Sensitive measures of cognition in Mild Cognitive Impairment

Impaired language and semantics in MCI

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Abstract

Sensitive measures of cognition are needed in preclinical and prodromal Alzheimer's disease (AD) to track cognitive change and evaluate potential interventions. We hypothesize that measures of semantic richness and figurative language are sensitive to cognitive impairment in prodromal AD. The neurofibrillary tangle (NFT) pathology of AD is first observed in BA35, the medial portion of the perirhinal cortex. The importance of the perirhinal cortex for semantic memory may explain early impairments of semantic memory in preclinical AD. Additionally, our research has tied figurative language impairment to neurodegenerative disease. We predict that people with Mild Cognitive Impairment (MCI) will perform worse on these tasks than participants with normal cognition (CN), and task performance will relate to atrophy in Brodmann Area 35 (BA35). On productive and receptive measures of semantic memory and tests of figurative language comprehension (including metaphor and verbal analogy), CN participants performed better than people with MCI. These experimental tasks outperformed standard neuropsychological assessments in differentiating patients with MCI from CN. Performance on the semantic memory tasks related to MTL structural integrity, including BA35, while standard neuropsychological assessments of semantic memory did not, demonstrating the sensitivity of these experimental measures. A visuo-spatial analogy task did not differentiate groups, confirming the specificity of semantic and figurative language tasks. These experimental measures appear sensitive to cognitive change and neurodegeneration early in the AD trajectory and may prove useful in tracking cognitive change in clinical trials aimed at early intervention.

Key Words: Medial Temporal Lobe; Perirhinal Cortex; Cognition; Semantic memory; Figurative language; Mild Cognitive Impairment; Alzheimer's disease.

Introduction

Potential interventions in Alzheimer's Disease (AD) are most likely to be effective if implemented as early as possible (Brooks & Loewenstein, 2010). As such, sensitive measures of cognition that differentiate the earliest stages of AD from healthy aging are needed (Mortamais et al., 2017). To define this "predementia" period, criteria have been developed to classify individuals as having preclinical and prodromal AD, the latter being the Mild Cognitive Impairment (MCI) stage of disease (Sperling et al., 2011, Albert et al., 2011; Jack et al., 2018).

Standard psychometric assessments appear relatively insensitive to preclinical AD (Rentz et al., 2013; Loewenstein et al., 2018). Developing cognitive measures that differentiate preclinical AD from healthy aging promises to improve understanding of the disease and to provide a way to track cognitive changes in this population. These measures would help assess the efficacy of interventions when applied early in the disease. While imaging and fluid biomarkers appear sensitive to some aspects of preclinical disease (Sutphen et al., 2015; Villemagne et al., 2011), a sensitive cognitive measure would have greater face validity than biomarkers as outcome

measures in clinical trials, since the ultimate goal of treatment is to improve or protect against cognitive decline (Vellas et al., 2015).

The current study evaluates the utility of a battery of cognitive tasks predicted to be sensitive to MCI. We hypothesized that measures of semantic richness and comprehension of figurative language are sensitive to cognitive impairment in prodromal AD, and depend on intact MTL subregions, including those first affected in AD. We predicted that people with MCI would perform worse on these tasks than cognitively normal (CN) participants, and that task performance would relate to atrophy in Brodmann Area 35 (BA35).

The pathological processes contributing to AD begin years to decades before there are obvious cognitive consequences as measured with standard tools. Neurofibrillary tangle pathology begins in the medial portion of Brodmann Area 35 (BA35) in the perirhinal cortex, also referred to as the trans-entorhinal region, before spreading medially into entorhinal cortex and the hippocampus, and laterally to cortical temporal regions (Braak & Braak 1991; Taylor & Probst 2008). The perirhinal cortex has been shown to support semantic memory (Venneri et al., 2008; Wang et al., 2010; Davies et al., 2004; Taylor et al., 2006; Murray & Richmond 2001; Clarke & Tyler 2014; Hirni et al., 2013), especially when making fine-grained semantic distinctions (Tyler et al., 2004; Kivisaari et al., 2012; Wright et al., 2015). Semantic impairments are reported in preclinical AD (Papp et al., 2017; Vonk et al., 2019; Hirni et al., 2016), leading some investigators (e.g. Venneri et al., 2016) to propose that semantic memory should be a greater research focus in these populations rather than the traditional and dominant emphasis on episodic memory.

