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Declarative Learning, Priming, and Procedural Learning Performances comparing Individuals with Amnestic Mild Cognitive Impairment, and Cognitively Unimpaired Older Adults

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Abstract

Objective: While declarative learning is dependent on the hippocampus, procedural learning and repetition priming can operate independently from the hippocampus, making them potential targets for behavioral interventions that utilize non-declarative memory systems to compensate for the declarative learning deficits associated with hippocampal insult. Few studies have assessed procedural learning and repetition priming in individuals with amnestic mild cognitive impairment (aMCI). **Method:** This study offers an overview across declarative, conceptual repetition priming, and procedural learning tasks by providing between-group effect sizes and Bayes Factors (BFs) comparing individuals with aMCI and controls. Seventy-six individuals with aMCI and 83 cognitively unimpaired controls were assessed. We hypothesized to see the largest differences between individuals with aMCI and controls on declarative learning, followed by conceptual repetition priming, with the smallest differences on procedural learning. **Results:** Consistent with our hypotheses, we found large differences between groups with supporting BFs on declarative learning. For conceptual repetition priming, we found a small-to-moderate between-group effect size and a non-conclusive BF somewhat in favor of a difference between groups. We found more variable but overall trivial differences on procedural learning tasks, with inconclusive BFs, in line with expectations. **Conclusions:** The current results suggest that conceptual repetition priming does not remain intact in individuals with aMCI while procedural learning may remain intact. While additional studies are needed, our results contribute to the evidence-base that suggests that procedural learning may remain spared in aMCI and helps inform behavioral interventions that aim to utilize procedural learning in this population.

Keywords: Alzheimer disease, Memory disorders, Learning, Cognitive dysfunction, Bayes theorem, Cross-sectional studies

INTRODUCTION

The notion that there are memory systems that are able to operate independently from the hippocampus first became apparent in the case study H.M. H.M. acquired declarative memory impairment due to the surgical removal of parts of his medial temporal lobes including his hippocampi (Milner, Corkin, & Teuber, 1968) after which he was no longer able to learn new facts and events. In contrast, on procedural learning tasks such as the Mirror Tracing task, his performance improved with repetition, showing an ability to learn (Corkin, 1968). Squire (2004) defined declarative memory as the conscious recollection about facts and events. As can be inferred from H.M., this ability heavily relies on the medial temporal lobe (Eichenbaum & Lipton, 2008; van Strien, Cappaert, & Witter, 2009), among other brain areas. In contrast, non-declarative memory was defined as a collection of abilities that are expressed through the benefit from previous experiences rather than recollection.

Early researchers distinguished between the non-declarative" (or "implicit") and "declarative" (or "explicit") memory systems based on whether or not these types of memory were reliant on the medial temporal lobe (Henke, 2010;

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Squire, 2004). Other researchers distinguished between these types of memory based on the presence of conscious awareness: they found that conscious awareness of the learned information was required for declarative memory while it was not required for non-declarative memory (Squire & Dede, 2015). Both binary ways of distinguishing between declarative and non-declarative memory are now thought to be too simplistic, but the notion that there are multiple memory systems remains well accepted (Henke, 2010). Two of the main subtypes of non-declarative memory are repetition priming and procedural learning. Repetition priming is defined as the facilitation of retrieval that results from previous exposure, which can be achieved outside of conscious awareness (Schacter et al., 1987). Procedural learning encompasses skill learning, pattern learning, and habit learning (Squire & Dede, 2015). Skill learning tasks typically involve observable skills that improve with practice. Pattern learning tasks are tasks in which a pattern is repeated multiple times, with improved performance resulting from this repetition.

Cases like H.M. (Milner et al., 1968) inspired researchers to try to find double-dissociations between these different types of learning and memory. Impaired procedural learning with intact declarative learning was found in individuals with basal ganglia and cerebellum-related disorders such as individuals with early Parkinson's and Huntington's disease, and individuals with cerebellar atrophy (Knowlton, Squire, Paulsen, Swerdlow, & Swenson, 1996; Sanes, Dimitrov, & Hallett, 1990; Seger, 2006). A similar double-dissociation was found for perceptual repetition priming but not for conceptual repetition priming (Gabrieli, Fleischman, Keane, Reminger, & Morrell, 1995; Keane, Gabrieli, Mapstone, Johnson, & Corkin, 1995). Other studies demonstrated a double-dissociation between priming and skill learning (Butters, Heindel, & Salmon, 1990; Deweer et al., 1994; Yeates & Enrile, 2005), suggesting that these different subtypes of non-declarative learning are also mediated by different brain areas.

Alzheimer's disease (AD) is the most common cause of dementia, characterized by progressive cognitive decline that hampers independent functioning (Alzheimer's Association, 2020). AD-related neurofibrillary lesions are typically found first in the medial perirhinal and entorhinal cortices and then spread to the neocortex and the other parts of the parahippocampal gyrus as the disease progresses (Braak & Braak, 1991; Braak, Tredeci, Schultz, & Braak, 2000; Krumm et al., 2016). Other brain areas such as the primary motor and sensory cortices, the brain stem, and the cerebellum remain intact until the disease progresses (Fox et al., 2001; Whitwell et al., 2008).

