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Prefrontal contributions to relational encoding in amnestic mild cognitive impairment

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ABSTRACT

Relational memory declines are well documented as an early marker for amnestic mild cognitive impairment (aMCI). Episodic memory formation relies on relational processing supported by two mnemonic mechanisms, generation and binding. Neuroimaging studies using functional magnetic resonance imaging (fMRI) have primarily focused on binding deficits which are thought to be mediated by medial temporal lobe dysfunction. In this study, prefrontal contributions to relational encoding were also investigated using fMRI by parametrically manipulating generation demands during the encoding of word triads. Participants diagnosed with aMCI and healthy control subjects encoded word triads consisting of a category word with either, zero, one, or two semantically related exemplars. As the need to generate increased (i.e., two- to one- to zero-link triads), both groups recruited a core set of regions associated with the encoding of word triads including the parahippocampal gyrus, superior temporal gyrus, and superior parietal lobule. Participants diagnosed with aMCI also parametrically recruited several frontal regions including the inferior frontal gyrus and middle frontal gyrus as the need to generate increased, whereas the control participants did not show this modulation. While there is some functional overlap in regions recruited by generation demands between the groups, the recruitment of frontal regions in the aMCI participants coincides with worse memory performance, likely representing a form of neural inefficiency associated with Alzheimer's disease.

1. Introduction

Amnestic mild cognitive impairment (aMCI) is a transitional period between normal aging and very early AD (Albert et al., 2011; Gauthier et al., 2006; Petersen et al., 1999). An early hallmark of aMCI is a deficit in episodic memory, defined as the encoding and retrieval of contextually-specific information such as the time and place of an event (Tulving, 1983). Episodic memories are inherently associative, requiring relational memory processing to bind items to their context, or items to each other within a context. Individuals with aMCI show reduced performance on tests of episodic memory that require relational processing (e.g., paired-associate learning and associative recall), and such tasks are sensitive to the earliest stages of aMCI (Anderson et al., 2008; Bäckman et al., 2005; Fowler et al., 2002; Giovanello et al., 2012; Swainson et al., 2001, Troyer et al., 2008).

In a prior study, Troyer et al. (2008) compared healthy controls and an aMCI group on standardized measures of item and associative recall. Associative recall was found to be lower than item recall in both groups; however, the aMCI group showed this deficit in associative recall to a greater degree than normal control participants. The disproportionate deficit in associative recall was evident on both tests, despite the fact that one relied on intentional encoding and the other on incidental encoding (Troyer et al., 2008). Further, a meta-analysis investigating measures most sensitive to cognitive impairment due to pre-clinical Alzheimer's disease has shown that tests of episodic memory using delayed recall or delayed recognition procedures yield large effect sizes for differences between healthy aging versus aMCI (Bäckman et al., 2005). Differences across intentionality of encoding and type of memory test suggest that the processes mediating associative deficits in aMCI do

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not reflect changes in attention, effort, or strategy, but are more likely due to changes underlying the core mechanisms involved in the formation of associative memories.

Forging relational memories is thought to depend upon two mnemonic mechanisms: the generation of associations between distinct elements *and* binding elements into an integrated memory trace (Addis et al., 2014; Addis and McAndrews, 2006; Fernández and Tendolkar, 2001). Generating associations aids in successful episodic memory through the strategic organization of item information. Such processing could occur through the formation of an association between items (Addis and McAndrews, 2006; Fletcher et al., 2000), chunking multiple items to create a unit (Bor et al., 2004), or engaging in deep processing of items (Mandzia et al., 2004). Generated associations must then be bound into a single episodic memory trace for later retrieval. Binding is the process by which disparate elements in the environment are combined within an episode to create a cohesive representation for later recall.

Functional magnetic resonance imaging studies (fMRI) of healthy participants have shown that generation and binding mechanisms rely on the contribution of the prefrontal cortex (PFC) (Blumenfeld and Ranganath, 2006; Buckner et al., 1999; Kapur et al., 1994; Lepage et al., 2000; Spaniol et al., 2009; Sperling et al., 2001) and medial temporal cortices, respectively (Achim and Lepage, 2005; Addis and McAndrews, 2006; Buckner, 2003; Davachi and Wagner, 2002; Eldridge et al., 2005; Giovanello et al., 2004; Lepage et al., 2000). More specifically, the generation of semantic associations for successful relational encoding in young adults is thought to rely on the left ventrolateral PFC (VLPFC) and dorsolateral PFC (DLPFC) (Achim and Lepage, 2005; Addis and McAndrews, 2006; Fletcher et al., 2000; Lepage et al., 2000). However, in healthy aging it has been shown that while younger adults do show such PFC modulation (Addis et al., 2014, Rand-Giovannetti et al., 2006; Sperling et al., 2003), older adults do not upregulate PFC activity in response to increased encoding task demands. For example, Addis et al. (2014) used a semantic-relatedness encoding task to investigate parametric responses in PFC regions to generation demands. In this task, the number of given semantic relationships between three words is manipulated (e.g., no words are related, two of the words are related, or all three words are related). While younger adults recruited the VLPFC more as semantic generation demands increased, VLPFC activity in older adults was similar regardless of semantic generation demands.

Importantly, semantic tasks have generally elicited greater frontal activity in aMCI and AD during both encoding and retrieval (Wierenga et al., 2011; Woodard et al., 2009), suggesting that increased PFC activity during semantic memory tasks may be a hallmark of aMCI. However, to our knowledge, no prior studies have assessed the effect of manipulating the demands placed on semantic generation processes in individuals with aMCI. Therefore, it remains unclear whether this pattern of activity simply represents a general increase in PFC activity or whether it is modulated by increased demands on generative mnemonic processes. This distinction will offer critical insight into the nature of increased fMRI activity in aMCI. If aMCI participants show greater activity that is not modulated by task demands, it would suggest that such increased activity occurs at all task levels and may not reflect generation processes per se. If aMCI participants' greater recruitment is modulated by task demands, it would suggest that increased frontal activity in aMCI is specific to the demands of the task. Further, if the increased modulation correlates positively with behavior, then the activity likely represents a compensatory process. Finally, if the increased frontal activity is negatively correlated with behavior, it would provide evidence that such increased recruitment is likely a result of neural inefficiency. Thus, the current study offers unique insight into the relationship between observed fMRI activity and memory performance in aMCI.

