediger, 2002) is particularly relevant in the study of interference since it accounts for both the implicit activation mechanisms underlying interference, and the impact of executive factors (monitoring) in interference management. According to the first component of this theory, the implicit associative response account (IAR; Roediger & McDermott, 1995) suggests that the activation of an item in semantic memory (e.g., dog) spreads to other items belonging to the same semantic category (e.g., pets), making them more salient (primed) and thus more likely to be confused and recalled at the expense of the target information. Following these unconscious and automatic processes, executive monitoring mechanisms enable verification of the accuracy and the source of memory traces to manage interference and allow the selection of the target information and inhibition of competing representations (Gallo & Roediger, 2002; Johnson et al., 1993; Johnson & Raye, 1981; Koriat & Goldsmith, 1996; Langevin et al., 2009; Persson et al., 2013).

In the past decade, Loewenstein and colleagues have developed a cognitive test specifically designed to assess semantic interference in DAT and its early stages, the Loewenstein Acevedo Scale for Semantic Interference and Learning (LASSI-L; Curiel et al., 2013). In this test, the subject is asked to learn two competing word lists sharing similar semantic features (the same semantic categories). Results of these studies showed that vulnerability to proactive interference and the number of intrusion errors could discriminate patients with DAT and aMCI from older controls with a high level of sensitivity and specificity (correct classification rate of 90%) (Capp et al., 2020; Crocco et al., 2014). This test also distinguished individuals with subjective cognitive decline (SCD) who will further progress to aMCI from those who will revert to normal on longitudinal follow-up (Crocco et al., 2021; Curiel et al., 2018; Loewenstein et al., 2016). Scores on the LASSI-L were also found to be highly correlated with medial temporal lobe atrophy and beta-amyloid (Aβ) load (Curiel et al., 2013; Loewenstein et al., 2015).

However, in LASSI-L studies, only vulnerability to interference from semantic material was examined. In fact, taking into account the findings of the studies previously mentioned, which suggest that interference management is an executive process, it is our view that the cognitive marker studied by Loewenstein and colleagues (semantic interference) actually reflects two distinct interacting phenomena, namely (1) the general vulnerability to interference managed by executive functions such as inhibition and processing of competing information, and (2) the degradation of semantic memory. Thus, it is not known whether aMCI patients would have been equally vulnerable to interference of another type (suggesting more generalized vulnerability to interference), or whether it is their semantic impairments specifically that explain their vulnerability. In order to isolate the specific contribution of each of these factors in aMCI, it would be necessary to integrate a homologous non-semantic condition. Indeed, in addition to

semantic memory impairment, aMCI and DAT patients present executive dysfunctions that make them particularly prone to intrusion errors arising from deficient frontal mechanisms such as inhibitory processes (Amieva et al., 2004; Borella et al., 2017; Desgranges et al., 2002; Perry & Hodges, 1999).

Furthermore, previous studies obtained conflicting results concerning the impact of semantic knowledge breakdown on vulnerability to semantic interference. For example, some case studies of patients with isolated semantic or phonological deficits showed that the former were equally vulnerable to both types of interference due to global deficits in control processes (Hamilton & Martin, 2007), or even demonstrated heightened phonological interference and facilitated management of semantic interference (Harris et al., 2014). These results are also in line with those obtained by Wilson and colleagues (2018) in older adults and the Representational-Hierarchical theory (RH theory) presented in their study. This theory posits that recognition memory should be protected from semantic but not perceptual interference when higher-level treatment is impaired. This suggests that if the ability to perform higher-level processing such as semantic elaboration and association is impaired, the interference effect based on these links should also be weakened. Indeed, semantic interference operates at the level of associations (which requires adequate treatment and analysis of inter-item semantic associations to be effective) whereas phonological interference operates at the level of basic perceptual treatment (requiring no further higher-level treatment to be potent).

In addition, studies focusing on memory recognition processes also reported that DAT patients were more vulnerable to phonological interference than older controls (Sommers & Huff, 2003), and that those with aMCI were more vulnerable to interference in general than older controls,

regardless of the type of material presented or the severity of semantic impairment (Hanseeuw et al., 2010). Taken together, these studies suggest that the vulnerability to semantic interference observed in aMCI by Lowenstein and colleagues (Curiel et al., 2013; Curiel et al., 2013, 2018; Snitz et al., 2010) may be explained, at least in part, by executive weaknesses (e.g. inhibitory and monitoring process) above and beyond semantic deficits. Moreover, discrepancies between the findings of studies on interference may also arise from the various paradigms used to assess interference effects. Indeed, most studies comparing semantic and phonological interference have used working memory build-up of interference paradigms (Hamilton & Martin, 2007; Hanseeuw et al., 2010; Harris et al., 2014), or focused on generating false memories using DRM paradigms (Wilson et al., 2018; Ballou & Sommers, 2008; Sommers & Huff, 2003; Sommers & Lewis, 1999). Comparing these two types of interference in aMCI using concurrent word list learning tasks such as the LASSI-L, which allows for interference to be analyzed across a wider range of memory processes (e.g. proactive interference, retroactive interference, difference in interference vulnerability between cued and free recall, delayed recall and recognition) would provide the more inclusive perspective required to begin to reconcile the findings of studies on interference that used very diverse paradigms.

Taking into account all of these considerations, the present study therefore aims to investigate the vulnerability to interference in learning of healthy older and aMCI participants across a wide range of memory processes using two similarly designed semantic and phonological interference tests. More precisely, we aim to determine whether the increased vulnerability to semantic interference previously reported in individuals at increased risk of DAT (aMCI) is specifically associated with semantic processing or whether it also affects other types of learning, suggesting more generalized and non-specific vulnerability to interference. To do so, we administered the

French version of the LASSI-L as well as the TIP-A (Chasles et al., 2022), an experimental test using the same procedure as the LASSI-L but generating phonological rather than semantic interference. To the best of our knowledge, this is the first study to directly compare aMCI patients' vulnerability to interference under two homologous conditions (semantic and phonological), using such a comprehensive paradigm. First, since the main diagnostic criterion for aMCI is memory impairment, it is expected that patients will have marked memory impairments (learning and forgetfulness) in both semantic and phonological conditions compared to healthy older adults. We also expect them to be globally more vulnerable to interference than older controls. However, given the early semantic impairment associated with the disease, we expect disproportionately poorer performance of aMCI patients in the semantic context (poorer memory capacity and greater vulnerability to semantic than to phonological interference). In other words, we expect more pronounced deficits on the LASSI-L than on the TIP-A in aMCI patients compared to healthy older adults.