In line with the typical spread in AD pathology, declarative learning and memory decline in the early stages of AD as atrophy tends to occur first in the hippocampus and entorhinal cortex (Stoub, Rogalski, Leurgans, Bennett, & deToledo-Morrell, 2010). Brain structures involved in priming tasks are dependent on task characteristics (Schacter, Dobbins, & Schnyer, 2004), however, conceptual repetition priming is thought to rely on the inferior frontal and temporal regions including the fusiform gyrus and parahippocampal gyrus (Buckner, Koutstaal, Schacter, & Rosen, 2000; De Wit et al., 2021; Schacter, Wig, & Stevens, 2007), which are likely impacted once the AD pathology spreads throughout the temporal lobe. Procedural learning is thought to rely on the subcortical brain areas that are thought to remain intact until the severe stages of AD (Knowlton et al., 1996; Sanes et al., 1990; Seger, 2006). As a result, both repetition priming and procedural learning are thought to remain intact in the very early stages of AD, with procedural learning remaining intact until the disease progresses to the severe stages (De Wit et al., 2021, 2020).

The pre-dementia stage during which cognitive impairment is present but does not significantly interfere with daily functioning is typically referred to as the mild cognitive impairment (MCI) phase of AD (Albert et al., 2011). When declarative memory impairment is present in MCI regardless of the etiology, the syndrome is referred to as amnestic MCI (aMCI; Petersen, 2004). Because pharmacological interventions to date fail to halt or reverse cognitive decline in AD, behavioral interventions offer a promising approach to help preserve cognitive health and function in MCI due to AD (Chandler et al., 2019; National Academies of Sciences, 2017; Ngandu et al., 2015; Olazarán et al., 2010).

The existence of non-hippocampus-reliant memory systems, such as the procedural learning system, has inspired researchers to develop behavioral interventions for individuals with early AD that utilize procedural learning to help compensate for the declarative learning and memory deficit (Fleischman, 2007; Greenaway, Hanna, Lepore, & Smith, 2008). However, the literature regarding the degree of sparing in procedural learning and repetition priming across the AD severity spectrum remains inconclusive, which may prevent the incorporation of techniques based on these memory systems into clinical practice. Two meta-analyses that assessed procedural learning and repetition priming comparing individuals with aMCI or AD dementia to controls highlighted that only three studies assessed procedural learning and only four studies thus far assessed repetition priming in MCI compared to controls (De Wit et al., 2021, 2020). Procedural learning was shown to be similar in individuals with aMCI/AD dementia and controls, with no statistical or meaningful differences, suggesting sparing in aMCI/AD dementia (De Wit et al., 2020). However, the literature on repetition priming in AD dementia is less conclusive (De Wit et al., 2021) and, therefore, more studies on repetition priming in the MCI phase of AD are needed.

Another concern related to the literature on sparing of procedural learning and repetition priming is that many studies attempting to assess whether these types of learning remain spared in AD assessed only procedural learning or only repetition priming in their sample and typically do not report effect sizes. Drawing conclusions regarding memory sparing based on the absence of a significant difference between groups is problematic because of the role that statistical power plays in such comparisons. In addition, drawing conclusions about memory sparing based on the absence of a

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significant difference between groups results in a binary distinction of spared versus impaired functioning. This binary distinction fails to consider the possibility of a continuous degree of sparing/impairment across the AD severity spectrum in procedural learning and repetition priming. Such a continuum might be expected based on the patterns of localization and spread of AD-related pathology. The use of Bayesian statistics, which allows researcher to draw more continuous conclusions about the presence of an effect versus the null hypothesis along with the strength of the evidence (Lakens, McLatchie, Isager, Scheel, & Dienes, 2020) has not been applied yet in the context of memory sparing in AD or aMCI.

The present study extends the literature by assessing procedural memory, conceptual repetition priming, and declarative learning in individuals with aMCI and cognitively healthy older adults in a single study. We aim to provide an overview across the different types of learning by reporting between-group effect sizes as well as Bayes Factors for declarative learning, conceptual repetition priming, and procedural learning in individuals with aMCI and cognitively unimpaired older adults, measured within the same group of individuals. Given the neuropathological staging discussed above, when comparing aMCI and cognitively unimpaired older adults, we hypothesize to see a large between-group effect size and a Bayes Factor in favor of a between-group difference on declarative learning as declarative impairments define the diagnosis of aMCI. We hypothesize to see a small-to-moderate between-group effect size and a Bayes Factor in favor of a between-group difference on conceptual repetition priming. Last, we hypothesize to observe the smallest between-group effect size and a Bayes Factor in favor of the null hypothesis when comparing both groups on procedural learning.

METHODS

Design

The current, transnational study builds on the "Physical Exercise And Cognitive Engagement Outcomes For Mild Neurocognitive Disorder" (PEACEOFMND) study and the "Memory-Dementia & Mild Cognitive Impairment" (M-DeMi) study. The PEACEOFMND study is a multi-site, group-randomized trial that took place at the University of Florida, Mayo Jacksonville, and Tallahassee Memorial HealthCare, Florida, USA. The present study utilizes data collected during the baseline visit prior to any intervention (De Wit et al., 2018). The M-DeMi study is a cross-sectional imaging study in cognitively unimpaired older adults and individuals with aMCI at Radboud University in Nijmegen, the Netherlands. The M-DeMi study aims to investigate different factors related to learning and memory performances. Both studies recruited individuals with aMCI and cognitively unimpaired older adults. The study samples and the eligibility screening processes are discussed in more detail in the Participants and the Procedures section below.

Measures

Screening measures

The Telephone Interview for Cognitive Status for Memory. The Modified Telephone Interview for Cognitive Status for Memory (TICS-M; Welsh, Breitner, & Magruder-Habib, 1993) was administered to all participants in the PEACEOFMND study. The TICS-M is a cognitive phone screener that is effective in identifying individuals with aMCI (Cook, Marsiske, & McCoy, 2009; Graff-Radford et al., 2006). The 50-item version of the TICS-M was used for the present study.