Standard neuropsychological tests of semantic memory (e.g. picture naming) may not be sensitive enough to detect subtle impairments at the preclinical and prodromal stages of AD. The psycholinguistic and language learning literatures differentiate surface-level knowledge of a word or concept, from deep, rich meaning (Pexman et al., 2008; Read 1998). Shallow word knowledge enables a participant to correctly name a picture or provide a simple 3- or 4-word definition. Deeper mastery involves richer information associated with a word – its different senses, the number of features of a concept, and other words with which it is associated. The N400, an electrophysiological marker of semantic richness, is larger for words with greater number of associates, features, and senses (Pexman et al., 2008).

As an example of the sensitivity of tests of semantic memory, we reported that people with hippocampal amnesia have previously unappreciated deficits of semantic knowledge (Klooster & Duff 2015). Previously acquired, remote semantic knowledge had been considered intact in people with hippocampal amnesia who performed normally on standard clinical neuropsychological assessments of these abilities. However, on more sensitive measures, the patients' knowledge appeared impoverished. While surface level knowledge was intact, patients associated less information with common words than healthy and brain damaged comparison participants. They provided fewer features and senses to target words and identified fewer correctly matching word associates. Similarly, people with preclinical and prodromal AD, who typically have MTL injury, might also be vulnerable to impairments of semantic richness despite normal performance on traditional neuropsychological assessments such as naming and category fluency.

Assessments of figurative language comprehension also show promise as sensitive measures of cognition and may map onto aspects of semantic knowledge. Figurative language, such as metaphor comprehension, can be impaired despite normal literal language abilities (Cardillo, McQuire, & Chatterjee 2018; Ianni et al., 2014). Successful metaphor processing requires working memory, cognitive flexibility, inhibition of literal meaning, abstract thinking, executive demands, and semantic memory. Decrements in any of these subdomains can lead to impairment. Metaphor comprehension is impaired following left-hemisphere neurodegeneration (Klooster et al., in press), and in AD (Winner & Gardner, 1977; Papagno 2001; Amanzio et al., 2008). Figurative language abilities more broadly are impaired in AD (Papagno et al., 2003) and Mild Cognitive Impairment (Cardoso et al., 2014). Metaphor comprehension may be an especially fragile cognitive ability and, consequently a sensitive measure of cognitive decline early in the AD trajectory.

The current study evaluates the usefulness of a battery of tasks predicted to be sensitive to early stages of AD in a sample of cognitively normal older adults and people with MCI, a population enriched in individuals with prodromal AD. We predicted that tests of semantic richness would better discriminate the groups than standard neuropsychological assessments of semantic memory in prodromal AD. Tests of metaphor comprehension and verbal analogy were chosen because the complex cognitive skills needed to successfully resolve the meaning of novel figurative language may be specifically affected in early AD. A visuo-spatial analogy task was included as a control task to evaluate a potential dissociation from language and semantic tasks. We also examined brain-behavior relationships in this population. Our primary anatomical analyses relate task performance to integrity of BA35, the first region affected by neurofibrillary tangles of AD. If these tasks rely on the integrity of this region, this brain-behavior relationship would support a potential role for these measures in preclinical AD. Finally, we conducted exploratory analyses to examine relationships with other MTL subregions and with brain regions outside the MTL.

METHODS

Participants

Cognitively normal older adults (CN) included 56 participants without prior medical or neurologic conditions that may affect cognition. CN participants were an average of 72.84 (± 7.34) years old and completed an average of 15.53 (± 2.75) years of education. All CN (MMSE: $M = 29.28 \pm 0.77$) are participants in the Penn Alzheimer's Disease Core Center in which they undergo annual medical, neurological and psychometric evaluation. Consensus designation of cognitively normal status is made annually.

Participants with a clinical diagnosis of amnesic Mild Cognitive Impairment (MCI) consisted of 35 people. Two participants were borderline MCI; They did not have a subjective complaint, but had objective evidence of cognitive decline, and within the subsequent year were diagnosed with amnesic MCI. MCI status was determined based on clinical evaluation and standard psychometric testing following NIA-AA guidelines (Albert et al., 2011). This group does not include individuals with prior neurological or medical conditions that affect cognition. Patients

were matched to the CN group on age (72.68 ± 6.84 , $p > 0.9$), but completed more years of formal education on average (17.06 ± 2.57 , $p < 0.01$). All participants completed evaluations from the Uniform Data Set (UDS 3: Weintraub et al., 2009). MCI patients performed worse than CN participants on tests of overall cognition (MMSE $p < 0.01$. MOCA $p < 0.01$) indicating mildly impaired cognition, and on tests of semantic memory (Animal fluency: $p < 0.01$; Vegetable fluency: $p < 0.01$) and other domains (see Table 1).

All participants were native English speakers, gave informed consent in accordance with procedures of the University of Pennsylvania Institutional Review Board, and were paid \$20/hour for their time.