Methods

Participants

A total of 72 French-speaking Caucasian participants (N = 72) divided into two groups (aMCI N=33 and NC N=39) matched for age and education were included in the study. French had to be one of their mother tongues, they had to have completed at least primary school, and they had to have lived in Quebec for the past 30 years (similar cultural exposure needed for some of the semantic tests administered). Potential participants were excluded if they had any of the following conditions : (1) history of neurological disease or metabolic condition that may

interfere with current cognitive functioning (except the diagnosis of aMCI for the patient group), (2) history of multiple head injuries, or head injury with loss of consciousness in the past year, (3) history of current untreated psychiatric or mood disorder, (4) drug or alcohol abuse, (5) polypharmacy or general anesthesia in the past 6 months, (6) sensory or motor deficit that may invalidate the assessment; (7) history of neurodevelopmental disorder (autism, ADHD, dyslexia, etc.).

Amnestic mild cognitive impairment group. Thirty-three patients (*n = 33*) aged 66 to 89 years old were included. They were referred by the outpatient clinic of the Institut Universitaire de Gériatrie de Montréal (IUGM) and of the Centre hospitalier de l'Université de Montréal (CHUM). Patients were diagnosed as having amnestic Mild Cognitive Impairment (aMCI), according to 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 SD below the mean for age and education on at least two tests of anterograde episodic memory), (3) no significant impact of cognitive decline on activities of daily living as assessed during a clinical interview, (4) failure to meet DSM-5 diagnostic criteria for any major neurocognitive disorder (Albert et al., 2011; Petersen, 2003; Petersen, 2011).

Normal control group. Thirty-nine healthy older adults (n = 39) aged 66 to 88 years old were included in the study. They were selected from the CRIUGM voluntary participant pool. Participants were excluded if they had any of the following conditions: (1) meeting criteria for mild or major neurocognitive disorder as defined by the DSM-5, (2) scoring below (< 1.5 standard deviations) on the Montreal Cognitive Assessment (MoCA) considering age and

education (Nasreddine et al., 2005). Participants' normal cognitive functioning was assessed using a range of standardized neuropsychological tests.

Procedures and measures

The present study is part of a larger research project investigating semantic memory disorders in normal aging and MCI. That project was approved by the Comité d'Éthique de la Recherche Vieillissement-Neuroimagerie (CER-VN-IUGM)) and from the CRCHUM research ethics boards. All participants provided signed and informed written consent. The objectives and requirements of the study were explained to potential participants during a phone call, and a short questionnaire was administered to ensure their eligibility. Two assessment sessions of two hours each were conducted at one- to three-week intervals. They took place at the IUGM research center or at the participant's home. The phonological interference test (TIP-A) and the semantic interference test (LASSI-L), which have very similar procedures, were administered on different days and the order in which these tasks were administered was counterbalanced to avoid a possible order effect. Moreover, since the RAVLT was used for different studies that were part of the wider research project, performance on this test had to remain free of possible interference. Thus, our interference tasks were administered after the RAVLT. Half of the sample (half aMCI and half of the controls) performed the RAVLT and the LASSI-L in the same session, and the other half the RAVLT and the TIP-A in the same session. Thus, any interference by the RAVLT with performance would be equivalent for both groups.

Interference tests

Loewenstein-Acevedo scales for semantic interference and learning (LASSI-L)

The French adaptation of the LASSI-L with an added recognition condition (Chasles et al., 2022) was used to assess vulnerability to semantic interference. The LASSI-L procedure consists of presenting an initial list (List A) of 15 words belonging to the following categories: fruits, musical instruments, or items of clothing (5 words per category). Participants are informed from the outset of the three categories to which the words belong. Each word is presented individually on a card for 4 seconds, and the participant is instructed to read each one aloud. These two features (telling participants the categories from the outset, and multimodal encoding by seeing, reading, pronouncing, and hearing the words) are designed to encourage more active and deeper encoding of the targets (see: Curiel et al., 2013). Immediately after the 15 words are read, the subject is asked to recall as many words as possible in 60 seconds regardless of the order (Free Recall A: FRA). Following this recall, the participant is asked to recall the words according to their category (20 sec./category): "*I would like you to tell me again all the words in the list that were fruits*" (Cued recall 1A: CRA1). Then, List A is presented again using the same procedure, and a second cued recall is performed (CRA2). A new list of 15 words (List B) belonging to the same semantic categories (fruits, musical instruments, clothes) is then presented in the same way, followed by a free recall (FRB), a cued recall (CRB1), a second presentation of List B, and a second cued recall (CRB2). Without further encoding, the participant is asked to recall as many words from list A as possible (Short-Term Free Recall A: STFA), followed by a recall by category (Short-Term Cued Recall A: STCA). Finally, after a 20-minute break, a delayed free recall (DR) of all words (list A and B) is performed. Correctly recalled words and intrusion errors

are scored across recalls (Crocco et al., 2014). The French version also includes a recognition condition in which the participant must recognize the 15 words from list A mixed with distractors from list B, words not presented in the test but belonging to the same semantic categories, and words unrelated to the study items.

Phonological interference and learning test (TIP-A)

To assess vulnerability to phonological interference, we administered the TIP-A (Chasles et al., 2022). The TIP-A is an experimental test that was designed to use the same procedure as the LASSI-L, but with induction of phonological rather than semantic interference. The two tests thus consist of two lists of 15 words, using the same instructions, procedures and recall times, and the same format for material. Both the TIP-A and LASSI-L require processing interference induced by two competing lists of words in memory that share similar characteristics. The difference between the tests lies mainly in the type of items used to generate the interference, namely phonological versus semantic. The TIP-A includes two lists of verbs (List A and List B) classified according to the initial letter of each word (15 verbs, with 5 words beginning with the letter C, 5 with A, and 5 with R). In addition, the items on list A and list B are phonological neighbors (e.g. *Chanter* [to sing] and *Changer* [to change]), without apparent semantic association. The TIP-A is an experimental test with promising psychometric properties (internal consistency between $\alpha = 0.87$ and $\alpha = 0.90$ for the different indices, convergent validity with the LASSI-L ranging from $r = .368$ and $r = .692$ despite their different type of material), that has been shown to be effective in generating phonological interference in healthy older adults in a previous experimental study (Chasles et al., 2022).