Within the MTL, however, it has been shown that hippocampal activity increases as the need to generate associations decreases both in younger and healthy older adults (Addis and McAndrews, 2006; Addis et al., 2014). In aMCI, there appears to be a continuum of change within MTL regions, whereby aMCI patients who show less memory impairment tend to show greater levels of MTL activity than aMCI patients with greater impairment (De Santi et al., 2008; Dickerson et al., 2004, 2005; Johnson et al., 2006, Machulda et al., 2003). For example, Dickerson et al. (2005) used a face-name association task and compared novel face-name pairs (i.e., a condition where binding is necessary) to repeated face-name pairs (i.e., a condition where binding has already occurred or where binding demands are reduced). Interestingly, a greater extent of activation within the hippocampus is correlated with better memory performance. Further, group comparisons have typically shown hyperactivation in MTL regions in aMCI as compared to healthy aging (Dickerson et al., 2004, 2005, Hämäläinen et al., 2007). Given the positive correlations between hyperactivity and behavior, hyperactivity may be thought of as compensatory; however, Bakker et al. (2012) have shown that reducing hyperactivity actually improves memory in aMCI participants. Therefore, hyperactivity is likely caused by a combination of factors and should be thought of as a hallmark of the disease process itself (Dickerson et al., 2005).

In order to explore both MTL and PFC contributions to associative encoding in aMCI, we adapted a paradigm used previously in healthy aging to assess the contribution of MTL and PFC cortices to relational memory generation (Addis et al., 2014). Critically, this design modulates the degree to which generation processes are utilized during successful memory encoding. We hypothesize that aMCI participants, as compared to healthy control subjects, will show hyperactivity in prefrontal regions, and similar to healthy older adults will not modulate PFC activity across different generation demands. We also predict that aMCI participants will show hyperactivity in the MTL during relational encoding. However, because of the significant relational memory performance impairments documented in aMCI, it is unclear if these individuals, as healthy older adults, will modulate MTL activity across the generation demands of the task.

2. Material and methods

2.1. Participants

Sixteen healthy controls and fourteen individuals with aMCI were recruited for this study through the Bryan Alzheimer's Disease Research Center (ADRC) at Duke Medical Center and the University of North Carolina at Chapel Hill (UNC-CH) Memory Disorders Clinic. Four of the control participants were excluded from the final analysis, one due to a technical error occurring in data collection, one due to chance performance, and two who failed to understand the task. Of the fourteen aMCI participants, data from two were excluded due to chance performance and one participant did not fit comfortably in the scanner. The data reported in this analysis include twelve healthy controls and eleven aMCI participants. This study was approved by the UNC-CH and Duke Medical Center Institutional Review Boards. Informed consent was obtained from each participant. All subjects were paid for their participation. The classification of healthy control and aMCI was based on the input of two sources: the neurologist's (JRB or DIK) clinical opinion based on their interview and examination of the participants and cognitive test results interpreted by the neuropsychologist (see below).

2.1.1. aMCI participants

aMCI was defined by the following criteria: (1) memory complaint corroborated by an informant, (2) not normal for age (as determined by the neurologists' and neuropsychologists' clinical judgment), (3) not demented, (4) mild cognitive impairment, (5) essentially normal functional activities, (6) memory was the only cognitive domain mildly impaired relative to normal comparison, and (7) hippocampal atrophy as indicated by structural MRI.

2.1.2. Healthy control participants

Healthy control older adults met the following criteria: (1) no cognitive complaints, (2) no active neurological or psychiatric illness, (3) independently functioning community dwellers, (4) normal neurological and neuropsychological exam, and (5) not taking any medications in doses that would impact cognitive performance.

2.1.3. Exclusion criteria

Exclusion criteria were as follows: (1) diagnosis other than cognitively normal (i.e., healthy control) or aMCI, (2) left-handedness, (3) non-native English speaker, (3) dementia, (4) medical contraindications for MRI, (5) structural abnormalities (e.g., infarctions), and (6) concurrent illnesses interfering with cognitive function other than aMCI (i.e., heart/liver/renal failure, psychiatric disorders, and substance abuse).

2.1.4. Neuropsychological testing

Neuropsychological testing was completed within 6 months of participation in the study. The battery employed is one used in longitudinal studies at the Bryan ADRC (e.g. Tschanz et al., 2006) and includes all the requisite measures of the National Alzheimer's Coordinating Center (NACC; see Hayden et al., 2011). Episodic memory was assessed by performance on Logical Memory Immediate and Delay subtests, Story A, from the Wechsler Memory Scale — Revised (Wechsler, 1987), as well as by scores on subtests of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) list learning task (i.e., word list learning, recall intrusions, perseverations, recall, recognition, constructional praxis recall, and constructional praxis recognition; Morris et al., 1989). Language tests measured object naming (30 item version of the Boston Naming Test, Kaplan et al., 1983), phonemic fluency (Controlled Oral Word Association Test; COWAT), and category fluency (animals, Morris et al., 1989 and vegetables). Attention and executive tests included the Trail-making test Parts A and B (Spreen and Strauss, 1991) and both the Digit Span and Digit Symbol subtests from the Wechsler Adult Intelligence Scale — Revised (Wechsler, 1981). Additional tests included the AD8 (a screening test that assesses memory, orientation, executive functioning, and interest in activities; 2005, Washington University, St. Louis, MO), the Shipley Vocabulary Test (as an estimate of premorbid function and intelligence; Shipley, 1967), the Mini-mental Status Exam (MMSE; Folstein et al., 1975), the Geriatric Depression Scale, and the Hachinski Ischaemia Questionnaire (Hachinski et al., 1975).