Table 1 Neuropsychological Assessment

Group	MMSE	MOCA	ANIMAL Fluency	VEGETABLE Fluency	TRAILA	TRAILB	CRAFTVRS
MCI	26.68 (2.25)	21.96 (3.31)	17.28 (4.87)	10.08 (3.90)	37.36 (13.21)	163.16 (188.67)	11.8 (6.16)
CN	29.29 (0.75) ***	27.10 (2.25) ***	23.04 (5.39) ***	14.83 (4.42) ***	30.12 (7.81) ***	68.13 (26.99) ***	22.81 (5.32) ***

CRAFTDVR	UDSBENTC	UDSBENTD	DIGFORCT	DIGBACCT	MINT	UDSVERFC	UDSVERLC	Word List Memory	Word List Recall	Clock Draw
5.72 (6.00)	15.08 (1.68)	5.32 (4.59)	7.4 (2.38)	5.72 (1.86)	27.4 (3.51)	11.64 (4.53)	12.44 (5.21)	16.4 (3.84)	4.60 (2.25)	2.16 (1.55)
20.44 (5.98) ***	15.71 (1.46)	11.85 (2.68) ***	8.58 (2.29) *	7.73 (2.25) ***	30.19 (2.21) ***	16.21 (4.45) ***	14.54 (4.52) **	24.46 (3.39) ***	8.50 (1.60) ***	1.21 (0.78) ***

Table 1 Key: MCI: Patients with Mild Cognitive Impairment. CN: Healthy participants with normal cognition. MMSE: Mini-Mental State Exam. MoCA: Montreal Cognitive Assessment. CRAFTVRS: Craft Story immediate recall. CRAFTDVR: Craft story delayed recall. UDSBENTC: Benson Complex Figure Copy. UDSBENDT: Benson Complex Figure Delayed. DIGFORCT: Number span forward. DIGBACCT: Number span backward. MINT: Multilingual Naming Test. UDSVERFC: Verbal Fluency Phonemic Test ‘F’. UDSVERLC: Verbal Fluency Phonemic Test ‘L’. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.005$.

Experimental tasks

Senses listing task. Our productive measure of semantic richness (See Klooster & Duff (2015) for task details), the senses task, presents participants with a target word (e.g. Pen.). Participants are given one minute to list as many different senses of the word as possible (e.g. “A writing instrument,” “To write a letter,” “An enclosure for animals,” “University of Pennsylvania”). Stimuli include the same 20 words chosen from normed databases (Nelson et al., 1980; Twilley et al., 1994). Responses are recorded for later transcription and analysis.

Transcription and coding of responses. The first author transcribed all responses. A research assistant, blind to participant status and study hypotheses, transcribed 10% of the data for each participant chosen at random. This transcription was compared to the first author’s transcription to examine agreement. Inter-rater reliability was $\kappa = 0.89$, indicating near perfect agreement (Landis & Koch, 1977). These transcriptions were then evaluated and coded. Responses were evaluated with those in Wordnet, a normative database for polysemy (Miller 2010), and with the Merriam Webster Dictionary (Dictionary, M. W., 2002). Responses included in Wordnet were coded as correct responses, as were responses matching one of the definitions in Merriam Webster. Homophones to the target word and proper nouns were coded as correct responses. Other responses were coded as incorrect and were excluded from analysis.

Word Associates Task (WAT). For a receptive measure of depth of semantic knowledge, participants are given a paper and pencil version of John Read’s 1998 WAT form (Read, 1998). Consisting of 40 items, each has a target word in bold with eight possible associates below it and participants choose the four correctly matching associates. Words on the left are possible synonyms and words on the right are possible collocates, words that might follow the target word in a phrase or a sentence. After instructions explaining the task, participants complete two practice problems and receive feedback. Each correct response is scored for a total of 160 possible points. Points are not deducted for incorrect responses.

Metaphor. Stimuli from the Metaphor Multiple Choice task (Ianni et al., 2014; Humphries et al., 2019) include 120 sentences, 60 novel metaphorical sentences, and 60 literal sentences, matched on the base term of the metaphor (See Table 2). The 60 sentence-pairs for this study were selected from a normative database designed for neuropsychological and imaging studies (Cardillo et al., 2010; 2017) with the aid of Stochastic Optimization of Stimuli (Armstrong, Watson, & Plaut, 2012). Sentences were matched group-wise on average frequency and concreteness, familiarity, naturalness, imageability, number of words, and number of content words.