The following indices were calculated for each of the two interference tests (A = list A, B = list B, FR = free recall, CR = cued recall, ST = short-term recall):

- FRPI: free recall proactive interference percentage ((FRA-FRB)/FRA)*100
- CRPI: cued recall proactive interference percentage ((CRA-CRB)/CRA)*100
- FrPI: failure to recover from proactive interference (1-CRB2/CRA2)*100, indicating the percentage of performance the participant failed to recover in B2 compared to A2 (maximum storage).
- Release PI: release from proactive interference ((CRB2-CRB1)/CRB1)*100, representing improvement from B1 (PI) to B2 (second learning of list B to release PI).
- FRRI: free recall retroactive interference percentage ((FRA-STFA)/FRA)*100
- CRRI: cued recall retroactive interference percentage ((CRA-STCA)/CRA)*100
- PIE pro: percentage of intrusion errors occurring during proactive interference (CRBintrusion errors/(CRB + CRBintrusion errors)) x 100
- PIE retro: percentage of intrusion errors occurring during retroactive interference (STCAintrusion errors / (STCA + STCAintrusion errors)) x 100
- Total PIE: total percentage of intrusion errors during the test ((Total intrusion errors/(Total correct recalls + Total intrusion errors)) x 100

Neuropsychological assessment

Participants' global cognitive functioning was assessed using the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), and by means of questionnaires and a comprehensive neuropsychological test battery. Among these are standardized tests to assess attention and executive function (Trail making test A & B, D-KEFS Stroop, phonological and semantic verbal fluency: P & Animals, WAIS-III Digit Span), verbal episodic memory (RAVLT, WMS-III Logical Memory) and semantic memory (Pyramids and Palm trees test, the clock drawing test, picture naming, as well as object characteristics and unique semantic entities tests, e.g. famous personalities [POP-40: Benoit et al., 2018], media events [PUB-40: Langlois et al., 2015], and

logo and public places identification (Montembeault et al., 2017). A summary of the neuropsychological test results for both groups can be found in Table 7.

Statistical analyses

Preliminary analyses identified seven extreme values (+4 SDs), four on LASSI-L scores (FRPI, CRRI, False recognition percentage and total PIE) and three on TIP-A scores (FRPI, CRPI, CRRI). A Winsorization was performed on these seven individual extreme values, reassigning them to a value of 3.29 SD. All recall and interference scores on both tests were normally distributed. Prior to each analysis, statistical and visual inspection was performed to ensure compliance with the preliminary assumptions of the ANOVA and ROC curves. All participants were included in the statistical analysis, with the exception of two aMCI participants who did not complete the TIP-A test. There was no other missing data for any variable of interest.

Independent samples t-tests were performed to compare age, education and MoCA performance between groups. A chi-square test was performed to compare the ratio of women to men between groups. We performed a mixed ANOVA (2x2) on the memory scores (number of words correctly recalled in every trial) and percentage of intrusion errors, using the Group (2 levels: NC, aMCI) as the between-group factor, and the Condition (2 levels: semantic, phonological) as within-subjects factor. In addition, we performed a mixed ANCOVA (2x2) on the interference score ratios using the Group (2 levels: NC, aMCI) as the between-group factor, and the Condition (2 levels: semantic, phonological) as within-subjects factor, this time controlling for the initial learning capacity (performance on List A recall) to isolate the vulnerability to interference effect (as in Curiel et al., 2018). Finally, we also performed ROC (Receiver Operating Characteristic)

curves analysis for discriminating between groups on all variables of both tests (semantic and phonological). The best cutoff values were estimated according to the Youden index.

Transparency and openness

We report how we constructed our sample, the manipulations performed, and the measures we used in the study. We follow JARS (Kazak, 2018), and strive to provide all the information necessary to understand, evaluate, and potentially replicate the study. The data, analysis code, and research materials are not available online, but can be supplied upon request. Data were analyzed using the Statistical Package of Social Science (IBM SPSS 27) with an alpha significance level of $p < .05$. This study's design and its analysis were not pre-registered.

Results

As expected, there was no difference between groups in terms of age, $t(70) = -1.84$, $p = .070$, n.s., or education, $t(70) = 0.18$, $p = .862$, n.s. Results of the chi-square test revealed no significant gender difference between groups, X^2 (1) = 2.27, $p = .132$, n.s. Demographic characteristics for NC and aMCI participants are presented in **Table 1.** To examine test administration order effects, *t*-tests were performed and there was no difference in performance between participants who started with the LASSI-L first vs. those who started with the TIP-A, nor between those who performed the LASSI-L in the same session as the RAVLT and those who performed them in different sessions.

[Insert Table 1. here]

Performance analyses between groups

Recall, intrusion errors and recognition

Results of the mixed ANOVA performed on memory scores (number of words correctly recalled) revealed, for all recall trials, a significant main effect of Group, a significant main effect of Condition (semantic vs. phonological), and a significant Group x Condition interaction (**Table 2**). Analysis of main effects revealed that the aMCI group recalled significantly fewer words than the NC group on all recall trials of both tests, and that fewer words were recalled on the TIP-A than on the LASSI-L in both groups. The significant interaction effect can be explained by the fact that aMCIs showed a smaller discrepancy between semantic and phonological performance than NCs, due to poorer performance in the semantic condition.

Looking more closely at recognition (**Figure 1**), for which the data were slightly different from recalls even though interaction and main effects were still significant, we observed that NCs were significantly better at recognizing words in the semantic than in the phonological condition, while this was not the case for the aMCI group. Moreover, aMCIs and NCs did not differ in their ability to recognize targets in the phonological condition. Concerning false recognition errors (**Figure 1**), results of the mixed ANOVA revealed a main effect of Group, $F(1,68) = 28.555$, $p < .001$, $\eta_p^2 = 0.296$, a main effect of Condition, $F(1,68) = 7.242$, $p < .01$, $\eta_p^2 = 0.096$ and a significant Group x Condition interaction, $F(1, 68) = 3.960$, $p = .05$, $\eta_p^2 = 0.055$. Simple effects analysis revealed that aMCIs committed more false recognition errors than NCs in both conditions. In addition, while NCs made a comparable number of semantic and phonological false recognition errors, aMCIs made significantly more false recognition errors in the phonological than in the semantic condition.

[Insert Table 2. & Figure. 1. here]

Regarding intrusion errors (**Table 3**), results of the mixed ANOVA performed on the percentage of intrusion errors (PIE) made during the trials in which proactive and retroactive interference took place (recall B and short-term recall of A) generally revealed a significant main effect of Group, a significant main effect of Condition, but no significant interaction effect (Group x Condition) except for the percentage of intrusion errors made during the first cued recall of list B (CRB1; score where proactive interference is the highest). Analysis of simple effects generally revealed that the aMCI group made a significantly higher percentage of intrusion errors than the NC group in both conditions, and that more intrusion errors were made in the phonological context for both groups. Concerning the significant interaction for the percentage of intrusion errors made at CRB1 (**Figure 2**), simple effect analysis revealed that NCs made significantly less intrusion errors in the semantic than in the phonological condition, whereas aMCIs had a similar rate of intrusion errors in both conditions. Moreover, there was no significant difference between the percentage of phonological intrusion errors between groups, but the aMCI group made significantly more semantic intrusion errors than the NC group.

