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Amnestic Mild Cognitive Impairment is Characterized by the Inability to Recover from Proactive Semantic Interference across Multiple Learning Trials

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Abstract

BACKGROUND: Difficulties in inhibition and self-monitoring are early features of incipient Alzheimer's disease and may manifest as susceptibility to proactive semantic interference. However, due to limitations of traditional memory assessment paradigms, recovery from interference effects following repeated learning opportunities has not been explored.

OBJECTIVE: This study employed a novel computerized list learning test consisting of repeated learning trials to assess recovery from proactive and retroactive semantic interference.

DESIGN: The design was cross-sectional.

SETTING: Participants were recruited from the community as part of a longitudinal study on normal and abnormal aging.

Participants: The sample consisted of 46 cognitively normal individuals and 30 participants with amnestic mild cognitive impairment.

MEASUREMENTS: Participants were administered the Cognitive Stress Test and traditional neuropsychological measures. Step-wise logistic regression was applied to determine which Cognitive Stress Test measures best discriminated between diagnostic groups. This was followed by receiver operating characteristic analyses.

RESULTS: Cued A3 recall, Cued B3 recall and Cued B2 intrusions were all independent predictors of diagnostic status. The overall predictive utility of the model yielded 75.9% sensitivity, 91.1% specificity, and an overall correct classification rate of 85.1%. When these variables were jointly entered into receiver operating characteristic analyses, the area under the curve was .923 ($p < .001$).

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Conflict of interest: This study was supported by the National Institute on Aging (NIA). The CST measure was developed by and is intellectual property held by Drs. Loewenstein and Curiel at the University of Miami.

Ethical standards: This study was IRB approved and met all national and international standards for the protection of human subjects.

CONCLUSIONS: This novel paradigm's use of repeated learning trials offers a unique opportunity to assess recovery from proactive and retroactive semantic interference. Participants with mild cognitive impairment exhibited a continued failure to recover from proactive interference that could not be explained by mere learning deficits.

Keywords

Proactive semantic interference; retroactive semantic interference; prodromal Alzheimer's disease; mild cognitive impairment; intrusions

Introduction

Hasher and Zacks (1988) first described age-related changes in inhibitory processes that diminished the ability to ignore distracting information (1). This was confirmed in subsequent studies (2–4). Difficulties in inhibitory processes and self-monitoring have also been seen as early features of incipient Alzheimer's disease (AD; 5–8). Loewenstein and colleagues (2004) posited that learning deficits are related to deficiencies in the semantic network and found that proactive interference of competing to-be-remembered lists of semantically related targets were especially sensitive to the mild cognitive impairment (MCI) stages of AD (6). Curiel et al (2013) employed a novel paradigm (9), the Loewenstein and Acevedo Scales for Semantic Interference and Learning (LASSI-L™) that required learning a list of 15 target items representing three semantic categories (fruits, musical instruments, and articles of clothing). Maximal learning was facilitated by category cues at both acquisition and recall. Proactive semantic interference (PSI) and the failure to recover from PSI (frPSI) were assessed by having the examinee attempt to learn 15 new targets on List B (representing the identical semantic categories used for List A targets) over two additional learning trials while using these identical category cues during both acquisition and retrieval.

Subsequent studies conducted in independent cohorts in the United States and other countries have found that performance deficits on the LASSI-L were superior to several traditionally used memory tests (e.g., list learning measures, delayed paragraph recall) in distinguishing between cognitively normal older adults and those with preclinical AD or early and late stage MCI. Various studies on the LASSI-L have related these early cognitive changes to biological markers of AD such as in-vivo amyloid imaging (10–12) and neurodegeneration measured by magnetic resonance imaging (MRI; 13–14), functional MRI (15), and fluorodeoxyglucose positron emission tomography (PET/CT; 16). In a majority of these studies, AD pathology was more associated with deficits in frPSI than impairments in initial PSI. Using Receiver Operator Characteristic Curve (ROC) analyses, Matias-Guiu and colleagues found that the LASSI-L was superior to the Free and Cued Selective Reminding Test (FCSRT), in detecting MCI patients with suspected AD (16) and in differentiating both early and late stage MCI individuals from cognitively normal older adults.