Answer choices

Each sentence has four possible answers, the correct target answer and three foils. Answers consist of two words, an adjective-noun combination. Foils for literal sentences include 1) a category associate of the agent of the sentence not implied by the sentence, 2) the opposite of the literal meaning, and 3) an unrelated answer. Foils for the metaphor stimuli include 1) the literal meaning of the sentence, 2) the opposite of the metaphorical meaning, and 3) an unrelated answer. Answers were matched on average frequency and concreteness.

Table 2 Metaphor task examples

Sentence	Target	Foil 1	Foil 2	Foil 3
The uncle groaned in the other room	physical suffering	generous parent	comfortable rest	broken mirror
The inn groaned at the new guests	crowded accommodations	audible grumble	plentiful vacancies	winding road

Procedure

The metaphor task was run in E-Prime 2.0. The target sentence appeared at the top of the screen, with the four answers in a square below it. Participants were instructed to select the answer that best expresses the meaning of the sentence. The position of the target and foils were randomized per item. Participants responded using keyboard button presses, responding as quickly and accurately as possible. The order of sentences was randomized across participants. Instructions were read aloud and participants completed practice trials to ensure comprehension of the task

Verbal Analogy. Participants completed the verbal analogy task based on Green et al., (2010). As depicted in Figure 1, participants see a relationship at the top of the screen and two possible response sets at the bottom. Participants choose one set from the possibilities at the bottom that are related in the same way as the words at the top. The task was administered through ePrime and included 30 trials. Order of trials was randomized across participants. Each correct response was scored for a total of 30 possible points.

Visual-spatial analogy. The visual analogy task served as a control task. Participants completed the visual analogy task described in Watson & Chatterjee (2012). As depicted in Figure 1, for each trial three sets of colored shapes were presented, the source set at the top of the screen and two possible response sets below it. Participants chose the response set that contained the same pattern of spatial relations as the source. The pattern can be based on color or shape. When the basis of the analogy was the relations between colors, all sets contained the same pattern of shapes. When the basis of the analogy was the relations of shapes, all sets contained the same pattern of colors. The task was administered through ePrime 2.0 and includes 30 trials. Order of trials was randomized across participants. Each correct response was scored for a total of 30 possible points.

Figure 1. Example stimuli from shape and color trials of visuospatial analogical reasoning task (VSA) and within-domain and cross-domain verbal analogical reasoning task (VGA), derived from Watson & Chatterjee (2012) and Green et al (2010), respectively.

Statistical Methods

Linear Mixed-Effects Modelling (LMEM) was used to predict task performance from fixed effects of group, age, and education and random effects of item and participant. The lme4 package (Bates et al., 2014) in R (Version 3.6.3) was used for the following analyses.

Linear discriminant analysis was used to compare the relative performance of cognitive variables in discriminating participant group (CN and MCI). The *lda* function from the MASS package in R (Version 3.6.3) was used for these analyses.

Anatomical Methods

MRI scans were acquired on a 3T Siemens Prisma scanner at the Hospital of the University of Pennsylvania using a 64-channel array coil. The protocol includes T1-weighted (MPRAGE) whole-brain scan with the following parameters: TR/TE/TI=2400/2.24/1060 ms, 8° flip angle, $0.8 \times 0.8 \times 0.8 \text{ mm}^3$ resolution, acquisition time 6:38 min. MTL segmentation was performed in T1-weighted MRI using an analysis pipeline optimized for extracting subregional MTL measures, including anterior/posterior hippocampus, entorhinal cortex (ERC), BA35 (i.e. transentorhinal cortex), BA36, and parahippocampal cortex using an automatic pipeline, Automatic Segmentation of Hippocampal Subfields – T1 (ASHS-T1; Xie et al., 2019). This technique is tailored to reduce confounds of other approaches in this region, such as anatomic variability and segmentation of dural tissue from grey matter (Xie et al., 2019).

Anterior/posterior hippocampal volumes and cortical thickness of extrahippocampal MTL subregions (entorhinal cortex, BA35, BA36 and parahippocampal cortex) were calculated from ASHS-T1 output (Xie et al, 2017).

The participant groups were combined to examine brain-behavior relationships. LMEMs predicted task performance from the fixed effects of group, age and education and the random effects of participant and task item. First, the relationship between integrity of our region of interest, BA35, and task performance was examined. Next, exploratory analyses were run examining integrity of other MTL subregions and performance. The Holm method was used to control for multiple comparisons.

Finally, exploratory whole-brain cortical thickness analysis was performed using the ANTs cortical thickness pipeline that implements the DiReCT thickness estimation method (Das et al.,

2009). These analyses relate performance on each task to cortical thickness in the collapsed groups. Regression analyses between cortical thickness values and performance on each task was performed at each voxel in a population template space. The randomize tool in FSL was used to run non-parametric permutations ($n = 10,000$) were run for each score. Clusters that met a height threshold of $p < 0.05$ uncorrected with threshold-free cluster enhancement and a minimum of 25 adjacent voxels are reported.