[Insert Table 3. & Figure 2 here]

Interference

Results of the mixed ANCOVA performed on the percentage of interference scores (**Table 4**) were more equivocal than those on the memory scores. They often revealed no significant main effect of Group or interaction (Group x Condition). The only interesting results were a trend toward a significant interaction for cued recall retroactive interference (CRRI) and a significant

interaction for mean recall retroactive interference (free + cued). As shown in **Figure 3**, analysis revealed that the NC group was significantly less vulnerable to retroactive interference in the semantic than in the phonological condition, whereas the aMCI group showed a similar vulnerability to retroactive interference in both conditions, and even a trend toward greater retroactive interference in the semantic condition. On average (mean retroactive interference), aMCIs were significantly more vulnerable to retroactive interference in a semantic context than NCs, while no significant difference was observed in the phonological context.

[Insert Table 4. & Figure 3. here]

Discrimination capacity

Additional ROC curves analyses using areas under the curve (AUC) were performed to estimate the discrimination capacity between groups on both tests. Results are summarized in Figure 4, Table 5 and Table 6.

Discussion

The present study aimed to investigate and compare vulnerability to interference and memory performance in aMCI and healthy older participants. More specifically, we aimed to determine whether the increased vulnerability to semantic interference previously reported in individuals at increased risk of DAT (aMCI) is specifically associated with semantic processing or whether it also affects other types of learning, suggesting more generalized vulnerability to interference. To our knowledge, the current study is the first to systematically compare vulnerability to interference in aMCI and older controls, using two similarly designed semantic and phonological

word list learning tasks. The paradigm used also enabled investigation of these effects across a wider range of memory processes (e.g. proactive interference, retroactive interference, difference in interference vulnerability between cued and free recall, delayed recall and recognition).

Overall, all the results obtained converge towards the conclusion that vulnerability to semantic interference in aMCI seems to be explained by both executive factors (generalized source control and inhibition impairment) and an inability to process semantic material as efficiently as controls. It should be noted that aMCI patients do not perform worse in a semantic than in a phonological context, but rather lose the benefit generally conferred by semantic material in normal aging. These conclusions provide a coherent explanation of all the results obtained, i.e. the performance profiles for both groups reflected in memory scores (recall and recognition) and interference scores (intrusion errors and decrease in percentage of correct word recalled between two learning trials).

Memory performance

Our main findings show, for aMCI patients, (1) disproportionate difficulties in recall and recognition in the semantic context, and (2), what initially appears to be counter-intuitively, an increased tendency to make phonological false recognition errors.

First, although both tasks require verbal learning, the LASSI-L places a higher demand on semantic processing. Therefore, the lower performance of aMCI on this task seems to reflect their disproportionate semantic impairment, when compared to normal aging. This finding aligns with extensive research demonstrating semantic deficits in aMCI (Chasles et al., 2020; Didic et al., 2011; Hodges et al., 2006; Joubert et al., 2010, Joubert et al., 2021; Marra et al., 2021; Molinuevo

et al., 2011; Murphy et al., 2006; Pineault et al., 2018; Raoux et al., 2008; Wilson et al., 2011; Gainotti et al., 2014). Also, unsurprisingly, aMCI patients generally showed poorer memory performance than controls in both conditions (semantic and phonological), and memory performance was also poorer overall in a phonological than in a semantic condition, irrespective of group. These results were expected within the framework of the level-of-processing theory (Craik & Lockhart, 1972) and dual-process theories such as the Fuzzy-trace theory (Brainerd & Reyna, 2001), according to which there is deeper processing of semantic material (or *gist*) than phonological material (or *verbatim* trace) (Chasles et al., 2022; Brainerd & Reyna, 2001, 2004; Reyna & Brainerd, 1995; Sachs, 1967; Craik & Lockhart, 1972). Second, while healthy controls made a similar number of false recognition errors in both conditions, aMCI patients made significantly more phonological than semantic false recognition errors, even though they made more errors than controls in both conditions. These results indicate that aMCI patients seem to be more vulnerable to being lured by distractors than older controls, especially when the lures share phonological features with the targets.

aMCI participants' increased difficulty in the semantic context during recall and recognition, but conversely greater propensity to phonological vs. semantic false recognition errors, may seem contradictory. However, it is easily explained by the different level of processing required by the two tasks (Level-of-processing theory: semantic processing being deeper and stronger). During recall and recognition of learned words, aMCI patients do not seem to benefit as much as controls from the depth of processing usually offered by the semantic material. Therefore, aMCI patients recall fewer words than expected in a semantic context, and their recognition of semantically processed targets is not significantly better than that of more superficially processed phonological targets. On the other hand, shallower processing of items, at the expense of achieving higher-

level deep processing (based on semantic associations and elaboration), thus logically makes aMCI patients more likely to be fooled by lures that share superficial perceptual properties, rather than semantic properties, with the targets. These results are consistent with the main prediction of the RH theory (Wilson et al., 2018): in a semantic context, the source of interference occurs at the level of disrupted semantic association (those with aMCI are then less able to grasp and encode the interfering associative relationships between target items and lures), whereas perceptual interference occurs at the level of preserved features processing, which causes more potent interference. Similarly, false recognition error pattern is also consistent with the dual-process Activation/Monitoring Theory (Gallo & Roediger, 2002). First, the associative component of the model would predict that, given the degradation of the semantic memory network in aMCI, the implicit activation of semantically related items within the network would be weakened, reducing their salience and thus the risk that they would be falsely recognized in comparison with preserved implicit activation of similar phonological representations. Second, the monitoring component of this theory could explain the overall greater tendency toward false recognition errors in aMCI, which would be attributable to less efficient executive/inhibitory processes leading to more frequent false recognition of lures in both conditions (positive response bias).

Intrusion errors and interference

Concerning percentage of intrusion errors and vulnerability to interference, our main findings show, for aMCI patients, a generalized vulnerability to interference (more intrusions errors, false recognition errors and interference than controls in both conditions) combined with a more specific vulnerability to semantic interference in certain contexts, including : (1)

disproportionately more semantic intrusion errors during proactive interference than controls, and (2) an increased vulnerability to semantic retroactive interference.