The Clinical Dementia Rating scale. The Clinical Dementia Rating (CDR) was administered as part of both the PEACEOFMND and M-DeMi studies (Morris, 1997). The CDR is a tool that assesses the influence of cognitive impairment on ADLs. The CDR is widely accepted as a reliable and valid measure for cognitive severity staging in individuals with cognitive impairment (Morris, 1993). The current study only included participants with a CDR of 0 or 0.5.

Cognitive measures

The Dementia Rating Scale-2. The Dementia Rating Scale-2 (DRS-2) was used to assess global cognitive functioning in the individuals with aMCI that were part of the PEACEOFMND study. The DRS-2 is an instrument that assesses several cognitive domains including conceptualization, attention, initiation/perseveration, construction, and declarative memory (Jurica, Leitten, & Mattis, 2001).

The Montreal Cognitive Assessment. The Montreal Cognitive Assessment (MoCA) was used to assess global cognitive functioning in all participants of the M-DeMi study. The MoCA is a cognitive screener that assesses multiple cognitive domains including visuospatial/executive functioning, construction, naming, declarative memory, attention, and abstraction (Nasreddine et al., 2005).

The Rey Auditory Verbal Learning Test. The Rey Auditory Verbal Learning Test (AVLT; Rey, 1964) was administered to assess declarative learning and memory. The AVLT consists of five consecutive 15-word list trials that were read to the participants. Total Recall was measured by the total number of words recalled after five trials (Trials 1–5). The Learning Score was calculated by multiplying the number of words on the first trial by five and subtracting this from the Total Recall score (Ivnik et al., 1990). Finally, delayed recall is determined by the number of words recalled after a 30-minute delay. This task was only administered to the individuals in the PEACEOFMND study.

The Mirror Tracing Task. The Mirror Tracing Task (MTT; Corkin, 1968) was used to assess visuomotor procedural learning. Participants were asked to trace the outline of a five-point star without touching the edges while viewing their hand and the stimulus in a mirror, during which the direct

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vision of hand and the stimulus was blocked. Completion time and errors were calculated for each trial. Two blocks of five trials, separated by an interval of 15 minutes, were administered. To mitigate frustration, a 300 second time limit per trial was used. The main outcome measures were the individual's linear change slopes across the 10 blocks for both errors (maximum of 100 errors) and time (in seconds) per trial. The generation of these slopes is described in more detail in the Slope Generation paragraph of the Data Analyses section.

The Serial Reaction Time Task. The Serial Reaction Time Task (SRTT) is a procedural learning task that involves pattern learning. The task in the present study was developed based on the paradigm of a previous study (Gabriel et al., 2013). It was administered on an Android-run tablet (Samsung SM-T580NZWAXAR 10.1 Galaxy Tab A T580) using OpenSesame software (Mathôt, Schreij, & Theeuwes, 2012). Participants were required to touch the cue as quickly possible. Each trial ended when the participants touched the cue or after 5000 milliseconds. A cue could appear in each quadrant of the screen, and the locations where a cue might appear remained visible at all times. The first six blocks were learning blocks during which the cue appears in a 12-element sequence that is repeated eight times per block, resulting in a total of 48 repetitions of the 12-element sequence. The seventh block was a transfer block during which a different 12-element sequence is repeated eight times.

Several procedural memory outcome measures were generated from this task all based on the median reaction time per block of block 1 through 7. First, a "pattern learning slope" was generated on the first six blocks. Additionally, a simple "pattern-transfer score" was generated based on the median reaction time of block 6 to 7. The generation of these slopes using is described in more detail in the Slope Generation paragraph of the Data Analyses section.

The Word-Stem Completion Task. The Word-Stem Completion Task (WSCT; Warrington & Weiskrantz, 1974) consisted of a set of 40 concrete nouns of 5-7 letters (e.g. "LEMON") with a mean occurrence frequency of 40 per million (Rajaram & Roediger, 1993). The test occurred in two phases. First, participants were shown 13 words on a rating scale. Of these 13 words, one was added to the start and two words were added at the end of the rating scale to reduce primacy and recency effects, respectively; these extra three words were not part of the 40-word set. Participants were asked to rate how much they liked each word on a 5-point Likert scale. They were not told that they would be asked about the words again at a later stage. Immediately after, twenty visual word-stems on cards (e.g. LEM) were shown, one at a time, and participants were asked to complete the word-stems with the first word that came to mind. Fifty percent of the stems could be completed using the words from the rating scale they were previously exposed to, and the other fifty percent of the stems could not be completed with words they were previously exposed to in order to determine baseline guessing rates. During the second phase, which occurred right after the completion of the first phase, the full procedure was repeated using a new 13-word list and 20 word-stems. The main outcome variable was the ratio of the number of stems that were completed with the 20 words from the set of 20 words to which they were previously exposed divided by the number of stems that were completed with any word from the 40-wordset in total. This task was only administered to the individuals in the PEACEOFMND study.

Participants

The Study Characteristics of the samples can be found in Tables 1 and 2. Both studies recruited individuals with clinical diagnoses of aMCI (Albert et al., 2011) and cognitively unimpaired older adults. Clinical diagnoses were made based on available medical records, often including neuro-imaging and neuropsychological evaluations. Additional criteria for participation are listed in Tables A1 and A2. The study eligibility screening process is discussed in more detail as part of the Procedures section below. The sample demographics for the participants are listed in Table 1. Overall, 85 cognitively unimpaired controls and 81 participants with aMCI participated in the study. The inclusion of individuals with aMCI was based on clinical diagnoses rather than cut-off scores on cognitive screeners. The lowest score on the MoCA for individuals as part of the M-DeMi study was 22. The lowest score on the TICS-M for individuals as part of the PEACEOFMND study was 21.