2.2. Materials

2.2.1. Encoding task

The semantic-relatedness encoding task (Mathews, 1977) involves the presentation of triads consisting of a category name and two category exemplars (see Fig. 1A). All triads used in this study were identical to those used by Addis and McAndrews (2006), and constructed using the Battig and Montague (1969) and Murdock (1976) norms, such that only exemplars frequently associated with a category were used. Over the duration of scanning, 105 encoding triads were shown (35 trials per run), 35 of each of three trial types: (1) triads in which no exemplars related to the category name ("zero-link" trials); (2) triads in which only one exemplar related to the category name ("one-link" trials); and (3) triads in which both exemplars related semantically to the category name ("two-link" trials). Encoding and control triads were presented for 6 s, considered sufficient for triad encoding (Addis and McAndrews, 2006; Lepage et al., 2000). For each encoding triad, participants were required to decide how many of the words in the lower portion of the triad could be considered exemplars of the category named in the top portion of the triad. The buttons on the response box assigned to each response were as follows: "none" (right index finger); "one" (right middle finger) or "all" (right ring finger). Thus, the three encoding trial types (zero, one, and two link) were identical in terms of the decision task to be performed, and varied in terms of the number of semantic associations provided and thus the degree to which generation of associations was required (from high-generation, zero-link trials to low-generation, two-link trials).

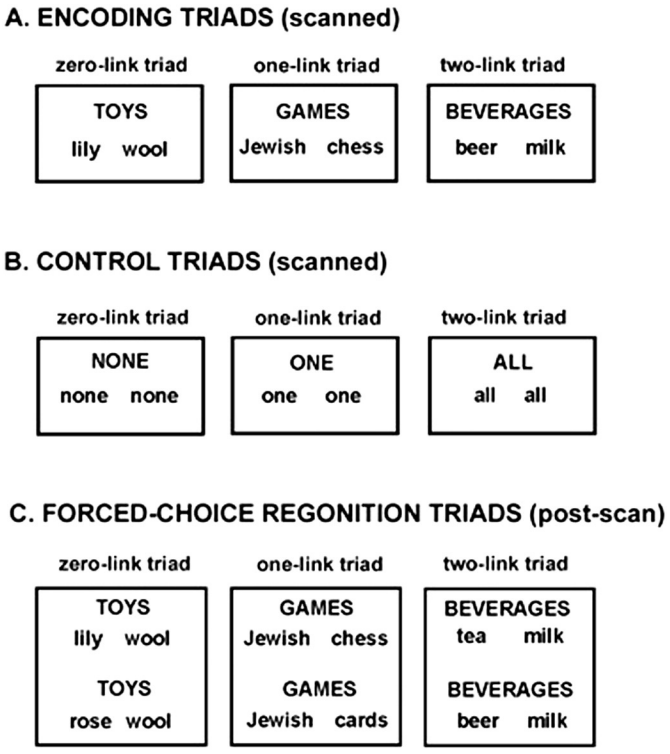

Fig. 1. Experimental paradigm. (A) Examples of to-be-encoded triads from each condition. All triads consisted of a category word presented on top of exemplar words where either none were related to the category word (zero-link), one was related to the category word (one-link), or two were related to the category word (two-link). (B) Control trials were presented as an active baseline and a response was collected in the same way as they were for to-be-encoded triads. (C) Post scanning, participants were given a forced-choice recognition test between a previously seen triad and a new triad. New triads were created by altering one exemplar in the triad. Adapted from Addis and McAndrews (2006).

Thirty-six control trials were also shown; these trials consisted of triads of one word corresponding to a response option (i.e., either "none," "one" or "all"; Fig. 1B). Participants were required to respond according to the word shown (i.e., to select the response key corresponding to "none," "one" or "all"). Baseline trials (between 90 and 100 trials) consisted of a fixation cross and ranged in length from 2 to 14 s. In order to counterbalance the use of stimuli in different conditions, categories cycled through the different link conditions. Thus, for each of the 105 category names, 3 triads were constructed (a zero-link, one-link, and two-link triad). Moreover, stimuli cycled through runs, so that in each counterbalanced version, category names were presented in a different run; participants were randomly assigned to a counterbalanced version. The task was divided across 3 scanning runs (8 min 24 s each). During each run, 76–80 trials (baseline, control, zero-, one- and two-link triads) were presented in a pseudo-random order; the order of trial presentation and number and length of baseline trials were determined using Optseq2 (http://surfer.nmr.mgh.harvard.edu/optseq/), an algorithm for optimizing power in event-related fMRI designs.

2.2.2. Forced-choice recognition task

Identification of successfully encoded triads was based on subsequent recognition of triads during forced-choice recognition. One hundred and five trials, each consisting of an old triad (shown during scanning) and a new triad (see Fig. 1c), were presented. New triads

were identical to old triads, except for one exemplar being replaced with a semantically-related foil that was taken from the same category in the category norms (Battig and Montague, 1969; Murdock, 1976). The position of the old and new triads (i.e., top or bottom half of the screen) was assigned randomly. Furthermore, the position of the foil (i.e., whether the left or right exemplar was replaced), and whether the foil replaced a related or non-related exemplar in one-link triads, was also assigned randomly to triads. Each old-new trial was displayed for as long as the participant needed. The participant indicated which triad was seen during scanning by pressing the number 1 on a keyboard for the top triad or the number 2 for the bottom triad. When a response was made the display automatically moved to the next forced-choice recognition trial.