First, a significant difference between the two groups' intrusion error patterns across conditions was observed for only one of the intrusion scores: the percentage of intrusion errors during the first cued recall of list B (CRB1). As the first cued recall of interfering list B, it is the trial with the highest risk of generating words belonging to the correct categories, but not to the correct list (either from list A or not present at all in the task). Therefore, this recall taps further into source memory and mechanisms needed to resist proactive interference. Results on the CRB1 showed that aMCI patients committed a similar percentage of intrusion errors in both conditions, equivalent to older controls in the phonological context, but significantly more than their counterparts in the semantic context. Many previous studies on LASSI-L have shown an increased vulnerability to semantic intrusion errors in aMCIs compared to older controls across many learning trials, and particularly cued recall (Capp et al., 2020; Crocco et al., 2014; Kitaigorodsky et al., 2021; Matías-Guiu et al., 2017; Torres, Rosselli, Loewenstein, Curiel, Vélez Uribe, et al., 2019). However, by having a second non-semantic condition, our study demonstrated that aMCI patients are more prone to intrusion errors than controls in general, above and beyond the type of material (suggesting generalized difficulties in source memory), with the exception of the CRB1 trial, where they were increasingly impaired in the semantic context. Our paradigm also demonstrates that aMCIs are not *per se* more prone to semantic than to phonological intrusion errors, but rather lose the benefit of semantic deeper processing, resulting in a comparable percentage of intrusion errors in both conditions (a profile similar to that obtained in recall and recognition). These results are in line with recent studies suggesting that the percentage of semantic intrusion errors related *specifically* to proactive interference on

the LASSI-L (CRB1) is a clear marker to differentiate aMCIs from normally aging older adults (Capp et al., 2020; Kitaigorodsky et al., 2021), also shown to uniquely differentiate Amyloid+ and Amyloid− aMCI patients (Loewenstein et al., 2018) and even distinguish between those at-risk individuals with PreMCI who progressed to MCI over time from those who reverted to normal on longitudinal follow-up (Crocco et al., 2021).

Second, concerning interference (the decrease in percentage of correct words recalled between the two lists), as reported in previous studies (Crocco et al., 2014), our results indicate that aMCI patients are more vulnerable to retroactive semantic interference than older controls. Indeed, older controls were more prone to phonological than semantic retroactive interference, whereas aMCI patients showed an inverse tendency. However, regarding vulnerability to proactive interference, no significant difference was observed between groups. Both groups were equally vulnerable to PI interference, with a globally higher vulnerability in the semantic than in the phonological context. Our results differ from those reported in previous studies using the LASSI-L (Crocco et al., 2014; Curiel et al., 2018), which showed a greater vulnerability to semantic proactive interference and a higher failure to recover from semantic PI in aMCIs compared to older controls. This discrepancy may result from a lack of statistical power related to our somewhat small sample size. However, our trends do not seem to suggest additional proactive interference that would be *specifically* associated with semantic material (very similar patterns in both conditions). Also, some studies (Loewenstein, Curiel, DeKosky, et al., 2017; Loewenstein, Curiel, Wright, et al., 2017) used the CRB1 and CRB2 recall scores directly as indicators of proactive interference and release from PI, rather than the decrease from one recall to the other. This method may also explain the discrepancies, as these scores, taken directly, could primarily reflect memory rather than interference. Other studies using the LASSI-L have obtained

equivocal results on the vulnerability of aMCI patients to semantic proactive interference, highlighting the need for further research (e.g. in their Spanish validation of the LASSI-L, Matías-Guiu et al. 2017). All in all, our results suggest that the analysis of errors committed due to PI would be a better marker of pathological cognitive change than the decrease in the number of words correctly recalled, a conclusion also raised in the literature (Gainotti et al., 2014; Kitaigorodsky et al., 2021; Torres et al., 2019).

One key difference between PI and RI is that RI always involves the passage of time (time lapse between the original recall and the short delay recall). According to level-of-processing theory, it is then expected that more superficial processing of phonological material, in contrast to deeper processing for semantic material, makes phonological learning more sensitive to retroactive interference after the presentation of a new list and the passage of time. Thus, the fact that aMCI patients present greater semantic retroactive interference suggests more superficial processing of semantic material, resulting in greater forgetting over time compared to controls. In summary, for aMCI patients, all the results obtained converge towards more generalized source control and inhibition impairment in addition to a loss of the benefit generally observed during the processing of semantic material compared to phonological processing. The classical level-of processing theory, in conjunction with the Activation/Monitoring theory (implicit activation mechanisms + executive monitoring mechanisms, Gallo & Roediger, 2002), therefore constitute an ideal theoretical canvas to explain and predict aMCI patients' performance when facing different types of interference. Other studies have suggested that partial encoding of semantic material may be the cornerstone of the vulnerability to semantic interference (Rouleau et al., 2001; Vallet et al., 2016).

Limitations

The present study has some limitations. First, the somewhat small sample size lowered statistical power and may have prevented us from finding significant results, despite small to moderate effect sizes. Second, our sample was made up of individuals from a homogeneous cultural background (Caucasian, French-speaking, living in Quebec), which may limit the generalization of the findings to other cultural populations. Furthermore, the diagnosis of aMCI in patients was made and confirmed solely on the basis of their cognitive profile, and no biomarker (e.g. amyloid PET, FDG) was available to support the diagnosis and etiology. Moreover, inclusion of a group of patients diagnosed with Alzheimer's disease would have allowed us to confirm the similarities between the aMCI and the DAT patients, and further predict the source and evolution of the cognitive difficulties with progression of the disease. We also used a cross-sectional design, which does not allow us to state with certainty that the aMCI patients included in the study are those who will further progress to dementia. Replication of the present study, directly comparing semantic and phonological interference in homologous word list learning tasks, with a larger sample, also including a group of patients with a diagnosis of Alzheimer's disease, brain imaging or biomarkers and ultimately follow-up would be particularly useful for determining which markers are most predictive of the disease. Finally, we believe that the results obtained could be applied to an English-speaking population since the French LASSI-L was shown to be equivalent to the original English version (Chasles et al., 2022) and obtained similar diagnostic properties in the present study. However, to demonstrate the generalizability of the results to an English-speaking population would pose adaptation challenges for the TIP-A, which would have to be completely redone (by using phonologically similar verbs such as "walk" and "talk", "take" and "bake" etc.).