RESULTS

Tests of semantic memory, metaphor comprehension, and analogy comprehension were evaluated for their sensitivity to MCI and to cortical thickness of BA35.

Behavioral Results

Senses Task

54 CN participants and 32 people with MCI completed the Senses Task. A LMEM was used to analyze the relationships between group (MCI, CN), years of education completed, age, and the number of senses produced. As random effects, participant and item were included as intercepts. These analyses (Table 3) revealed a significant effect of Group ($p < 0.0005$), with CN outperforming MCI, a significant effect of Education ($p < 0.0005$), with those with higher levels of education performing better, and a fixed effect of Age ($p < 0.05$) with older participants performing worse than younger.

Table 3: Senses Task Fixed Effects

Parameter	Estimate	Std. Error	t-value
Intercept	2.98335	0.67458	4.422***
Group (CN)	0.49503	0.13318	3.717***
Education	0.08979	0.02176	4.127***
Age	-0.02074	0.00901	-2.302*

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. CN: Cognitively normal participants.

Figure 2. Senses produced (adjusted for differences in age and level of education) from participants with normal cognition (CN) and participants with Mild Cognitive Impairment (MCI). * $p < 0.05$.

WAT

To examine group differences, 56 CN and 32 people with MCI completed the WAT. A LMEM was used to predict WAT performance from fixed effects of group and education with the random intercepts of item and participant. These analyses (Table 4 and Figure 3) reveal a significant effect of Group ($p < 0.0005$) and Education ($p < 0.005$).

Table 4: WAT Fixed Effects

Parameter	Estimate	Std. Error	t-value
Intercept	2.855645	0.178273	16.018***
Group (CN)	0.224264	0.060688	3.695***
Education	0.031285	0.009746	3.210**

** $p < 0.01$; *** $p < 0.001$. CN: Cognitively normal participants.

Figure 3. Word associates correctly identified (adjusted for differences in age and level of education) from healthy comparison participants (CN) and patients with Mild Cognitive Impairment (MCI) on the Word Associates Test. * $p < 0.05$.

Metaphor Task

51 CN and 34 MCI people completed the metaphor task. A LMEM was used to analyze the relationships between Group (CN, MCI), Figurativeness (Literal, Metaphor) and accuracy. As random effects, participant and item were included as intercepts with a by-subject random slope included for the effect of Figurativeness. These analyses (Table 5 and Figure 4), reveal a significant effect of Figurativeness ($p < 0.0001$), with more accurate responses to Literal sentences than Metaphors, a significant effect of Group ($p < 0.005$), with CN outperforming MCI, and an interaction between Figurativeness and Education ($p < 0.0005$) with education more important for metaphor than literal trials. There was no interaction between group and figurativeness ($p > 0.8$).

Table 5: Metaphor Task Fixed Effects

Parameter	Estimate	Std. Error	t-value
Intercept	0.861038	0.043663	19.720***

Group (CN)	0.042061	0.014290	2.943**
Education	0.003079	0.002334	1.319
Figurativeness (Met.)	-0.318967	0.050570	-6.307***
Fig. (Met.) x Ed	0.012411	0.002819	4.402***

**p < 0.01; ***p < 0.001. CN: Cognitively normal participants. Met: Metaphor trials. Ed: Level of education.

Figure 4. Metaphor task accuracy (adjusted for level of education) by cognitively normal participants (CN) and patients with Mild Cognitive Impairment (MCI) on Literal (Lit) and Metaphor (Met) trials.

Verbal Analogy

52 CN participants and 35 people with MCI completed the Verbal Analogy Task. A LMEM was used to predict performance from fixed effects of group and education with the random

intercepts of item and participant and a by-item random slope of Group. These analyses (Table 6 and Figure 5) reveal a significant effect of Group ($p < 0.01$) and Education ($p < 0.05$).

Table 6: Verbal Analogy Fixed Effect

Parameter	Estimate	Std. Error	t-value
Intercept	0.732183	0.062138	11.783***
Group (CN)	0.058571	0.021634	2.707**
Education	0.009061	0.003449	2.627*

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. CN: Cognitively normal participants.

Figure 5. Verbal analogy task performance (adjusted for group differences in education) by healthy comparison participants (CN) and patients with Mild Cognitive Impairment (MCI). * $p < 0.05$.