2.3. Procedure

Prior to scanning, participants were familiarized with the encoding task during four practice trials. Participants were told that they would engage in a problem solving task and were not informed that they would be asked to remember the triads. Immediately following scanning, and approximately10 min after the end of the encoding task, individuals completed the forced-choice recognition task.

2.4. MR acquisition and analysis

2.4.1. Data acquisition

All imaging data were acquired at the UNC-CH's Biomedical Research Imaging Center on a Siemens 3 Tesla Allegra head-only imaging system equipped for echo planar imaging (EPI; Siemens Medical Systems, Iselin, NJ) using a 3-axis gradient head coil. For each participant, the following protocol was used. An anatomical scan was acquired using a high resolution T1-weighted MPRAGE sequence (TR = 1750 ms, TE = 4.38 ms, flip angle = 8°, 176 slices, FOV = 256, matrix = 256 × 256, 1 × 1 × 1 mm resolution). After the anatomical scan, three functional runs were acquired during the encoding phase. For the functional runs, imaging was performed using a T2*-weighted EPI sequence (TR = 2000 ms, TE = 30 ms, flip angle = 80°). Each brain volume was composed of 34 5 mm slices (FOV = 192, matrix = 64 × 64, 3 × 3 × 5 mm resolution) oriented parallel to the long axis of the hippocampus, collected interleaved, inferior to superior. For all functional runs, data from the first two volumes were discarded to allow for stabilization of magnetic fields. Stimuli were presented in black text on a white background and back-projected onto a white screen viewed by the participants through an MR-compatible mirror mounted in the head coil. MacStim (CogState Ltd., Melbourne, Australia) was used for the presentation and timing of stimuli and collection of reaction times and response data. Responses were made on an MR-compatible response box. Head motion was restricted with a pillow and foam inserts. Subjects requiring vision correction were given MRI-compatible glasses with prescriptions approximating their own.

2.4.2. Data preprocessing

Preprocessing and analyses of imaging data was performed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK). Standard preprocessing of functional images was performed, including rigid-body motion correction and unwarping, slice-timing correction, spatial normalization to the Montreal Neurological Institute (MNI) template (resampled at 2 × 2 × 2 mm^3) and spatial smoothing (using an 8 mm full-width half maximum isotropic Gaussian kernel). Data were high-pass filtered to account for low-frequency drifts; a cut-off value of 128 was used.

2.4.3. Parametric modulation analyses

At the fixed effects level, a parametric modulation model for successful hits only was computed for each subject to examine the linear effects of generation. Each stimulus event was modeled with a canonical hrf (applied when the button press was made for the relatedness judgment) and the number of semantic links provided was specified as a parametric modulation regressor. Two contrasts were subsequently specified: one to identify regions with a negative slope (e.g., activity = 0 link > 1 link > 2 link), indicating more activity as the number of associations provided decreased (i.e., as the need to generate associations increased); and another to identify regions with a positive slope (e.g., activity = 0 link < 1 link < 2 link), indicating more activity as the number of associations provided increased (i.e., as the need to generate associations decreased). Relevant contrast images were entered into a series of random-effects analyses.

Random-effects conjunction analyses were used to identify those regions in which parametric responses to variations in the degree of generation (i.e., semantic relatedness) were similar across the two groups (i.e., healthy controls and MCI-AD patients), such that for both groups, neural activity in a region was modulated by the number of given associations in either a positive or negative manner. Thus, two conjunction analyses were computed using SPM's masking function to select voxels to include or exclude. For any given contrast of interest (e.g., positive parametric modulation), a one-sample t-test was computed for the healthy control group and activated voxels were used to form a mask. A second one-sample t-test for the same contrast of interest but now in the aMCI group was computed with the healthy control mask applied, such that the resulting conjunction revealed regions active in both groups for this contrast of interest. Each of the one-sample t-tests created in this process was thresholded at p < .0225, resulting in a conjoint voxel-level probability, estimated using Fisher's method (Fisher, 1950; Lazar et al., 2002), of $p < .005$, uncorrected (Addis and Schacter, 2008).

To identify regions in which neural responses to the amount of generation differed across the two groups, relevant contrast images from fixed effects analyses were entered into a random-effects independent samples t-test model. In order to account for differences in encoding performance, we included recognition accuracy as a subject-level covariate. Two contrasts were computed: (1) healthy controls > aMCI participants; and (2) aMCI participants > healthy controls. These contrasts identified voxels for which the slope of the regression line for the covariate of interest (i.e., the number of to-be generated associations) differed significantly between groups.

This approach can therefore detect voxels in which the slope of the regression line is opposite in sign (e.g., the parametric effect in a region is positive for healthy older adults but negative for aMCI participants) or of the same sign, but significantly different in magnitude (e.g., the parametric effect is weakly negative for healthy older adults and strongly negative for aMCI participants). To clarify the nature of any significant differences and to distinguish between these two scenarios (where the slope is of opposite sign or of same sign, but different magnitude), the average estimated slope of the regression line for each group was extracted from relevant beta images to determine the sign and strength of the modulation effects. Additionally, even if significant group differences emerged, the degree of modulation within each group may not be significantly different from zero. We therefore determined whether parametric modulation effects were significant within group for any regions exhibiting a group difference by computing a whole-brain one-sample random-effects *t*-test for each parametric modulation effect. The significance threshold for these contrast analyses was also set at $p < .005$ uncorrected, with at least 10 contiguous voxels. For visualization purposes, parameter estimates (beta weights) associated with encoding of zero-, one-, and two-link triads were extracted from peak voxels in selected clusters. For localization, peak MNI co-ordinates were converted to Talairach space and localized in reference to a standard stereotaxic atlas (Talairach and Tournoux, 1988).