Conclusion

In conclusion, to our knowledge, this is the first study to meticulously compare vulnerability to interference and its impact on memory processes in two homologous concurrent word list learning tasks with different types of material (semantic vs. phonological). This procedure allowed us to isolate the impact of the semantic aspect of the material on learning, vulnerability to proactive interference, retroactive interference and source memory of aMCI patients, in order to better understand the interaction between memory impairment (including semantic memory) and more generalized executive difficulties (interference vulnerability, inhibition process, source memory). Our results suggest that the semantic aspect of the material has a very important impact on the quality of aMCI patients' learning, who show overall inferior memory performance than older controls, but even more so in a semantic than in a phonological condition. Regarding vulnerability to interference, we showed that aMCI patients present generalized difficulties in source memory and inhibition in addition to specific semantic difficulties, resulting in more intrusion errors in general, specifically more semantic errors during proactive interference, and a greater vulnerability to semantic retroactive interference than controls. In summary, our results suggest that difficulties in semantic memory prevent aMCI patients from benefiting as much as healthy older adults from the depth of processing offered by semantic material. This, in addition to general executive/monitoring weaknesses, represents the cornerstone of their memory impairment and vulnerability to errors and interference. These early difficulties in semantic memory, above and beyond executive difficulties related to inhibition, source memory and vulnerability to interference, are supported by the higher discrimination capacity obtained for the maximum storage and delayed recall scores in the semantic condition. The present study

paradigm is particularly informative regarding the mechanisms involved in learning and vulnerability to interference in normal aging and aMCI. In the future, it would be relevant to use the same paradigm among populations with other neurodegenerative diseases. For example, distinct profiles could be obtained for patients suffering from neurodegenerative diseases known to cause early executive difficulties, or early phonological difficulties (e.g. logopenic progressive aphasia, LPA), thus increasing our understanding of these diseases and improving diagnostic processes.

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Conflict of interest

The authors report no conflict of interest.

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Tables

Table 1.

Demographic data for both groups

	NC group (n= 39)	**aMCI group (n=33)**
Age (years)	77.10 (5.94)	79.62 (5.59)
Age range	66-88	66-89
Education (years)	14.28 (2.78)	14.14 (4.24)
Education range	10-20	7-24
Sex (Women/Men)	29/10	19/14
MoCA	27.44 (1.97)	24.09 (2.44) **
MoCA range	23-30	18-29

Note: Mean score with standard deviations in parentheses; NC = normal controls; aMCI = amnestic mild cognitive impairment, MoCA = Montreal Cognitive Assessment.

** $p < .001$ aMCI group performed significantly more poorly than NC group on the MoCA but there was no other significant difference between groups on demographic variables.

Tables

Table 2.

Mixed ANOVAs - semantic versus phonological memory performance in aMCI and NC groups

	NC (n = 39)		aMCI (n = 31)		F (p-value)	η_p^2
	LASSI-L	TIP-A	LASSI-L	TIP-A		
FRA	9.70(2.74)	4.95(1.64)	6.45(2.51)	3.56(1.53)	9.72 (< .01)**	.125
CRA1	10.85(2.65)	4.38(1.80)	6.55(2.35)	2.74(1.88)	21.52(< .001)***	.240
CRA2	13.69(1.45)	6.46(1.82)	9.84(2.83)	4.52(2.26)	12.97 (.001)**	.160
FRB1	6.95(2.18)	4.30(1.78)	4.42(2.14)	3.04(1.42)	5.88 (< .05)*	.080
CRB1	7.38(2.82)	3.23(1.53)	4.16(2.60)	2.20(1.33)	9.69 (< .01)**	.125
CRB2	11.31(2.34)	5.70(2.05)	7.74(2.88)	3.58(1.34)	5.68 (< .05)*	.077
STFA	6.38(2.68)	0.91(0.63)	2.35(2.01)	0.45(0.50)	39.02 (< .001)***	.365
STCA	8.33(2.40)	1.11(0.55)	4.19(2.55)	0.84(0.50)	45.70 (< .001)***	.402
DR	18.13(4.22)	8.15(3.80)	10.87(5.48)	3.32(2.50)	6.83 (< .05)*	.091
REC	11.64(2.49)	8.51(2.46)	10.03(2.94)	9.03(2.55)^{NS}	7.62 (< .01)**	.101

Note: Mean(standard deviation); NC = normal controls; aMCI = amnestic mild cognitive impairment; F (of the interaction); A = list A; B = list B
FR = free recall; CR = cued recall; STF = short term free recall; STC = short term cued recall; DR = Delayed recall; REC = recognition
* = significant at < .05, ** = significant at < .01, *** = significant at < .001
^{NS} no significant difference between LASSI-L and TIP-A recognition in aMCI, no significant difference between NC and aMCI groups' TIP-A recognition

Tables

Table 3.

Mixed ANOVAs - percentage of semantic versus phonological intrusion errors (PIE) in aMCI and NC groups.

	NC (*n* = *39*)		**aMCI (*n* = *31*)**		**F (*p*-value)**	**η_p^2**
	LASSI-L	**TIP-A**	**LASSI-L**	**TIP-A**		
PIE CRB1	19.15(20.11)	43.75(25.01)	46.54(25.61)	53.57(25.46)	4.03 (< .05)*	.057
PIE CRB2	10.49(11.72)	19.55(20.86)	22.46(16.93)	33.81(18.87)	0.230 (.633)	.003
PIE STCA	23.26(14.75)	38.28(31.26)	36.04(23.53)	54.44(31.43)	0.160 (.690)	.002
Total PIE	6.79(4.16)	17.43(10.07)	15.05(8.08)	27.60(9.19)	0.748 (.390)	.011

Note: Mean (standard deviation); NC = normal controls; aMCI = amnestic mild cognitive impairment; F (of the interaction); PIE = intrusion errors percentage; CRB1 = first cued recall of list B; CRB2 = second cued recall of list B; STCA = short term cued recall of list A.
* significant at < .05

Tables

Table 4.

Mixed ANCOVAs - percentage of semantic versus phonological interference in aMCI and NC groups.

	NC (*n* = *39*)		**aMCI (*n* = *31*)**		**F (*p*-value)**	**η_p^2**
	LASSI-L	**TIP-A**	**LASSI-L**	**TIP-A**		
FRPI	17.58(5.93)	-1.66(8.89)	34.04(6.79)	7.24(10.17)	0.181 (.672)	.003
CRPI	27.96(5.94)	-0.41(9.49)	37.14(6.87)	24.81(10.99)	0.642 (.426)	.010
PI mean	24.06(5.22)	-14.68(19.98)	33.97(5.98)	-8.73(22.86)	0.012 (.912)	.000
frPI	13.44(4.15)	-3.63(6.01)	23.83(6.01)	18.85(6.97)	1.089 (.301)	.016
Release PI	108.97(19.27)	126.69(18.43)	91.09(22.03)	89.45(21.07)	0.236 (.628)	.004
FRRI	32.52(5.37)	64.70(5.33)	62.71(5.33)	72.83(6.09)	2.993(.088)^T	.043^T
CRRI	18.12(5.58)	34.64(9.34)	40.39(6.45)	32.42(10.82)	1.695 (.198)	.025
RI mean	24.72(4.76)	48.66(8.91)	51.41(5.45)	40.55(10.19)	4.183 (.045)*	.060*

Note: estimated marginal mean (standard error); NC = normal controls; aMCI = amnestic mild cognitive impairment; F (of the interaction); FR = free recall; CR = cued recall; PI = proactive interference; RI = retroactive interference; frPI = failure to recover from proactive interference; A negative value signifies improvement, as opposed to interference.