Visual-spatial Analogy

To examine potential group differences, 52 CN participants and 35 people with MCI completed the Visual-spatial Analogy Task. A LMEM was used to predict performance from fixed effects

of group and education with the random intercepts of item and participant. These analyses show no difference between groups ($p > 0.235$) and no effect of education ($p > 0.293$).

Linear discriminant analyses

Linear discriminant analyses were performed to examine which experimental and neuropsychological tests best differentiate groups (MCI vs CN, Table 7). These analyses reveal that the experimental measures better differentiate MCI from CN groups than standard neuropsychological assessments. Test scores with a coefficient greater than 0.1 are listed in Table 7. Semantic measures of animal and vegetable fluency had coefficients < 0.1 .

Table 7 Coefficients of Linear Discriminants

Test	Coefficients of linear discriminants
Metaphor trials	3.640
Literal trials	2.105
Word Associates Test	1.096
Senses Task	0.557
Mini-Mental State Exam	0.268
Clock Draw	0.200
Multilingual Naming Test total	0.181
Benson Figure Copy	0.174
Word List Memory Total	0.131
Craft Story Delayed Recall	0.102

In summary, people with MCI perform worse on the tests of semantic richness, on the metaphor task, and on the verbal analogy task. Groups do not differ on the visuo-spatial analogy task. The experimental tasks better differentiate groups than the standard neuropsychological assessments.

Anatomical results

Senses Task

Anatomical data was available from 25 participants with MCI who completed the senses task and 52 CN participants.

First, the relationship between integrity of our region of interest, BA35, and task performance was examined. Across groups, mean BA35 cortical thickness predicted senses task performance ($p < 0.05$, Table 8 and Figure 6). A 1 mm decrease in BA35 thickness is associated with a 0.77 decrease in the number of senses produced.

Table 8: Senses x BA35 Fixed Effects

Parameter	Estimate	Std. Error	t-value
Intercept	1.20104	1.09642	1.095
Group (CN)	0.46299	0.15800	3.818**
Age	-0.01739	0.01025	-1.697
Education	0.08818	0.02331	3.783**

Mean BA35	0.77254	0.32650	3.238*

* $p < 0.05$; ** $p < 0.01$. CN: Cognitively normal participants. BA35: Brodmann Area 35.

Senses Task performance and BA35 thickness

Figure 6. Senses produced as a function of BA35 cortical thickness by cognitively normal participants (CN) and patients with mild cognitive impairment (MCI; $p < 0.05$).

Next, exploratory analyses were run examining integrity of other MTL subregions and task performance.

Across the combined groups, significant relationships were seen between senses task performance and integrity of mean anterior hippocampal volume ($p < 0.05$), mean BA36 thickness ($p < 0.001$) and mean parahippocampal cortex thickness ($p < 0.005$).

Next, we examined relationships between MTL structural integrity and task performance in each group separately. Within the MCI group, no relationships are seen between MTL subregional integrity and task performance. Within the CN group, mean BA35 thickness predicted the number of senses produced ($p < 0.05$), as did mean parahippocampal cortex thickness ($p < 0.01$).

Finally, exploratory full-brain analyses revealed no relationship between cortical thickness and task performance within or outside the MTL.

WAT

Anatomical data was available from 26 participants with MCI who completed the WAT and 55 CN participants.

Across groups, mean BA35 thickness predicted WAT performance ($p < 0.05$, Table 9 and Figure 7). No other MTL subregions show a relationship with task performance.

Table 9: WAT x BA35 Fixed Effects

Parameter	Estimate	Std. Error	t-value
Intercept	2.805618	0.493922	5.680***
Group (CN)	0.285037	0.071716	3.975***
Age	-0.005537	0.004599	-1.204
Education	0.036152	0.010738	3.367**
Mean BA35	0.328675	0.157183	2.091*

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. CN: Cognitively normal participants. BA35: Brodmann Area 35.

Within the MCI group, no relationships are seen between MTL subregional integrity and WAT performance.

Within the CN group, mean BA35 thickness predicted WAT performance ($p < 0.05$), as did mean parahippocampal cortex thickness ($p < 0.001$).

Figure 7. Mean word associates correctly identified as a function of BA35 cortical thickness by healthy comparison participants (CN) and patients with mild cognitive impairment (MCI; $p < 0.05$) on the Word Associates Test (WAT).

Exploratory full-brain voxel-based morphometry analyses reveal relationships between WAT performance and atrophy in the left hippocampus, the left anterior parahippocampal gyrus, and the right inferior temporal gyrus (Table 10 and Figure 8).