It has been proposed that both PSI and frPSI can be assessed in different manners (11). These include the number of correct responses on List B relative to List A or the number of semantic intrusions rendered on List B recall trials. In one recent study, MCI patients

that were amyloid positive and had presumptive AD evidenced significantly more intrusion errors than MCI participants who had a clinical history consistent with AD but were amyloid negative, or MCI participants diagnosed with other neurological and neuropsychiatric conditions who were also amyloid negative (11).

The finding that frPSI is particularly sensitive to incipient AD raises an interesting theoretical as well as empirical question. Will deficits in frPSI continue in the presence of additional opportunities to learn two competing semantic word lists? That is, could extending additional opportunities to learn both List A and List B provide deeper insights into initial learning deficits in aMCI participants at risk for AD, as well as their ability to completely recover from PSI deficits over time? An additional question is whether the failure to recover from retroactive interference (frRSI) is an issue in persons with aMCI. These issues have not been addressed by the LASSI-L and other paradigms.

To test the abovementioned potential limitations of this novel assessment paradigm, we employed the Cognitive Stress Test (CST). The CST required learning of 18 targets words, all of which belonged to one of three semantic categories: occupations, household items and types of transportation. Identical category cues were provided during each of the three learning trials as well as during each of the three cued recall trials for each list. This provided a unique opportunity to directly assess the immediate and persistent effects of semantic interference over multiple trials. In addition, we assessed the ability to recover from retroactive semantic interference, which has not been previously examined in aMCI and AD research. We hypothesized that failure to recover from proactive semantic interference would continue to be problematic for individuals with aMCI despite multiple trials that would allow the recovery from these deficits.

Methods

Participants were part of an NIH-funded longitudinal study on normal and abnormal aging. All participants provided informed consent for this IRB-approved study. In this investigation, we carefully selected 46 individuals classified as cognitively normal (CN) and 30 participants with amnesic mild cognitive impairment (aMCI). Inclusion and exclusion criteria are as follows.

Cognitively normal group (n=46)

Participants were classified as CN if there were: a) no subjective cognitive complaints made by the participant and/or a collateral informant; b) no evidence of memory or other cognitive decline after an extensive interview with the participant and an informant; c) Global Clinical Dementia Rating (CDR) scale score of 0 (17); and d) all memory (e.g.: Hopkins Verbal Learning Test, Revised (HVLT-R; 18) or delayed paragraph recall from the National Alzheimer's Coordinating Center Uniform Data Set (NACC UDS; 19) and non-memory measures (e.g., Category Fluency (20), Trails A and B (21), WAIS-IV Block Design subtest (22)) were less than 1.0 standard deviation below normal limits for age, education, and language group.

Amnesic MCI group (n=30)

Participants were classified as aMCI if: (a) they fulfilled Petersen's criteria (23) for MCI, b) subjective cognitive complaints were reported by the participant and/or collateral informant; c) Global CDR scale score was 0.5; and d) delayed recall was impaired (i.e., 1.5 standard deviations or more below the mean, accounting for age, education, and language of testing) on either the HVLT-R or delayed paragraph recall from the NACC UDS.

Exclusion Criteria for all study groups

Exclusion criteria included significant sensory or motor deficits (e.g., visual or hearing impairment, paralysis) or literacy lower than the 6th grade level on the WRAT-4 (24) evidenced during the clinical evaluation by Drs. Loewenstein or Curiel and judged to preclude completion of the study measures; 2) DSM-5 diagnosis of major depressive disorder, bipolar disorder, current psychotic disorder, substance use disorder or any DSM-5 Axis I diagnosis after an extensive interview by the study clinicians using the SCID (25). Individuals with major depressive disorder were excluded from the study given that this condition often results in attention and/or concentration difficulties and psychomotor slowing that may adversely affect test performance on neuropsychological measures. Individuals with major neurocognitive disorder were not included in this sample.

Cognitive Stress Test (CST)

We employed a novel computerized measure called the Cognitive Stress Test (CST) that expands upon our previous work with the widely-studied Loewenstein-Acevedo Scale for Semantic Interference and Learning (LASSI-L), including the computerized version of the LASSI-L which has evidenced high test-retest reliability and discriminative validity (Curiel et al, in press). The CST employs the following: 1) semantic cuing at both acquisition and retrieval of 18 List A targets representing three semantic categories (occupations, household items, or types of transportation) over three initial learning trials, 2) three consecutive presentations of a second list of 18 new targets (List B) representing the same categories as the first list to examine PSI and frPSI, and 3) use of category cues to elicit recall of List A targets to assess retroactive semantic interference (RSI), with an additional learning trial to examine failure to recover from retroactive semantic interference (frRSI). The CST represents an exciting approach to preclinical AD assessment in that it builds upon our previous work and is a fully computer-administered web-based task, which facilitates remote deliverability, reduces the need for a skilled psychometrist, and allows for automatically recording of correct responses, intrusions and other errors.