2.4.4. Group comparison of mean activity associated with encoding

The primary goal of the study was to investigate neural regions modulated by generation demands; however, to investigate whether patients with aMCI exhibited hyperactivity associated with encoding

in general, a univariate analysis was conducted. A fixed effects contrast of all hits greater than all control trials was computed for each participant. The resulting images were then entered into a random effects analysis. Again, we included recognition accuracy as a subject-level covariate. Since the univariate analysis was conducted to investigate regions that may be hyperactive in the patient group, we only computed the contrast of aMCI participants > healthy control participants using a threshold of $p < .005$ (uncorrected) with at least 10 contiguous voxels.

3. Results

3.1. Sample characteristics

Demographic and neuropsychological data are presented in Table 1. Pairwise t-tests comparing healthy controls and aMCI participants across each measure showed no difference in the demographic variables of age and education, vascular risk (Hachinski Score), mood depression, nor any differences on measures of vocabulary, naming, or generative fluency (all values $p > .43$). The two groups did differ significantly (all values $p < .05$) on global measures of cognition (MMSE and AD8), episodic learning and memory (Logical Memory Delayed, CERAD word list learning and recall, and CERAD delayed recall of constructional praxis figures), as well as on measures of speeded motor performance (Digit Symbol and Trail Making). These results were consistent with our recruitment of aMCI participants.

Table 1
Demographic and mean neuropsychological data for healthy control (HC) participants and individuals with amnestic mild cognitive impairment (aMCI).

	HC	aMCI
	n = 12	*n* = 11
Age, years	76.5 (6.9)	75.7 (8.6)
Male/female	9/3	6/5
Education, years	16.9 (2.7)	17.0 (3.6)
MMSE	29.4 (0.9)	26.0 (2.5)*
Hachinski score	1.3 (1.2)	2.1 (0.8)
AD8	.8 (1.1)	4.3 (2.0)*
Shipley vocabulary test	35.4 (6.4)	34.8 (4.8)
Digit span (WAIS-R) total	14.9 (2.0)	14.0 (1.9)
Logical memory immediate (WMS-R)†	16.3 (2.6)	12.0 (2.3)
Logical memory delay (WMS-R)†	15.7 (2.2)	6.8 (5.0)*
CERAD		
Word list learning	22.7 (1.9)	17.2 (2.5)*
Recall intrusions	<1 (0.3)	<1 (0.5)
Perseverations	<1 (.05)	<1 (0.6)
Recall	8.2 (1.1)	4.1 (2.7)*
Recognition correct yes	9.9 (0.3)	9.5 (0.8)
Recognition correct no	10.0 (0.3)	9.3 (1.6)
Immediate constructional praxis	10.4 (1.1)	10.3 (1.2)
Delay constructional praxis recall	9.1 (1.6)	6.2 (1.9)*
Delay constructional praxis recognition	4.0 (0.0)	3.9 (0.5)
Trails A errors	0.0 (0.0)	0.0 (0.0)
Trails A time	29.6 (7.9)	36.0 (9.2)
Trails B errors	<1 (0.3)	<1 (0.9)
Trails B time	71.5 (9.3)	87.7 (9.2)*
Digit symbol (WAIS-R)	49.1 (6.4)	35.8 (4.0)*
Boston naming test	27.9 (2.4)	25.5 (3.9)
Animal fluency	19.6 (5.4)	18.7 (5.8)
Vegetable fluency	14.0 (5.7)	12.6 (6.9)
COWAT	40.7 (9.5)	35.7 (8.1)
Geriatric depression scale	<1 (0.8)	1.2 (2.4)

Notes. MMSE, Mini-mental State Examination; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; WMS-R, Wechsler Memory Scale — Revised; WAIS-R, Wechsler Adult Intelligence Scale — Revised; COWAT, Controlled Oral Word Association tests; * indicates a significant difference between the two groups at $p < .05$. † Scores are for Story A only. Standard deviations are presented in parentheses.

Table 2
Behavioral results during encoding and recognition for healthy control (HC) participants and individuals with amnestic mild cognitive impairment (aMCI).

	Encoding hits			Recognition hits		
	0-link	1-link	2-link	0-link	1-link	2-link
HC	89.9(1.5)	91.2(1.3)	86.0(2.3)	75.9(3.5)	82.7(2.7)	90.9(1.6)
aMCI	82.2(3.7)	74.5(6.1)	84.2(4.1)	62.6(3.8)	69.1(3.5)	66.3(6.7)
	Encoding RT			Recognition RT		
	0-link	1-link	2-link	0-link	1-link	2-link
HC	3.08(.12)	2.83(.12)	2.91(.10)	7.64(.66)	6.73(.52)	5.83(.44)
aMCI	3.45(.13)	3.37(.14)	3.13(.15)	8.73(.88)	7.42(.64)	6.87(.60)

Notes. RT = reaction time; Hits represent percent correct; RT is presented in seconds; means are reported with standard errors in parentheses.

3.2. Behavioral results

3.2.1. Encoding judgments

The average accuracy and reaction times for the encoding judgments of healthy control participants and aMCI patients are presented in Table 2. For the accuracy data, a mixed factorial analysis of variance (ANOVA) with a repeated factor of condition (zero-, one- and two-link) and between factor of group (healthy control, aMCI) revealed neither a main effect of condition, $F_{2,42} = .45$, $p = .64$, nor a significant interaction, $F_{2,42} = 2.32$, $p = .11$. The groups, however, did differ in their accuracy during encoding, $F_{1,21} = 12.77$, $p = .002$, where healthy controls were more accurate than patients.