* significant at < .05, ^{T} trend towards significance with a small to moderate effect size.

Tables

Table 5.

Results of the ROC curves for the memory score on the LASSI-L and TIP-A

	LASSI-L		TIP-A	
	AUC (confidence interval)	***p*-value**	**AUC (confidence interval)**	***p*-value**
FRA	.802 (.702 - .902)	<.001	.742 (.626 - .859)	<.001
CRA1	.881 (.803 - .959)	<.001	.746 (.632 - .860)	<.001
CRA2	.899 (.825 - .972)	<.001	.754 (.636 - .872)	<.001
FRB1	.793 (.690 - .896)	<.001	.695 (.573 - .817)	<.010
CRB1	.798 (.697 - .900)	<.001	.708 (.578 - .828)	<.010
CRB2	.838 (.748 - .928)	<.001	.810 (.708 - .912)	<.001
STFA	.885 (.805 - .964)	<.001	.703 (.587 - .829)	<.010
STCA	.883 (.803 - .962)	<.001	.653 (.524 - .782)	<.010
DR	.856 (.772 - .940)	<.001	.870 (.787 - .952)	<.001
REC	.660 (.534 - .786)	<.05	.421 (.284 - .558)	.421, ns.

Note: AUC = Area under the curve; A = list A; B = list B; FR = free recall; CR = cued recall; STF = short term free recall; STC = short term cued recall; DR = delayed recall; REC = recognition

Tables

Table 6.

Best cutoff values for scores with the highest discrimination capacity between groups

		Cutoff Value	Sensitivity/specificity	J
LASSI-L	**CRA2**	12/15 or less	87.90% / 79.50%	0.67
	STFA	4/15 or less	84.80% / 79.50%	0.64
	STCA	6/15 or less	87.90% / 76.90%	0.65
	CRA1	12/15 or less	87.90% / 79.50%	0.67
	DR	15/30 or less	72.70% / 84.60%	0.57
	FRRI	42% or more	81.30% / 69.20%	0.51
TIP-A	**DR**	5/30 or less	83.90% / 79.50%	0.63
	CRB2	4/15 or less	77.40% / 69.20%	0.47

Note: Value = number of correct words recalled or % of interference, J = Youden's index; A = list A; B = list B; CR = cued recall; STFA = short term free recall of list A; STCA = short term cued recall of list A; DR = delayed recall

Tables

Table 7.

Neuropsychological test results for both groups

	NC group (n = 39)	**aMCI group (n = 33)**
RAVLT IR total (1-5)	53.23(9.25) 33-72	34.61(9.11) 19-51
RAVLT DR	11.26(2.85) 6-15	5.73(3.25) 0-12
WMS-III Logical Memory IR	45.23(9.31) 22-67	29.85(10.37) 13-55
WMS-III Logical Memory DR	30.13(7.74) 13-47	14.94(8.53) 0-33
ROCF IR	15.41(6.11) 5-26	8.68(4.83) 0-23
ROCF DR	14.58(6.48) 5-26	8.30(4.57) 1-20
ROCF Copy	30.13(2.85) 21.5-36	28.88(4.74) 16.5-35
Forward Digit Span (total)	9.51(2.65) 6-16	8.64(1.78) 6-12
Backward Digit Span (total)	8.56(2.42) 4-14	7.30(1.88) 4-11
TMT-A (sec.)	36.69(9.07) 15-59	47.67(13.33) 27-88
TMT-B (sec.)	83.23(31.62) 25-208	123.70(45.16) 52-260
Stroop Trial 3 (inhibition, sec.)	68.86(21.15) 45-152	82.88(24.98) 56-143
Stroop Trial 4 (flexibility, sec.)	71.05(16.66) 47-117	99.47(36.16) 50-206
Phonological Verbal Fluency (P, 60 s.)	15.31(3.18) 9-21	12.00(3.80) 5-23
Semantic Verbal Fluency (Animals, 60 s.)	17.31(3.62) 9-27	11.73(4.02) 4-20
PPTT Total	50.23(1.58) 46-52	47.97(3.37) 37-52
BNT (30 items)	29.18(1.36) 23-30	25.67(4.37) 11-30
Clock Drawing Test (/10)	9,10(1.30) 5-10	8,15(1.73) 4-10

Note : Mean score(standard deviations) and range; NC = normal controls; aMCI = amnestic mild cognitive impairment, IR = immediate recall DR = delayed recall, ROCF = Rey-Osterrieth Complex Figure, PPTT = Pyramids and Palm Trees Test, BNT = Boston Naming Test.

Figures

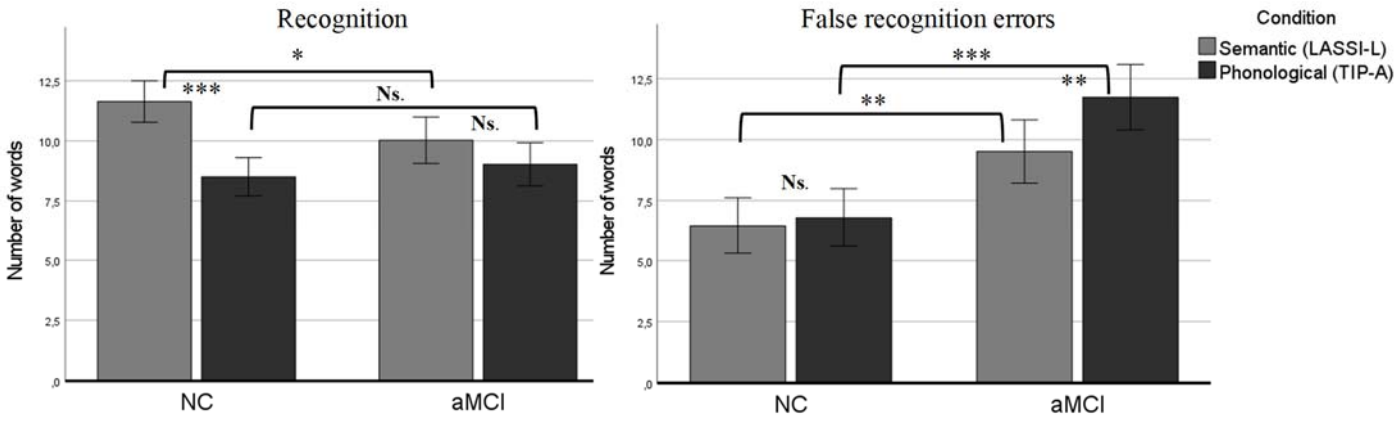

Figure 1. Recognition and false recognition errors for both groups and conditions. Error bars represent a 95% confidence interval, NC = normal control, aMCI = amnestic mild cognitive impairment, NS. = not significant, * = significant at $p < .05$, ** = significant at $p < .01$, *** = significant at $p < .001$.

