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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.