Study Procedures

Informed consent

All procedures were completed in accordance with the Helsinki Declaration. Only participants who provided both verbal and written informed consent were able to participate as approved by the Institutional Review Board of Medical Ethics Committee at each study site.

Study eligibility

Eligibility was determined by medical record review and a phone screening. Questions were asked about medications, language, physical abilities and basic demographic information such as age, gender, and contraindications to MRI (due to parent study aims). The criteria and procedures to ensure that the individuals with aMCI were in the MCI phase and that controls did not have cognitive impairment differed between the studies: as part of the PEACEOFMND study, the TICS-M (Welsh et al., 1993) was administered to both the individual with aMCI as well as the study partners, and the CDR was also administered. As part of the M-DeMi study, the MoCA (Nasreddine et al., 2005) was administered to all participants.

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Table 1. Sample demographics for the PEACEOFMND subsample

Cognitively unimpaired older adults ($n = 64$)	*M*	*SD*
Age (years)	68.0	10.7
Level of education (years)	16.3	2.7
TICS-M Score	36.8	3.5
Converted MMSE Score	27.1	1.6
Race/Ethnicity	*N*	%
White/Caucasian	54	84.4
African America/Black	3	4.7
Asian or Pacific Islander	2	3.1
Not reported	5	7.8
Gender	*N*	%
Men	22	37.3
Women	37	62.7
Individuals with aMCI ($n = 65$)	*M*	*SD*
Age (years)	73.9	7.4
Level of education (years)	16.1	2.7
TICS-M Score	28.9	4.0
Converted MMSE Score	22.8	2.1
DRS-2 Score	130.6	7.9
Race/Ethnicity	*N*	%
White/Caucasian	58	89.2
African America/Black	3	4.6
Asian	1	1.5
Hispanic or Latino	1	1.5
Not reported	2	3.0
Gender	*N*	%
Men	29	44.6
Women	36	55.4

Table 2. Sample demographics for the M-DeMi subsample

Cognitively unimpaired older adults ($n = 21$)	*M*	*SD*
Age (years)	71.2	7.0
Level of education (years)	18.3	5.1
Level of education (Verhage score*)	5.9	1.0
MoCA score	26.8	1.9
Converted MMSE score	29.1	1.0
Race/Ethnicity	*N*	%
White/Caucasian	21	100.0
Gender	*N*	%
Men	11	52.4
Women	10	47.6
Individuals with aMCI ($n = 11$)	*M*	*SD*
Age (years)	72.9	7.5
Level of education (years)	15.3	4.1
Level of education (Verhage Score*)	5.7	1.2
MoCa score	23.9	1.9
Converted MMSE score	27.8	1.40
Race/Ethnicity	*N*	%
White/Caucasian	11	100.0
Gender	*N*	%
Men	9	81.8
Women	2	18.2

*Dutch educational system categorized into levels from 1 = less than 6 years of primary education to 7 = university degree (Duits & Kessels, 2014).

Test visit

During the test visit, several cognitive measures were administered to both the individuals with aMCI and the cognitively unimpaired controls. The PEACEOFMND study used the DRS-2 and the M-DeMi study used the MoCA. The MTT and SRTT were administered as part of both studies. As part of the PEACEOFMND study, the AVLT and the WSCT were also administered.

Data Analysis

General analysis information and testing statistical assumptions

Data analyses were conducted using IBM® SPSS (Armonk, 2007) and R (Team, 2015). Prior to data analysis, all dependent variables were converted to *Z*-scores checked for their distribution, incorrect values, and outliers. Throughout this study, *Z*-scores of > 3 above or below the full sample mean were considered outliers. While the distributions were close to normal, the dependent variables that remained statistically non-normally distributed after excluding outliers were normalized by a Blom transformation (Blom, 1954). Age and level of education were explored as covariates in all analyses.

Procedural Learning Slope Generation

The MTT time and error slopes were generated for all participants that completed more than six trials and the SRTT pattern learning slope was generated for those who completed all six learning blocks. For the MTT, there were 27 participants that discontinued the MTT before or during the 6th trial, which was 15.9% of the participants who completed the MTT. For the SRTT, there were three participants (all individuals with aMCI from the PEACEOFMND study) that were excluded as their *Z*-score of the standard deviation of the median reaction time for the first 6 blocks was higher than three. Eight participants (two controls and six individuals with aMCI; one of the individuals with aMCI was from the M-DeMi otherwise all PEACEOFMND) were excluded because they made 30 or more errors during the six learning blocks.

For the MTT, both error and time slopes were generated based on the errors per trial and time to completion (in seconds) per trial, respectively. The trial variable was centered and served as the time IV for the MTT slopes. For the SRTT, a 'pattern learning' slope was generated based on the median reaction time per block of the six learning blocks. The block variable was centered and served as the time IV for the SRTT pattern learning slope. Three slopes were generated by outputting the coefficients when running individual linear Ordinary Least Squares regressions with the time variable as the IV in SPSS. Additionally, a "pattern-transfer" simple slope score was generated based on the median reaction time of block 6 to block 7 using the same method. The SRTT pattern learning slope, SRTT pattern-transfer score, MTT error

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slope, and MTT speed slope slopes were outputted and served as the procedural learning DVs in the main analyses.