Statistical Analyses

Statistical analyses were conducted using SPSS Version 26. First, age, gender, education, and language of testing and then global cognitive function were evaluated between diagnostic groups using one-way ANOVAs and Chi-square analyses with Yate's Correction for Discontinuity. CST cued recall and intrusion scores were compared using ANOVA while adjusting for factors that were distributed differently between diagnostic groups. The alpha cutoff value was adjusted using the Bonferroni correction for multiple comparisons. Step-wise logistic regression models were employed to determine the best independent

classification using CST variables. These were followed by a ROC analysis examining significant independent predictors with regards to area explained under the ROC curve.

Results

As depicted in Table 1, there were no statistically significant differences between aMCI and CN groups with regards to mean age, education and language of testing. Participants in the aMCI group had lower mean Mini-Mental State Examination (MMSE) scores (26) and there were more males in the aMCI group than the CN group.

Table 2 indicates that individuals with aMCI had lower scores on all CST trials. After adjusting for baseline differences in MMSE scores and using sex as a covariate, aMCI participants scored lower on all three List A initial learning trials and all three List B trials susceptible to PSI and frPSI. After covariate adjustment, there were no aMCI and CN differences on recall trials susceptible to retroactive semantic interference (RSI) or the ability to recover from RSI (frRSI). Table 3 denotes intrusion errors across the different CST trials. With and without adjustment for covariates, the only measures that differentiated groups were semantic intrusions on List B1 (which measures PSI), List B2 (which measures frPSI) and List B3 (which measures persistent frPSI after repeated learning trials).

We calculated PSI, the initial failure to recover from proactive semantic interference after 1 additional learning trial (frPSI1), and the persistence of proactive semantic interference after 2 additional learning trials (frPSI2). PSI was calculated using the ratio of Cued B1 Recall to Cued A1 Recall. FrPSI1 was calculated using the ratio of Cued B2 Recall to Cued A2 Recall. FrPSI2 was calculated using the ratio of Cued B3 Recall to Cued A3 Recall.

There were no aMCI versus CN differences in the Cued B1/Cued A1 ratio ($F(1.74)=1.59$; $p=.211$). However, aMCI participants demonstrated more frPSI1 ($F(1.74)=8.25$; $p=.005$) and frPSI2 ($F(1.74)=19.45$; $p<.001$). As depicted in Table 4, on the Cued B3 recall trial, which followed two additional learning trials of List B items, CN participants were able to recover so that they could recall an average of 88.6% of the that they recalled during Cued A3 recall. In contrast, participants with aMCI were only able to recover an average of 67.4% of the items that they recalled during Cued A3 recall.

Step-wise logistic regression was employed to determine which of the initial learning and PSI measures best discriminated between aMCI and CN groups. As indicated in Table 5, Cued A3 recall, Cued B3 recall and Cued B2 intrusions were predictors of diagnostic status. The overall predictive utility of the model yielded 75.9% sensitivity and 91.1% specificity, and overall correct classification rate of 85.1%. When these variables were jointly entered into ROC analyses, the area under the ROC curve was .923 ($p<.001$).

Discussion

The current investigation used a novel computerized paradigm with semantically competing target word lists, the Cognitive Stress Test, to investigate whether the effects of proactive semantic interference (PSI) and the initial failure to recover from PSI (frPSI) would persist or diminish with additional learning trials. The obtained pattern of results indicated that,

despite repeated administrations of the second list, participants with amnesic MCI had a persistent failure to recover from proactive semantic interference (frPSI). This cannot be explained by mere learning deficits alone since proactive semantic interference deficit ratios adjusted for initial learning on the corresponding trial of List A targets. The unique nature of proactive semantic interference deficits was also evidenced by increased intrusion errors, which were produced by aMCI participants on Cued B1, Cued B2 and Cued B3 trials but not on additional trials of List A susceptible to retroactive interference. In fact, no measure of retroactive interference reached statistical significance, which is consistent with the notion that PSI is uniquely related to early cognitive function in older adults with aMCI at risk for AD (17, 27). Previous studies have suggested that PSI effects may be more associated with MCI and early AD than RSI (27–28). In contrast, in 2012 Ricci and colleagues (29) found RSI but lack of PSI effects using the Rey Auditory Verbal learning Test (RAVLT). It should be noted, however, that the RAVLT list-learning task did not specifically elicit semantic interference, which is the focus of the current investigation.