A mixed factorial ANOVA (with repeated factor of condition and between factor of group) of encoding reaction time data revealed a significant effect of condition, $F_{2,42} = 4.81$, $p = .013$, where reaction time decreased as the need to generate associations decreased. There was a main effect of group, $F_{1,21} = 6.79$, $p = .016$, with no significant interaction, $F_{2,42} = 2.12$, $p = .133$, indicating aMCI patients were overall slower than healthy controls.

3.2.2. Recognition

Average forced-choice recognition accuracy and reaction time data from all participants are also presented in Table 2. A mixed factorial ANOVA (repeated factor of condition, between factor of group) confirmed that there was a significant effect of condition (zero-, one- and two-link) for accuracy, $F_{2,42} = 4.32$, $p = .02$, but no significant interaction, $F_{2,42} = 1.97$, $p = .157$, indicating that participants were more accurate as the need for generation decreased. There was also a significant effect of group, $F_{1,21} = 22.65$, $p < .001$, where aMCI patients performed more poorly than healthy controls. As such, recognition accuracy (as a measure of encoding performance) was used as a subject-level covariate in the group fMRI contrasts.

A mixed factorial ANOVA (repeated factor of condition, between factor of group) of reaction time data also revealed a significant effect of condition, $F_{2,42} = 22.11$, $p < .001$, and again, this effect reflected a decrease in reaction times as generation demands decreased. Reaction times did not differ significantly between the groups, $F_{1,21} = 1.42$, $p = .247$, and there was no significant interaction, $F_{2,42} = .318$, $p = .729$.

3.3. fMRI results

3.3.1. Common modulations of activity by number of given associations

Conjunction analyses examined whether the two groups exhibited either (1) common positive or (2) common negative modulation of activity in response to the number of provided associations (i.e., neural activity in a region was correlated with the number of associations in either a positive or negative manner, respectively). The first conjunction analysis revealed that there were no regions in which both groups

exhibited a common positive modulation of activity. In other words, there were no neural regions that were commonly up-regulated as the number of provided associations increased (i.e., 0-link to 1-link to 2-link — generation demands are decreasing). To elucidate whether the lack of common regions was due to no activations in either group, or simply different activations in each group, a within group one-sample t-test was conducted ($p < .005$ uncorrected, $k = 10$). Healthy controls modulated two regions, the left angular gyrus (BA 39, xyz = −44 −66 42) and left superior temporal gyrus (BA 39, xyz = −42 −52 32), while the aMCI group showed no significant modulations. The second conjunction analysis revealed that there were several regions in which both groups exhibited a common negative modulation of activity. These regions of activity included regions in the frontal lobe (right supplementary motor area), the MTL (right parahippocampal gyrus), posterior visuospatial regions (e.g., bilateral lateral occipital cortex, left superior parietal lobule, left cuneus, right fusiform gyrus), as well as the left thalamus and left cingulate (see Table 3 and Fig. 2). That is, both groups increased neural activity in these regions as the number of provided associations decreased (i.e., 2-link to 1-link to 0-link — generation demands are increasing).

3.3.2. Distinct group-based modulations of neural activity by generation demands

Contrast analyses were conducted to identify regions in which parametric responses to the number of provided associations significantly differed between the groups. The first analysis examined regions for which the aMCI group showed *significant* negative modulation of activity (i.e., 2-link to 1-link to 0-link) and the healthy control group showed either less or no negative modulation of activity in the same region. Three regions were identified for this analysis: left inferior frontal gyrus, right precuneus, and left middle frontal gyrus (see Fig. 2). Finally, a second analysis examined regions for which the aMCI group showed *significant* positive modulation of activity (i.e., 0-link to 1-link to 2-link) and the healthy control group showed either less or no positive modulation of activity in the same region. No significant regions were observed for this analysis.

Table 3
Regions of Significant Activity during Successful Encoding.

Location	Hemisphere	BA	MNI coordinates			t-Value	Voxels
			x	*y*	*z*		
Common negative modulation of neural activity for healthy controls and aMCI							
Superior occipital gyrus	L	19	−30	−80	34	6.02	174
	R	19	32	−70	32	4.31	73
Inferior occipital gyrus	L	19	−40	−80	0	4.66	159
	L	17	−20	−88	4	4.26	55
Cuneus	L	18	−16	−82	26	4.39	71
Superior parietal lobule	L	7	−16	−62	50	4.13	34
Fusiform gyrus	R	19	42	−64	−16	4.21	44
	R	37	36	−40	−18	3.12	43
Red nucleus	L	n/a	−6	−20	−4	3.84	88
Middle occipital gyrus	R	18	24	−86	14	3.67	48
Cingulate gyrus	L	32	−12	10	42	3.49	16
	R	31	16	−24	48	3.61	59
Precentral gyrus	L	6	−36	−12	42	3.37	68
Paracentral lobule	L	5	−6	−40	58	3.32	28
Superior temporal gyrus	R	22	36	4	−18	3.24	40
Thalamus	L	n/a	−18	−36	6	2.98	27
Supplementary motor area	R	31	4	−18	50	2.97	10
Parahippocampal gyrus	R	19	26	−48	−6	2.90	15
Negative modulation of neural activity greater for aMCI than healthy controls							
Inferior frontal gyrus	L	44	−42	6	12	3.72	26
Precuneus	R	31	22	−52	26	3.64	16
Middle frontal gyrus	L	9	−46	20	30	3.19	25

Notes. aMCI = amnestic mild cognitive impairment; BA = Brodmann Area; MNI = Montreal Neurological Institute.

3.3.3. Group comparison of mean activity associated with encoding

The univariate analysis investigated whether the aMCI group generally exhibited hyperactivity relative to healthy controls during the encoding of word triads. Results from the contrast of aMCI patients greater than healthy controls revealed no regions in which the aMCI group showed greater recruitment than healthy controls during encoding.