Main analyses

One-way analysis of covariance (ANCOVA) models were run; separate models were run for each of the dependent variables (i.e. the AVLT learning score, SRTT pattern learning slope, SRTT pattern-transfer score, MTT error slope, and MTT speed slope). Group (aMCI vs. healthy controls) served as the independent variable. The study (PEACEOFMND vs. M-DeMi), level of education, and age were included as covariates. The *F*-values outputted by the ANCOVA models were used to calculate effect sizes.

Effect size calculations

Between-group Hedges' *g* effect sizes comparing performance in aMCI to cognitively unimpaired older adults were calculated for each of the dependent variables in four sets of analyses. Cohen's *d*s and Hedges' *g*s are used to describe the standardized mean difference of an effect between groups and can be used to compare effects across measures or studies (Lakens, 2013).

In the first, third, and fourth sets of analyses, Cohen's *d*s were calculated without controlling for age and education in the full sample, and the PEACEOFMND and M-DeMi subsamples, respectively. In these three sets, Cohen's *d*s were calculated using the samples *n*s, means, and *SD*s. The Practical Meta-Analysis Effect Size Calculator by Wilson was used to derive separate between-group effect sizes (Cohen's *d*s) and effect size variances (retrieved in January 2021; Wilson, n.d.). Because Cohen's *d* can be inflated in small sample sizes, we converted all Cohen's *d* values to Hedges' *g* values. The procedural learning slopes were aggregated using the Robust Variance Estimation (RVE) method function for linear mixed effect models (Fisher & Tipton, 2015) using R studio (Team, 2015).

Effect size assumptions

Throughout this manuscript, a negative Hedges' *g* indicates that there was more learning in individuals with aMCI than in cognitively unimpaired controls. Further, a priori assumptions about the bounds of Hedges' *g* were made regarding what would be considered a meaningful effect. Per Cohen's criteria, a Hedges' *g* of 0.200 is considered 'small,' 0.500 is considered 'medium,' and 0.800 is considered 'large' (Cohen, 1977). Because a Hedges' *g* of 0.200 is typically considered small yet meaningful, a Hedges' *g* smaller than the absolute value of 0.200 is considered a trivial or non-meaningful difference for the present study.

Bayesian statistics

We repeated the analyses using Bayesian ANCOVAs in JASP (JASP Team, 2020) to calculate Bayes Factors (BF). BFs were used to determine how likely to be true the results obtained with each group comparison were, given the data. The main advantage of using Bayesian statistics is that it provides a quantification of the evidence in support of the null hypothesis, rather than only against it (Lakens et al., 2020). An uninformative prior was used across Bayesian analyses to allow closer alignment with null hypothesis testing. Further, using an uninformative prior allowed us to keep the prior consistent across all three types of memory, which facilitates more accurate comparisons across tasks. To facilitate our interpretation of the BFs, the benchmarks of Jeffreys (1961) were used. Per these benchmarks, a BF_{10} of ≥ 100 provides decisive evidence for H_1, a BF_{10} of 10–30 provides very strong evidence for H_1, a BF of 3–10 provides substantial evidence for H_1, a BF of 1–3 provides anecdotal evidence for H_1, a BF of 1 provides no evidence. Further, a BF_{10} between 1/3 and 1 provides anecdotal evidence for H_0, and a BF_{10} between 1/10 and 1/3 provides substantial evidence for H_0.

RESULTS

Results of Assumption Testing

After the slope generation, several outliers in scores (*z*-score $> \pm 3$) were identified and removed ($n = 1$ for AVLT learning score; $n = 2$ for MTT error slope; $n = 0$ for MTT time slope; $n = 1$ for SRTT pattern learning slope; $n = 1$ for SRTT pattern-transfer simple slope, and $n = 2$ for WSCT ratio score).

Main Results Comparing Individuals with Amnestic MCI to Controls

The Hedges' *g*s for all four sets of analyses are listed in Table 3. The results for these same analyses in the subsamples are listed in Table A3 to allow the comparison of these results separately for the PEACEOFMND and M-DeMi studies. The output of the ANCOVAs used to calculate Hedges' *g* controlled for age and education can be found in more detail in Table A4, and the information used to calculate Hedges' *g* for the full sample and the subsamples without controlling for the level of age and education can be found in Table A5.

Our results showed a significant learning difference ($p < .001$) on the AVLT, with a medium-to-large effect size ($g = 0.658$) and a Bayes Factor indicative of decisive evidence for the presence of a between-group difference ($BF_{10} = 859.046$) between cognitively unimpaired older adults and individuals with aMCI.

For the WSCT, no significant difference ($p = .067$) was found between cognitively unimpaired older adults and individuals with aMCI; although a small-to-medium effect size ($g = .333$) was obtained and the Bayes Factor provided anecdotal evidence for the presence of a between-group difference ($BF_{10} = 2.267$).