Table 10 Results of full-brain voxel-based morphometry analyses

cluster size	Peak p-value	x	y	z	Location
198	< 0.001	-29	-18	-20	Left hippocampus
416	< 0.001	46	-35	-21	Right inferior temporal gyrus (posterior division)
82	0.002	-32	-21	-27	Left anterior parahippocampus gyrus

Figure 8. Exploratory full-brain voxel-based morphometry showing relationships between performance on the Word Associates Test and brain atrophy. Clusters that meet a height threshold of $p < 0.005$ uncorrected with threshold-free cluster enhancement and a minimum of 25 adjacent voxels are depicted.

Metaphor

Anatomical data is available from 25 participants with MCI who completed the metaphor task and 51 CN participants.

For metaphor trials, mean BA35 thickness shows a trend in predicting accuracy ($p < 0.1$) across groups. No other MTL subregions showed a relationship with metaphor accuracy. Among CN participants, mean BA35 thickness shows a trend in predicting metaphor accuracy ($p < 0.06$). No other MTL subregions show a relationship with metaphor accuracy. No MTL subregions predict metaphor accuracy among MCI participants.

For literal trials, mean parahippocampal cortex thickness predicted accuracy ($p < 0.05$) across groups. Within both the MCI and CN participant groups, no MTL subregions predict literal accuracy. Exploratory full-brain analyses reveal no relationship between cortical thickness and task performance outside the MTL.

Analogy Tasks

Anatomical data was available from 52 CN participants and 28 participants with MCI who completed the verbal analogy and visual-spatial analogy tasks. There was no relationship between MTL subregional integrity and performance on either task.

Exploratory full-brain analyses reveal no relationship between cortical thickness and task performance outside the MTL.

Neuropsychological assessment and anatomy

MCI patients (Table 1) perform worse than CN participants on tests of overall cognition (MMSE $p < 0.01$. MOCA $p < 0.01$) and on tests of semantic memory (Animal fluency $p < 0.01$. Vegetable fluency $p < 0.01$).

Animal ($p > 0.9$) and vegetable ($p > 0.6$) fluency did not relate to BA35 thickness, or to other MTL subregion integrity ($ps > 0.2$).

In summary for the anatomical analyses, performance on the semantic richness tasks show relationships with BA35 integrity across groups and within the CN group. Metaphor task performance shows a trend. Performance on the analogy tasks and on standard neuropsychological assessments do not relate to atrophy in BA35.

Discussion

The goal of this study was to determine if novel measures of semantic knowledge and figurative language can discriminate MCI from cognitively normal older adults, and to determine the degree to which performance on these tasks relates to morphometric measures of the earliest regions of AD pathology. Such measures, if sensitive to cognitive decline in the earliest stages of Alzheimer's disease (AD), promise to inform monitoring of disease progression and response to treatment. We tested the hypothesis that semantic richness is impaired in early stages of AD because of the recently appreciated role of the medial temporal lobe in supporting semantics, and the fact that these areas are known to be affected early in the disease. We also tested the hypothesis that comprehension of figurative language is impaired in this population. As predicted, these measures differentiated people with MCI from CN participants, and were better at differentiating groups than standard psychometric tests. Further, performance on these semantic measures was related to integrity of BA35, which includes the transentorhinal region, the first region associated with the neurofibrillary tangle pathology of AD.

On productive and receptive measures of semantic richness and depth of knowledge, MCI patients performed worse than CN participants and performance related to integrity of MTL subregions. Previous work has documented impairments on these tasks in patients with focal and stable MTL lesions (Klooster & Duff, 2015; Klooster, Tranel, & Duff 2020). In the current study, semantic performance across groups, and remarkably within the CN group, related to integrity of BA35. Previous research has demonstrated a role for perirhinal cortex, including BA35, in supporting rich semantic memory (Tyler et al., 2004; Kivisaari et al., 2012; Wright et al., 2015). It is striking that the standard neuropsychological assessments of semantic memory, which contributed to diagnostic classification, did not differentiate the groups with as large of an effect size, nor relate as well to MTL atrophy, supporting the claim of greater sensitivity for our experimental measures.

Given the involvement of MTL structures with early AD pathology, studies of episodic memory have been a focus of the study of prodromal (Collie & Maruff, 2000; Wagner et al., 2012; Dubois, Picard, & Sarazin, 2009) and preclinical AD (Bäckman, Small, & Fratiglioni 2001; Pike et al., 2007; Bäckman et al., 2005). While episodic memory is undoubtedly affected early in the course of AD, language is another aspect of cognition that notably deteriorates with disease progression (Grossman et al., 1996; Taler & Phillips, 2008; Price et al., 1993). Further, the perirhinal cortex, the area first affected by AD pathology, has long been tied to semantic memory (Venneri et al., 2008; Taylor et al., 2006; Clarke & Tyler 2014; Hirni et al., 2013). The current results argue that greater attention should be focused on semantic memory and figurative language in the study of preclinical and prodromal AD.