4. Discussion

The goal of the current study was to characterize prefrontal and MTL contributions to relational encoding in aMCI as generation demands (i.e., number of provided associations) parametrically increased or decreased. Forming episodic memories depends on the generation of associations between distinct elements and the binding of those elements into an integrated memory trace (Addis et al., 2014; Addis and McAndrews, 2006; Fernández and Tendolkar, 2001; Fletcher et al., 2000). Prior research in healthy older adults suggests that a lack of PFC modulation as generation demands increase is related to relational memory deficits (Addis et al., 2014). In comparison, patients with aMCI typically exhibit hyperactivity in PFC regions during semantic memory tasks (Wierenga et al., 2011; Woodard et al., 2009) and in the MTL during relational memory tasks (De Santi et al., 2008; Dickerson et al., 2004, 2005; Johnson et al., 2006, Machulda et al., 2003). The current study specifically manipulated generation demands during the encoding of word triads to investigate whether the modulation of PFC and MTL activity by encoding task demands differed in aMCI relative to healthy controls. We hypothesized that aMCI participants, as compared to healthy control participants, would show hyperactivity in prefrontal regions, but, like healthy older adults, aMCI participants would not modulate frontal activity in response to task demands. We also predicted that aMCI participants would show hyperactivity in the MTL during relational encoding. Understanding more precisely what mediates increased fMRI activity in aMCI is a critical next step in elucidating the mechanisms underlying the disease.

In line with past research, aMCI participants' relational memory performance was significantly worse than that of the healthy older adult participants (Anderson et al., 2008; Bäckman et al., 2005; Fowler et al., 2002; Swainson et al., 2001; Troyer et al., 2008). However, aMCI participants showed an equivalent decrease in performance across all levels of the semantic relatedness task, relative to control participants, suggesting that aMCI does not alter the ability for semantic relatedness to boost recognition memory performance.

At the neural level, we hypothesized that the aMCI group would show hyperactivity in frontal regions, and potentially medial temporal regions, during the semantic-relatedness encoding task relative to healthy older adults. We did not find evidence for hyperactivation associated with encoding in general within the aMCI group. Hyperactivity has often been found within the hippocampus and parahippocampal cortex (Dickerson et al., 2004; 2005, Hämäläinen et al., 2007) as well as the frontal lobes (Wierenga et al., 2011; Woodard et al., 2009), although this is not always the case (Parra et al., 2013). Hyperactivation is typically found early in aMCI, but as the disease progresses, declines to be similar to that of AD patients. The aMCI group within the current study had MMSE scores ($M = 25.8$) that were lower than that of Dickerson et al. (2005; $M = 29.6$) who found hyperactivation, but were more similar to that of Parra et al. (2013; $M = 27.5$) who did not. Therefore it is likely that hyperactivity only occurs in the earliest stages of Alzheimer's disease.

However, both groups recruited a set of common regions as the need to generate associations increased (i.e., 2-link to 1-link to 0-link, number of provided associations decreased), including the right parahippocampal gyrus, left superior parietal lobule, right superior temporal gyrus, bilateral occipital regions, left cuneus, and left cingulate. The right parahippocampal cortex has generally been implicated in episodic memory (for review, see Schacter and Wagner, 1999). A recent theoretical

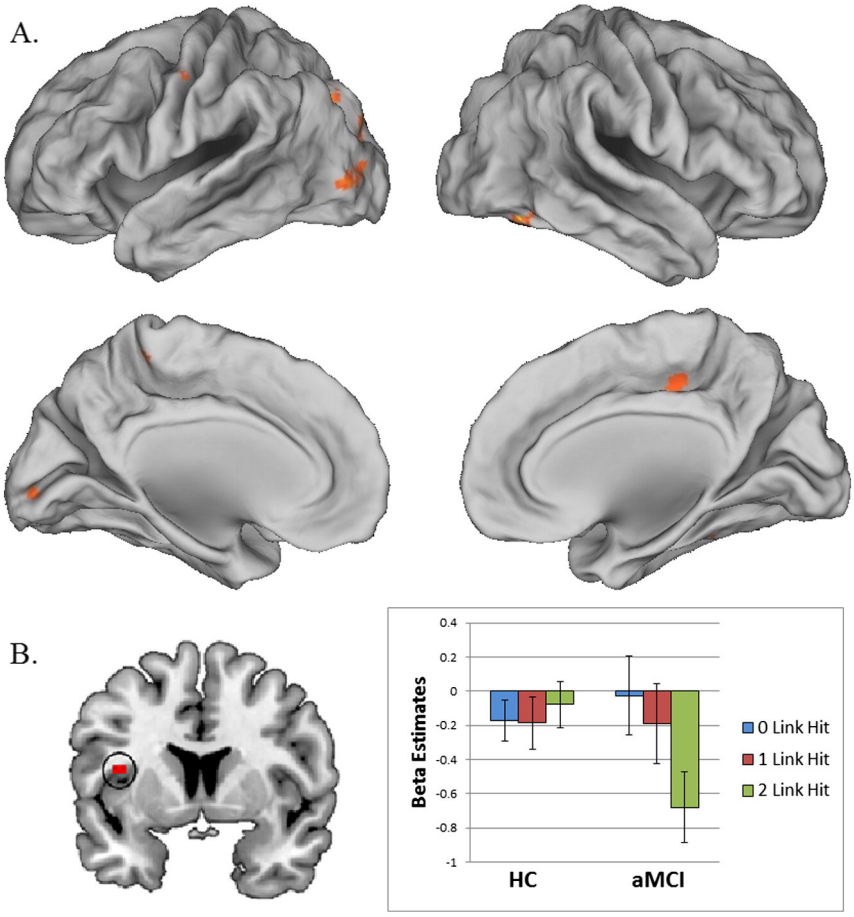

Fig. 2. (A) Regions that showed common negative modulations between the healthy controls (HC) and participants with amnestic mild cognitive impairment (aMCI) including the right parahippocampal gyrus and left superior parietal lobule. (B) Activity in the inferior frontal gyrus was modulated by the degree of generation during encoding for aMCI participants only.