For procedural learning, when comparing cognitively unimpaired older adults to individuals with aMCI and while controlling for age and education, we did not find any statically significant differences and found that Hedges' *g* was

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Table 3. Hedges' *g*s comparing individuals with aMCI to cognitively unimpaired older adults

	No covariates			Controlling for age & education		
	g	*gv*	BF_{10}	*g*	*gv*	BF_{10}
aMCI vs. controls						
AVLT learning score	0.769	0.034	663.284	0.658	0.033	859.046
SRTT learning slope	0.226	0.029	0.212	0.175	0.030	0.283
SRTT pattern-transfer	0.216	0.029	0.484	0.099	0.030	0.437
MTT error slope	–0.125	0.034	0.347	–0.230	0.036	0.656
MTT time slope	0.269	0.035	0.337	0.243	0.037	0.464
WSCT score	0.322	0.033	1.883	0.333	0.033	2.267

Note. *g* indicates Hedges' *g*; *gv* indicates the variance of Hedges' *g*; *BF* indicates Bayes Factors * indicates a significant difference between the groups at $p \leq .05$; The signs (negative vs. positive) of the Hedges' gs were reversed when required such that, for all scores, negative Hedges' *g*s indicate more learning in individuals with aMCI than in cognitively unimpaired controls.

smaller than the a priori set boundary of a meaningful difference for both the SRTT learning slope ($g = 0.175$, $p = 0.317$) and the SRTT pattern-transfer score ($g = 0.099$, $p = 0.570$). When looking at the BF, the SRTT learning slope provided substantial evidence for the null hypothesis ($BF_{10} = 0.283$) and the SRTT pattern-transfer score provided anecdotal evidence for the null hypothesis ($BF_{10} = 0.437$).

The pattern of findings for the MTT was more complex: we found no significant difference between cognitively unimpaired older adults and individuals with aMCI for the MTT error slope ($p = 0.682$) or time slope ($p = 0.204$). The Hedges' *g* was larger than the a priori set boundary of a meaningful difference for both the MTT error slope ($g = –0.230$) and the MTT time slope ($g = 0.243$). However, these two effect sizes were in opposite directions, with the cognitively unimpaired older adults showing more learning on the time slope and the individuals with aMCI showing more learning on the error slope. When looking at the Bayes Factors, both the MTT error and time slopes provided anecdotal evidence for the null hypothesis (MTT error slope: $BF_{10} = 0.656$; MTT time slope: $BF_{10} = 0.464$).

Aggregating all four Hedges' *g*s comparing cognitively unimpaired older adults to individuals with aMCI yielded a meta-Hedges' *g* of 0.075 ($SE = 0.067$, 95% *CI* [–0.765, 0.914]. This aggregated Hedges' *g* is smaller than the a priori set boundary of a meaningful difference. However, the confidence intervals expand beyond the a priori set boundary of a meaningful difference. Further, these aggregates are exploratory and should be interpreted with caution.

DISCUSSION

The present study assessed declarative learning, conceptual repetition priming, and procedural learning in individuals with aMCI in order to provide a direct comparison and nuanced overview of different aspects of learning, by examining between-group effect sizes across memory types in individuals with aMCI compared to cognitively unimpaired older adults. The current results suggest that in aMCI, declarative memory is impacted the most, followed by conceptual repetition priming, with procedural memory remaining largely spared.

Consistent with our hypotheses, when comparing individuals with aMCI and cognitively unimpaired older adults, our results showed a large between-group effect size and a Bayes Factor in favor of the presence of a between-group difference on declarative learning. This finding is expected because it is the presence of declarative memory deficits that generally leads to the diagnosis of aMCI. What is of greater interest is the pattern of effect sizes for procedural learning and conceptual repetition priming. For procedural learning, overall trivial but variable differences were seen, with Bayes Factors that were less conclusive but were somewhat in favor of the null hypothesis. The results regarding conceptual repetition priming fell in between the declarative and procedural learning, with a small-to-moderate between-group effect size and a Bayes Factor that was not conclusive but was slightly in favor of the presence of a between-group difference. These results suggest that a small-to-medium group difference between the individuals with aMCI and controls may be present in our sample but may not be detectable with our sample size due to statistical power.

Our priming results are consistent with the results from a recent meta-analysis on repetition priming that showed that the between-group effect sizes comparing individuals with aMCI to controls varied based on task characteristics, with the differences between individuals with aMCI and controls being the largest for tasks similar to the WSCT that require (1) conceptual processing and (2) production rather than the identification of primes in the test phase (De Wit et al., 2021). Our procedural learning results, while variable, were overall consistent with the results from a recent meta-analysis regarding procedural learning that demonstrated trivial between-group effect sizes (Hedges' *g* of <0.200) for individuals with aMCI and controls on procedural learning tasks (De Wit et al., 2020). These meta-analyses were only able to include three procedural learning and four priming studies that assessed individuals with aMCI in comparison to cognitively unimpaired older adults, thereby limiting ability to draw conclusions regarding sparing of these types of memory in the MCI phase of AD. The present study contributes to the literature by providing a larger sample of individuals with aMCI compared to cognitively unimpaired older adults on measures of

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procedural learning and priming and is of additional value as it provides a concurrent view of impairment and sparing across declarative memory, conceptual repetition priming, and procedural learning by (1) assessing these three types of learning in the same groups of individuals and (2) providing effect sizes as well as BFs. Given that our results regarding procedural learning in individuals with aMCI remain inconclusive, more research on this topic is warranted. While future research using similar types of procedural learning tasks may be helpful, the use of novel procedural learning paradigms that more closely resemble the procedural learning component of the use of a memory compensation tool may be of even more clinical benefit.

While not all aMCI subjects have an underlying pathology of AD, prior research suggests that AD is the most common etiology of aMCI (Petersen, 2016). Thus, our findings are consistent with the model that AD pathology impacts brain areas that are important for declarative memory, including the entorhinal cortex and hippocampus, followed by brain areas important for conceptual priming, including other parts of the parahippocampal gyrus and the fusiform gyrus; our results contribute to the evidence-base that suggests that subcortical areas important for procedural memory are not impacted until the more severe stages of the disease.