Unlike previous studies, the current investigation incorporated multiple trials of two sets of 18 different targets, each belonging to one of three semantic categories. The current findings suggest that even after repeated learning trials, aMCI participants are not able to overcome the effects of semantic interference. Our finding of a combined area under the ROC curve exceeding .92 for Cued A3 Recall, Cued B3 recall and Cued B2 intrusions indicates that aMCI participants have deficits in initial learning as well as a failure to recover from proactive interference. The latter is evidenced by increasing deficits in recall of List B relative to List A targets over time (percentage of correct responses), as well as intrusion errors on measures susceptible to proactive interference and the failure to recover from proactive interference. This suggests that different measures of failure to recover from proactive semantic interference may have different biological underpinnings. Indeed, using the LASSI-L, which only affords one opportunity to recover from proactive semantic interference, Cued B2 recall was correlated with atrophy in AD prone regions (13–14). In contrast, Loewenstein et al., (2018) showed that it was not Cued B2 recall but Cued B2 semantic intrusions that could differentiate between MCI groups who were amyloid positive versus other MCI groups who were amyloid negative (11), suggesting the potential specificity of intrusion errors as a cognitive breakdown associated with AD brain pathology. Similarly, Sanchez and colleagues (2017) found that among clinically asymptomatic middle-age offspring of AD parents, Cued B2 intrusions were highly related to abnormal limbic connectivity issues on fMRI (15).

Torres et al. (2019) conducted a qualitative analysis on List B intrusion errors and found that the vast majority were incorrect recall of List B targets followed by semantic errors related to the List B target but not explicitly derived from List A (30). This indicates potential disruptions in cortical-limbic difficulty observed by others (13) and suggests that semantic intrusions represent potentially greater deficits in executive inhibitory processes that allow the individual to access source memory and inhibit previously learned responses.

Strengths of the current paradigm include computerized and uniform administration of three learning trials of 18 targets (representing three different categories) to assess maximum learning using cues at both the encoding and retrieval stages. When applied to three

additional trials of 18 different targets (representing identical semantic categories), there was a unique opportunity to study proactive interference and failure to recover from proactive interference (as assessed by the ratio of correct recall on List B to correct recall of List A on the same trial) and semantic intrusions. Participants were comprehensively assessed by both clinical and neuropsychological assessment and compared to older adults of equivalent age with similar educational attainment. There did not appear to be any issues with ceiling or floor effects using 18 to-be-remembered targets, which may have been related to adequate category cues provided at acquisition and retrieval. Finally, the CST was not used in diagnostic formulation to avoid potential issues with circularity.

Potential limitations of the study involve relatively modest numbers of participants and lack of longitudinal follow-up. We intend to keep recruiting and following these participants and obtaining both structural MRI as well as amyloid and tau PET. Future work with fMRI may further elucidate the mechanisms underlying the inability of aMCI participants to break free from the effects of semantic interference when provided with additional learning opportunities. Normal controls appear to be able to increasingly recover from proactive semantic interference effects over time, but this does not hold true with individuals with aMCI. Further exploration into this phenomenon has significant theoretical and clinical implications.

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Table 1.

Demographics by Diagnostic Group

	Cognitively Normal (N=46)	Amnesic MCI (N=30)	F value or X ²	p value
Age (range: 60–94 years)	M=72.94, SD=8.4	M=73.33, SD=9.2	.40	.530
Education (range: 6–20 years)	M=15.43, SD=2.7	M=14.47, SD=3.8	1.65	.203
MMSE (range 22–30)	M=28.89, SD=1.2	M=27.00, SD=2.7	17.86	<.001
% Female	80.0%	30.0%	17.28	<.001
% English	82.2%	73.3%	.40	.527

Table 2.