framework also suggests the parahippocampal cortex, along with regions in the occipital cortex, cingulate, and superior temporal gyrus, are critical for the processing of contextual associations (Aminoff et al., 2013). Thus, one explanation for the increase in activity in these regions pertains to semantic relatedness, such that as word triads become less associated, there is greater need to integrate unrelated semantic concepts into a single contextual association. When both words are related to the conceptual category, a context is easily reinstated from past learning to support later memory. As the words become less related to the conceptual category, the generation of associations, as well as the creation of a unified context, is increasingly difficult to create. Importantly, Aminoff et al. (2013) suggested that these regions are generally involved in the processing of strong, relative to weak, contextual associations. However, the contextual association network was also activated during tasks that did not explicitly present a context, but in which one was created by the participant. Therefore, it is likely that when participants recognize a scene or display that has a strong context, this network is engaged. In contrast, when task demands require the creation of a new context, this network is increasingly activated as the need to generate a context is increased. Therefore, both healthy older adult participants and aMCI participants appear to recruit a similar episodic network to support successful encoding and, furthermore, recruit this network more as the need to generate contextual associations increases. In line with this idea, prior research has shown similar regions are activated during encoding of unrelated items for young, older, and aMCI participants (Addis and McAndrews, 2006; Giovanello et al., 2012; Leshikar et al., 2010).

We also hypothesized that aMCI participants would show a lack of modulation in frontal regions. Yet, group differences in modulation were observed within the prefrontal cortex and precuneus. Replicating prior research, healthy older adults did not modulate the inferior frontal gyrus (IFG) as generation demands increased (Addis et al., 2014). aMCI participants showed no evidence of hyperactivity within frontal regions; however, aMCI participants did modulate the IFG and middle frontal gyrus as the need to generate contextual associations increased (i.e., 0-link > 1-link > 2-link). The modulation of prefrontal regions during this task may represent frontally-mediated compensatory processes, or it may indicate neural inefficiency during semantic processing and episodic encoding. To elucidate this issue, a correlation was calculated between the degree of modulation of the IFG (i.e., difference in activity between zero- and two-link triads) and participants' recognition accuracy in each encoding condition (i.e., 0-link, 1-link, and 2-link). Additionally, a correlation was calculated between IFG modulations and recognition accuracy averaged across all encoding conditions. All correlations were in the same direction; however, only one significant negative relationship was found between the degree of modulation and recognition accuracy in the zero-link condition, $r(21) = -.45$, $p = .03$, such that the greater the increase in activity from two-link to zero-link triads the worse the accuracy in the zero-link condition. Therefore, the modulation of frontal activity likely represents neural inefficiency caused by an underlying change in neural processing due to Alzheimer's disease.

Past research on functional changes in aMCI have primarily focused on the medial temporal lobes (De Santi et al., 2008; Dickerson et al., 2004; Dickerson et al., 2005; Johnson et al., 2006, Machulda et al., 2003) with very few studies focusing on changes within the frontal lobes (Wierenga et al., 2011; Woodard et al., 2009). The current findings

suggest that both healthy older adults and older adults with aMCI modulate a network associated with the encoding and processing of semantic information as the need to generate associations increases. However, aMCI patients also modulate activity in frontal regions, including the IFG and middle frontal gyrus, and this additional modulation coincides with worse memory performance.

While our results suggest that increased activity in frontal regions is a general hallmark of aMCI, there are several limitations to the current study. First, our study includes a small sample size, making it more difficult to find reliable results that will replicate across experiments. Although we conclude that the lack of observed hyperactivity likely reflects a difference in participants between prior studies of aMCI and ours, it is possible that this finding may reflect an underpowered sample. We note, however, that our sample size is similar or larger than many of the studies from which our hypotheses were derived (e.g. Dickerson et al., 2004, 2005; Wieringa et al., 2011). Further, our interpretations of null results also replicate findings from the literature, namely that healthy older participants do not modulate the IFG across generation demands, suggesting that the finding is a true failure to modulate frontal activity and not simply a lack of power or an experimental design issue (Addis et al., 2014). Another limitation is the classification of the aMCI group. The classification criteria used in the current study reflect a diagnosis of aMCI, which means these participants likely have early stage AD; however, we cannot be certain of the underlying pathology (Gauthier et al., 2006; Petersen et al., 1999). As noted in Albert et al. (2011), knowing whether each participant also has a concomitant increase in beta-amyloid or tau deposits would better classify these participants as having MCI *due to* AD.

Pathophysiological changes present in aMCI occur years before the onset of cognitive impairments and have been proposed to allow for the diagnosis of AD before behavioral changes are observed (Jack et al., 2010; Sperling et al., 2011). These changes are thought to occur in a sequential cascade starting with amyloid-beta (Aβ) deposition, tau accumulation, neuroanatomical atrophy, and lastly cognitive impairment (Jack et al., 2010). While a great deal of work has been done in this area, diagnosing AD based strictly on non-cognitive biomarkers requires continued refinement (Sperling et al., 2011, Zaccai et al., 2008). Currently, clinical diagnostic criteria for aMCI require a decline in at least one cognitive domain (Albert et al., 2011; Gauthier et al., 2006; Petersen et al., 1999); this requirement may always be an integral piece of the aMCI profile as the sensitivity of pathophysiological biomarkers may never be capable of independently confirming the diagnosis. As such, investigating a combination of cognitive and non-cognitive biomarkers should provide measures that are more sensitive than either approach alone. Such findings of increased negative modulation observed in aMCI provide novel insights into functional changes that occur during the disease process, and may also prove useful for diagnostic markers before the onset of behavioral changes.

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