Limitations and Generalizability

A limitation of the present study is its cross-sectional nature. A longitudinal design could more accurately depict this change, and would also address the limitation that we do not know whether our aMCI subjects are indeed destined for AD dementia. However, longitudinal testing for skill learning represents a unique challenge due to practice effects: skills are only new during the first exposure. Similarly, procedural learning is often thought of as an unconscious process (Squire, 2004), and repeated testing can result in an increased awareness of the goal of procedural learning tasks, which is particularly true for the SRTT, and this increased awareness can interfere with researchers' ability to limit the influence of declarative learning on test performance. Thus, procedural learning does not lend itself well for repeated testing or longitudinal assessments. While it may be possible to asses procedural *memory* over time as evidenced by sustained performance gains on procedural memory tasks, this reflects a somewhat different process than procedural *learning* (much like the difference between declarative learning, i.e., the encoding process, vs. declarative memory, i.e. the information that is retained over time). Similarly, priming is often thought of as an unconscious process (Squire, 2004), and repeated testing can result in an increased awareness of the goal of the priming task in participants, which could interfere with researchers' ability to limit the influence of declarative learning on test performance. Another limitation of the present study is that the declarative learning (AVLT) and conceptual repetition priming (WSCT) tasks were only administered as part of the PEACEOFMND study and not as part of the M-DeMi study. Further, while the cross-national nature of the current study adds to external validity, another limitation of our study is that most of our participants were highly educated and from a predominantly Caucasian population with the ethnicity of the ethnic majority in each country. Another limitation of the current study is that slightly different inclusion criteria were used for both parent studies, although we do not believe that this impacted our results. Last, the current study did not include biomarkers of AD pathology. Future studies should recruit a more diverse sample and include AD biomarkers.

Implications and Conclusion

It is well known that declarative memory is impaired in both aMCI due to AD and AD dementia, but the extent to which non-declarative learning is spared remains unclear. The results of the present study suggest that conceptual priming may not remain intact in aMCI while procedural learning does appear to remain intact. Based on our findings, we recommend for studies that aim to build on spared functions in aMCI not to rely on conceptual repetition priming techniques. However, procedural memory-based cognitive interventions have potential utility in individuals with aMCI. Given that most procedural learning tasks used visuomotor learning, using a behavioral compensation technique that most heavily relies on a visuomotor component is currently the most supported approach. As an example, focusing the behavioral compensation intervention on the act of physically locating, opening, and using the compensatory tool consistently throughout the day may be most helpful, in line with the interventions used by several recent studies (Greenaway et al., 2008; Vasquez, Lloyd-Kuzik, & Moscovitch, 2021). As part of this approach, individuals with aMCI should be trained to use their compensatory tool consistently when they either (1) have forgotten information or (2) are hoping to remember specific information. Given that most compensatory tools also require the understanding of how to use the tool and considering that the complexity of such tools can vary widely, we recommend direct testing of any procedural memory-based cognitive interventions in an aMCI population before providing such interventions clinically.

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CONFLICT OF INTEREST

The authors have nothing to disclose.

ETHICAL STANDARDS

All procedures were completed in accordance with the Helsinki Declaration. Both parent studies were approved by the Institutional Review Board or the Medical Ethics Committee at each study site.

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APPENDIX:

Table A1. Inclusion and exclusion criteria for participation in the PEACEOFMND study

Inclusion criteria	Exclusion criteria
For the individuals with aMCI*: 1. A clinical diagnosis of aMCI (single domain or multi-domain). 2. A CDR score of 0 or 0.5. 3. ≥50 years of age. 4. Not taking nootropic(s) and/or pain medication, or being stable for at least 3 months on a dose and frequency that does not affect cognition. 5. English fluency. 6. A score of ≥ 25 on the TICS-M. For the study partner** (healthy control): 7. At least 21 years of age. 8. A score of ≥ 32 on the TICS-M. 9. Study partner has at least twice-weekly contact with the individual with aMCI.	For the individual with aMCI: 1. Contraindications for an MRI (e.g., ferrous metal in the body, claustrophobia). For both the individual with aMCI and the study partner (healthy control): 2. Physical impairments, language comprehension deficits, or significant hearing disturbances that would limit ability to perform tasks/ intervention participation.

Note: aMCI: amnestic Mild Cognitive Impairment. MRI: Magnetic Resonance Imaging; CDR: Clinical Dementia Rating Scale; TICS-M: Telephone Interview for Cognitive Status for Memory.*Individuals with aMCI were recruited from the Memory Disorder Clinics and the behavioral neurology and neuropsychology practices at Tallahassee Memorial HealthCare, Mayo Jacksonville, and the University of Florida.

** Inclusion for the PEACEOFMND study occurred in dyads, consisting of an individual with aMCI and a cognitively unimpaired study partner. The study partners served as cognitively unimpaired controls in the proposed study. Study-partners were spouses, adult-children, or friends, with at least twice-weekly contact with the individual with aMCI.

Table A2. Inclusion and exclusion criteria for participation in the M-DeMi study

Inclusion criteria:	Exclusion criteria:
For all participants: 1. Between 50 and 85 years of age. 2. Native Dutch speakers. For the individuals with aMCI*: 3. A clinical diagnosis of aMCI (single domain or multi-domain) 4. A CDR score of 0.5 (aMCI). For the cognitively unimpaired controls**: 5. A MoCa score of ≥ 26.	1. Hearing disturbances that would limit ability to perform tasks. 2. History of serious head trauma or brain surgery. 3. A clinical diagnosis of neurological or psychiatric disorders (other than of Alzheimer's; including Primary Progressive Aphasia 4. Vascular disease as the primary etiology of the cognitive impairment in those with MCI 5. Use of psychotropic medication or recreational drugs 6. MRI contraindications (e.g., ferrous metal in the body, claustrophobia).