The ability to understand novel metaphors differentiates CN from MCI participants. Previous work has documented metaphor impairments in the absence of literal language difficulty (as assessed by standard psychometric tools), in patients with focal brain lesions (Ianni et al., 2014) and patients with neurodegenerative disease (Klooster et al., in press; Humphries et al., 2019). These studies show that metaphor processing can be disproportionately impaired compared to literal sentence comprehension, suggesting that metaphor comprehension deficits could be a sensitive measure of cognitive change, revealing impairments while literal language is normal. Understanding a novel metaphor is a complex cognitive achievement requiring inhibition of literal meaning, and cognitive flexibility to compare concepts from different domains to highlight their shared features. Impairments in multiple aspects of cognition may lead to a metaphor comprehension impairment. With its distributed neural support and cognitive complexity, metaphor comprehension may be sensitive to early cognitive changes in a variety of neurodegenerative disease.

MCI participants showed deficits on the semantic tasks, the metaphor task, and the verbal analogy task. The lack of group difference on the visuo-spatial analogy task, which also requires complex reasoning abilities, demonstrates the specificity of these findings. It is not the case that MCI patients are impaired at any complex task; their impairment in our study was restricted to tests that involved language and meaning.

Importantly, relationships were observed between task performance and integrity of MTL subregions not only across groups, but also within the CN group. The CN group likely contains individuals with preclinical AD and varying degrees of changes to MTL subregional integrity. Our morphometric measure of BA35 has been shown to be sensitive to the presence of preclinical AD in cognitively normal populations (Wolk et al., 2017). The present results suggest these cognitive tasks are related to these subtle changes and, thus, provide promise that they might have utility in detecting cognitive consequences of preclinical AD. It is unclear why this relationship is absent in the MCI group. It is possible that degeneration beyond the MTL diminishes the specific relationship between BA35 and task performance. Additionally, the smaller sample size of this group may further reduce power to detect such a relationship.

In our exploratory analyses we confirmed the relationship between hippocampal integrity and performance on the semantic memory tasks, revealing the necessity of the medial temporal lobe (MTL) for semantic richness, replicating previous findings (Klooster & Duff, 2015). These exploratory analyses failed to uncover relationships between task performance and neural

regions outside of the medial temporal lobes, suggesting that MTL injury is sufficient to modulate performance on these tasks. This lack of correlation with additional cortical regions also may be related to that fact that in this population, tangle pathology, if present, would be largely confined to MTL structures. We predict that later in the course of AD, when degeneration spreads beyond the MTL, we would see relationships between degeneration and performance on the figurative language tasks. Novel metaphor comprehension, as tested in the current study, has previously been linked to bilateral inferior frontal gyri and the left posterior middle temporal gyrus (Klooster et al., In press; Cardillo et al., 2012). While the CN group outperformed MCI on the Verbal Analogy task, performance did not relate to MTL subregional anatomy. Task performance was previously tied to frontopolar activity (Green et al., 2010). Groups did not differ on Visuospatial Analogy performance and no relationship was observed with MTL integrity. Visuospatial analogy task performance was previously linked to bilateral rostrolateral prefrontal cortex (Watson & Chatterjee 2012). In more advanced AD, when degeneration spreads to the frontal lobes, there would likely be stronger relationships seen with figurative language tasks.

A limitation of the current study is that we did not have molecular markers of AD in enough individuals to include in the current analysis. Some participants in the CN group likely had preclinical AD with evidence of cerebral amyloid. Accounting for such participants would likely further differentiate preclinical and prodromal AD from healthy aging. Conversely, some MCI participants would likely show an absence of cerebral amyloid and have cognitive impairment because of another etiology. Accounting for these individuals would give a clearer view of cognitive impairment specifically due to prodromal AD.

Future directions for investigation include relating task performance to both amyloid and tau PET imaging. Useful cognitive screening instruments would ideally, in those with normal cognition, differentiate participants with and without cerebral amyloid. As the presence and location of neurofibrillary tangles often mirror the pattern of neurodegeneration and resulting cognitive decline (Brier et al., 2016; Pontecorvo et al., 2017), we predict that semantic task performances will be especially sensitive to the presence of Tau.

In summary, MCI patients performed worse than CN participants on measures of semantic richness and figurative language. Experimental tasks were more sensitive to MCI than standard neuropsychological assessment. Semantic task performance relates to atrophy of BA35, the area first impacted by AD pathology. The cognitive instruments evaluated here show promise in sensitivity to early stages of clinical AD.

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