CST Cued Recall Scores by Diagnostic Group

	Cognitively Normal (N=46)	Amnesic MCI (N=30)	F value	p value	F value adjusted for sex and MMSE	p value adjusted for sex and MMSE
Cued A Recall 1						
(range: 3–17)	M=10.24, SD=2.9	M=6.77, SD=2.8	26.84	<.001	16.54	<.001
Cued A Recall 2						
(range: 5–18)	M=13.80, SD=2.4	M=9.77, SD=2.8	45.20	<.001	22.94	<.001
Cued A Recall 3						
(range: 6–18)	M=15.22, SD=2.0	M=11.63, SD=2.7	44.86	<.001	22.21	<.001
Cued B Recall 1						
(range: 0–15)	M=7.50, SD=3.5	M=4.10, SD=2.2	22.06	<.001	11.89	<.001
Cued B Recall 2						
(range: 2–18)	M=11.80, SD=3.3	M=7.00, SD=2.9	41.44	<.001	22.13	<.001
Cued B Recall 3						
(range: 1–18)	M=13.48, SD=2.8	M=7.93, SD=3.7	53.90	<.001	26.63	<.001
Cued A Recall 4						
(range: 0–18)	M=8.93, SD=3.5	M=6.41, SD=3.0	10.22	.002	4.41	.039
Cued A Recall 5						
(range: 0–17)	M=11.76, SD=3.0	M=9.00, SD=2.2	18.52	<.001	8.18	.006

* Values survived Bonferroni Correction at 0.05/8=0.00625

Table 3.

CST Intrusion Errors by Diagnostic Group

	Cognitively Normal (N=46)	Amnesic MCI (N=30)	F value	p value	F value adjusted for sex and MMSE	p value adjusted for sex and MMSE
Cued A Recall 1						
(range: 0–5)	M=435, SD=1.0	M=1.20, SD=1.9	6.78	.011	2.82	.097
Cued A Recall 2						
(range: 0–6)	M=283, SD=.58	M=.867, SD=1.1	5.97	.017	1.86	.177
Cued A Recall 3						
(range: 0–6)	M=.174, SD=.38	M=.60, SD=1.4	3.95	<.051	2.52	.117
Cued B Recall 1						
(range: 0–7)	M= 1.11, SD=1.3	M=2.73, SD=2.3	15.53*	<.001*	9.89*	.002*
Cued B Recall 2						
(range: 0–9)	M=1.41, SD=1.5	M=3.41, SD=2.2	21.82	<.001	10.68*	.002*
Cued B Recall 3						
(range: 0–8)	M=1.24, SD=1.3	M=2.86, SD=2.0	18.81	<.001	10.01*	<.002*
Cued A Recall 4						
(range: 0–15)	M=2.57, SD=2.2	M=3.83, SD=3.3	2.69	.105	1.12	.293
Cued A Recall 5						
(range: 0–12)	M=2.37, SD=2.3	M=3.48, SD=2.7	3.54	.064	4.06	.048

* Values survived Bonferroni Correction at $p<.05$

Table 4.
Proactive Interference and Failure to Recover from Proactive Interference Ratios

	Cognitively Normal	Anamnestic MCI	F value	p value
Cued B1/Cued				
A1	M=.771, SD=.40	M=.653, SD=.40	1.59	.211
Cued B2/Cued				
A2	M=.850, SD=.18	M=.710, SD=.24	8.25	.005
Cued B3/Cued				
A3	M=.886, SD=.16	M=.674, SD=.26	19.45	<.001

Table 5.

Step-Wise Logistic Regression Using Measures of Initial Learning and Susceptibility to Proactive Interference to Distinguish Amnesic Mild Cognitive Impairment and Cognitively Normal Groups

	B	SE	Wald	Sig	Exp (B)	Lower CI	Upper CI
Step 1							
Cued B3	-.501	.115	18.87	<.001	.606	.484	.670
Recall							
Step 2							
Cued B3	-.504	.134	13.12	<.001	.604	.464	.786
Recall							
Cued B2							
Intrusions	.511	.197	6.737	.009	1.67	1.133	2.452
Step 3							
Cued A3	-.384	.19	4.02	.045	.681	.468	.991
Recall							
Cued B3	-.352	.15	5.62	.018	.703	.525	.941
Recall							
Cued B2	.556	.21	6.79	.009	1.744	1.148	2.650
Intrusions							

* Model at step 3 yielded 75.9% sensitivity and 91.1% specificity (overall classification 85.1%)