Note: aMCI: amnestic Mild Cognitive Impairment; MRI: Magnetic Resonance Imaging; CDR: Clinical Dementia Rating Scale.*Individuals with aMCI were recruited from the Radboud University Medical Center as well as from other local hospitals in the region (Canisius-Wilhelmina Ziekenhuis in Nijmegen, Maasziekenhuis Pantein in Boxmeer, and the Gelre Ziekenhuis in Apeldoorn).

** Cognitively unimpaired older adults were recruited by flyers and advertisement on social media.

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Table A3. Hedges' gs comparing individuals with aMCI to cognitively unimpaired older adults for the PEACEOFMND and M-DeMi subsamples without covariates

	PEACEOFMND		M-DeMi	
	g	*gv*	*g*	*gv*
SRTT learning slope	0.085	0.038	1.065	0.158
SRTT pattern-transfer	0.140	0.039	0.517	0.144
MTT error slope	−0.217	0.046	0.416	0.160
MTT time slope	0.287	0.047	0.384	0.159

Note. *g* indicates Hedges' *g*; *gv* indicates the variance of Hedges' *g*; * indicates a significant difference between the groups at $p \leq .05$; The signs (negative and positive) of the scores were reversed when required such that, for all scores, negative Hedges' *g*s indicate more learning in individuals with aMCI than in cognitively unimpaired controls.

Table A4. One-way analysis of covariance models in aMCI versus cognitively unimpaired older adults

	Controlling for site			Not controlling for site		
	SS	*F*	*p*	*SS*	*F*	*p*
AVLT learning score						
Age (years)	–	–	–	1.099	1.36	0.246
Level of education (years)	–	–	–	0.122	0.151	0.698
MCI – HC	–	–	–	11.055	13.687	<0.000
SRTT learning slope						
Age (years)	5.812	6.945	0.009	5.667	6.814	0.010
Years of education	0.326	0.389	0.534	0.286	0.343	0.559
Site	0.183	0.218	0.641	–	–	–
MCI – HC	0.722	0.863	0.355	0.841	1.011	0.317
SRTT pattern-transfer						
Age (years)	3.763	4.436	0.037	3.677	4.364	0.039
Years of education	2.730	3.218	0.075	2.854	3.387	0.068
Site	0.101	0.119	0.731	–	–	–
MCI – HC	0.225	0.265	0.608	0.274	0.325	0.570
MTT error slope						
Age (years)	0.005	0.005	0.946	0.001	0.001	0.975
Years of education	1.173	1.168	0.282	1.501	1.477	0.227
Site	2.316	2.306	0.132	–	–	–
MCI – HC	0.276	0.275	0.601	0.172	0.169	0.682
MTT time slope						
Age (years)	0.079	0.095	0.759	0.449	0.541	0.463
Years of education	0.386	0.464	0.497	0.231	0.279	0.598
Site	0.285	0.343	0.559	–	–	–
MCI – HC	0.457	0.550	0.460	1.355	1.635	0.204
WSCT score						
Age (years)	–	–	–	0.026	0.033	0.857
Level of education (years)	–	–	–	0.003	0.003	0.953
MCI – HC	–	–	–	2.681	3.423	0.067

Note. M*SS*: Sum of Squares. *F*: *F*-values *p: p*-values. *MS*: Mean Square values. *F*-values were used to calculate Hedges' *g*s controlling for age and education. * indicates significance at $p \leq .05$; ** indicates significance at $p \leq .01$.

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Table A5. Means (M), Standard Deviations (DVs), and sample sizes (ns) for the control group and the MCI groups that were used to calculate Hedges' *g*s

	$M_{controls}$	$SD_{controls}$	$n_{controls}$	M_{MCI}	SD_{MCI}	n_{MCI}
Full sample						
Age (years)	68.776	10.038	85	73.789***	7.345	76
Years of education	16.827	3.551	84	15.987	2.914	76
SRTT learning slope	–0.069	0.820	76	0.180	1.071	58
SRTT pattern-transfer	0.067	0.966	75	–0.136	0.904	58
MTT error slope	0.051	1.061	72	–0.009	0.908	45
MTT time slope	–0.040	0.943	70	0.235	0.833	45
PEACEOFMND sample						
Age (years)	67.984	10.787	64	73.938***	7.374	65
Years of education	16.333	2.724	63	16.108***	2.687	65
AVLT learning score	0.324	0.913	62	–0.368	0.875	64
SRTT learning slope	0.019	0.797	55	0.102	1.134	48
SRTT pattern-transfer	0.021	1.016	54	–0.119	0.962	48
MTT error slope	0.194	1.013	54	–0.023	0.962	36
MTT time slope	–0.070	0.960	52	0.195	0.848	36
WSCT score	0.154	0.823	61	–0.131	0.930	62
M-DeMi sample						
Age (years)	71.190	6.969	21	72.909	7.463	11
Years of education	18.310	5.125	21	15.273	4.101	11
SRTT learning slope	–0.299	0.852	21	0.554**	0.603	10
SRTT pattern-transfer	0.186	0.834	21	–0.217	0.572	10
MTT error slope	–0.377	1.115	18	0.050	0.692	9
MTT time slope	0.047	0.912	18	0.394	0.799	9

Note. *M*: Group mean, *n*: number of participants per group. *SD*: Standard Deviation of the group mean. ** indicates significance at $p \leq .01$; *** indicates significance at $p \leq .001$.

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