Figures

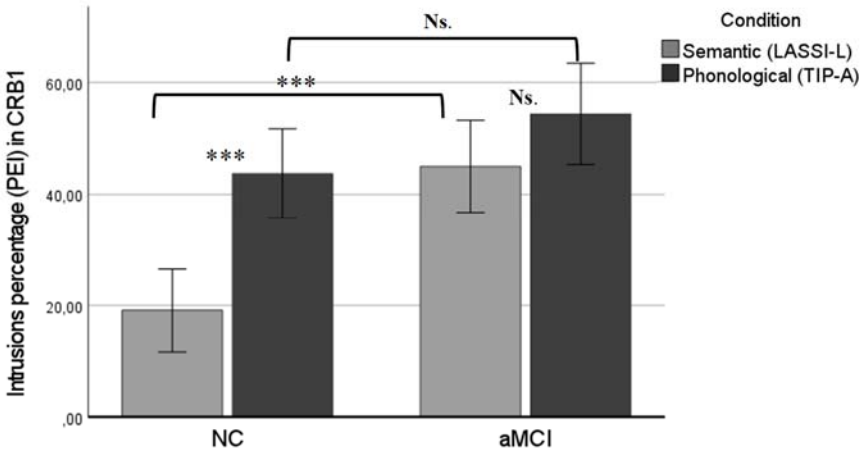

Figure 2. Percentage of intrusion errors (PIE) occurring during Cued Recall B1 (score at which proactive interference is highest). Error bars represent a 95% confidence interval, NC = normal control, aMCI = amnestic mild cognitive impairment, NS. = not significant, *** = significant at $p < .001$.

Figures

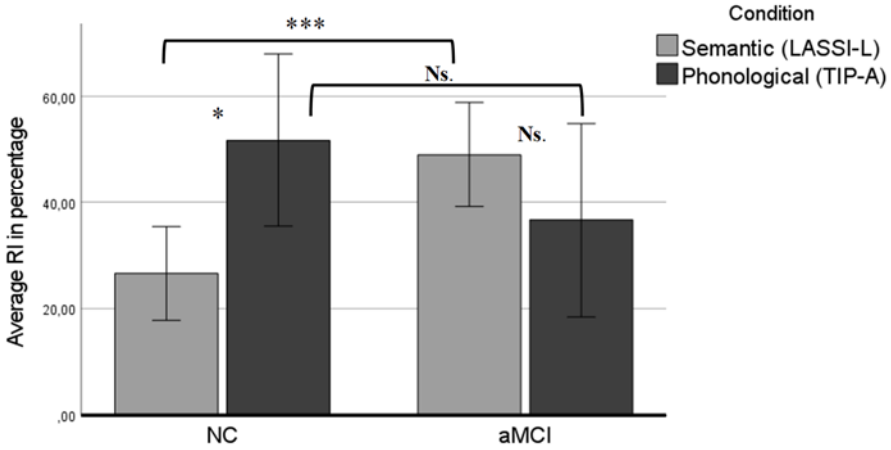

Figure 3. Average percentage of retroactive interference (free + cued recalls). Error bars represent a 95% confidence interval, NC = normal control, aMCI = amnestic mild cognitive impairment, NS. = not significant, * = significant at $p < .05$, *** = significant at $p < .001$.

Figures

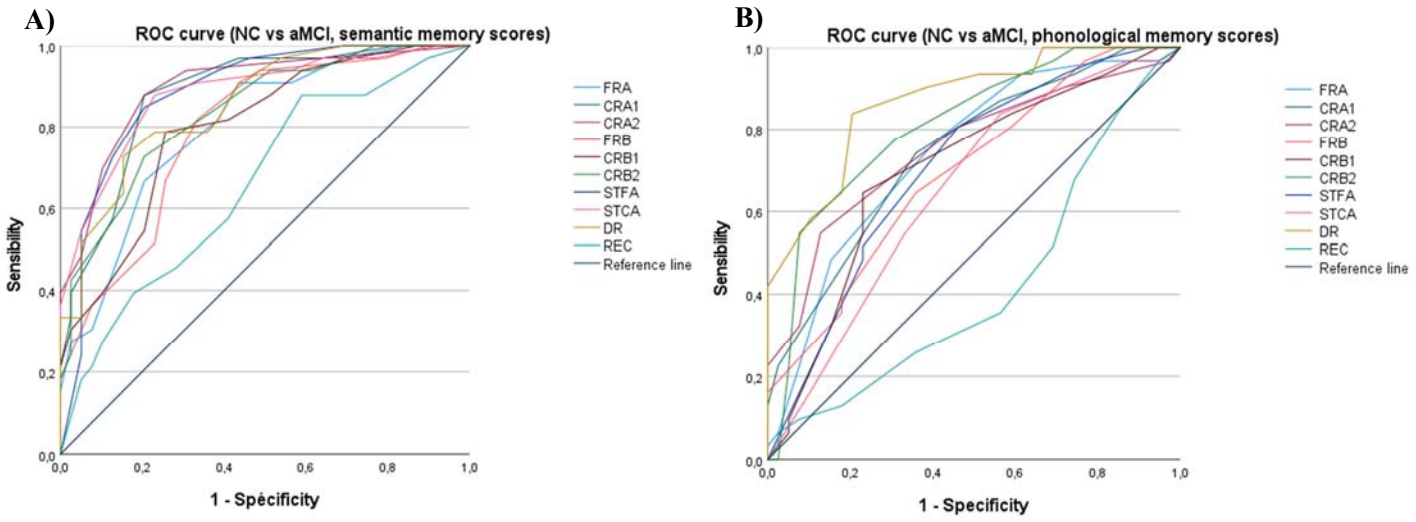

Figure 4. ROC curves analysis between groups. A) Semantic memory scores, B) Phonological memory scores. A = List A; B = List B; FR = free recall; CR = cued recall; STF = short term free recall; STC = short term cued recall; DR = delayed recall; REC = recognition.