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Influence of functional connectivity and structural MRI measures on episodic memory

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Abstract

Age-related memory decline is the consequence of multiple biological factors that lead to brain structural and functional change, including gray matter atrophy, white matter injury, and loss of functional coordination between regions. However, the independent roles that each of these brain changes play in mediating memory decline is not clear. Therefore, we used magnetic resonance imaging (MRI) to measure gray matter (GM) volume, white matter hyperintensity (WMH) volumes, and blood oxygen level-dependent (BOLD) functional magnetic resonance imaging-based functional connectivity among default mode network nodes in 76 cognitive normal older adults. We found that GM, WMH, and connectivity between left inferior parietal and medial prefrontal cortex (MPF_LIP) were independently associated with episodic memory performance. Within the group with GM volumes below the median, greater MPF_LIP connectivity was associated with better memory performance, whereas this association was not present for individuals with GM volume above the median. These findings confirm the heterogeneous nature of brain-behavior relationships in cognitive aging. In addition, the relationship between resting state functional connectivity and memory performance, particularly amongst those individuals with more brain atrophy, strongly suggests compensation against the effects of neuronal injury.

Keywords: MRI measures; Gray matter; White matter hyperintensity; Resting-state MRI; Functional connectivity; Episodic memory performance

1. Introduction

Decline in memory performance is a hallmark of the aging process (Grady, 2000; Grady and Craik, 2000). Successful performance on memory tasks, including encoding, consolidation, and retrieval, requires recruitment of several brain regions within medial temporal (Scoville and Milner, 1957; Squire, 2004; Squire et al., 2004), prefrontal, and parietal cortical areas (Frings et al., 2010; Jenkins and Ranganath, 2010; Staresina and Davachi, 2010). While activity in these regions tends to increase during memory task performance, activity in an additional set of brain regions in the prefrontal, parietal, precuneus, posterior cingulate, and medial temporal cortices, termed the default network (DMN), correspondingly decreases (Raichle et al., 2001). Because blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI)-based measures of connectivity among nodes in the DMN are known to be associated with memory performance in cognitively healthy elderly individuals (Damoiseaux and Greicius, 2009; Dickerson and Sperling, 2009), DMN connectivity has emerged as a potentially novel and sensitive measure of subtle brain injury associated with diminished cognition among otherwise healthy elders.

However, the independent value of DMN connectivity as a marker of age-related memory decline is unclear because

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its reductions occur against a backdrop of aging-associated neuronal injury (Greicius, 2004; Seshadri, 2007). Advancing age is associated with reduced integrity of white matter (WM) in frontal regions that participate in memory function (O'Sullivan et al., 2001; Pfefferbaum et al., 2000), as well as posterior regions (Lee et al., 2009, 2010), white matter hyperintensities (WMH) are common (Ylikoski et al., 1995) and can reflect damage to WM pathways required for memory performance (Pantoni and Garcia, 1997). Gray matter (GM) volume loss across the brain in older adults is also prominent, especially in frontal regions required for memory function (Raz et al., 1998). Growing evidence suggests that both GM and WM injury may independently contribute to age-related memory declines (Buckner, 2004; Hedden, 2004).

Thus, in the context of brain aging, it is unclear whether DMN connectivity reduction is simply a downstream result of injury to the underlying neuronal architecture, a functional consequence of neuropathology on cognition independent of structural injury to neurons (e.g., functional toxicity; Shanker et al., 2008), a background factor that helps to buffer the brain against the effects of neuronal injury, or some combination of all these factors. Addressing the independent role that DMN integrity has on cognitive aging in the absence of clinical impairment, therefore, may prove important to understanding some of the most basic mechanisms by which older individuals either maintain memory ability or develop impairment in memory.

In this study, we examined the independent effects of GM volume, WMH volume, and DMN integrity on memory performance in a group of cognitively normal older adults. We hypothesized that because aging-associated brain changes exacerbate neuronal dysfunction, even among neurons that are not yet structurally injured, retained coordination among DMN nodes would be associated with better memory performance even after accounting for the effects of GM and WM injury on memory performance.

2. Methods

2.1. Participants

This study included individuals older than the age of 60 who were clinically categorized as cognitively normal using standardized criteria based on a multidisciplinary clinical evaluation (see 2.2. Clinical Evaluation). Participants who had unstable major medical illness (i.e., any severe condition requiring emergency medical care at recurrent and unforeseen times), major primary psychiatric disorder (history of schizophrenia, bipolar disorder, or recurrent major depression), or substance abuse or dependence in the last 5 years were excluded from the study. Chronic cardiovascular conditions that allow independent daily functioning, such as hypertension and diabetes, were not excluded. Each of the participants signed an informed consent approved by the University of California (UC) Davis Institution Review Board. A total of 76 participants were included in our study; 67 (88%) were from community recruitment and 9 (12%) from memory clinic referral.

2.2. Clinical evaluation

Each participant received a multidisciplinary clinical evaluation through the UC, Davis, Alzheimer's Disease Center, which included a detailed medical history and physical and neurological examination. All participants received a standardized neuropsychological test battery (these diagnostic tests are distinct from the outcome measure used in analyses). Participants who had no clinically significant cognitive impairment (defined as performing better than 1.5 standard deviations below age and education adjusted means) were considered to have normal cognition. The UC, Davis institutional review board approved this study, and all subjects provided written informed consent.

2.3. Structural magnetic resonance imaging

Brain imaging was obtained at the UC, Davis Imaging Research Center on a 1.5 T GE Signa Horizon LX Echospeed system (GE Healthcare, Waukesha, WI, USA).

Segmentation of GM, WM, and cerebrospinal fluid (CSF) was performed on native T1-weighted Fast Spoiled Gradient Recalled Echo (FSPGR) images by an in-house implementation of a Bayesian maximum-likelihood expectation-maximization algorithm method (Dempster et al., 1977). Nonbrain elements were manually removed from fluid-attenuated inversion recovery (FLAIR) images by operator-guided tracing of the dura matter in the cranial vault. The resulting corrected image was modeled as a mixture of 2 Gaussian probability functions with the segmentation threshold determined at the minimum probability between these 2 distributions, followed by a single Gaussian distribution fitted to the image data using an a priori threshold of 3.5 SD in pixel intensity above the mean to identify WMH. Intrarater and interrater reliability of these methods are high and have been published previously (DeCarli et al., 2005).

The boundaries of the hippocampus were manually traced according to previously described methods (DeCarli et al., 2008). Intrarater reliability for both the right and left hippocampus using this method is good, with intraclass correlation coefficients of 0.98 for the right hippocampus and 0.96 for the left hippocampus.

2.4. Functional magnetic resonance imaging

2.4.1. Image acquisition

Participants received resting echo-planar imaging (EPI) BOLD fMRI scans with no specific instructions for 8 minutes using the following parameters: time repetition (TR) = 2.0 seconds; time echo (TE) = 40 ms; flip angle = 90°; skip = 0 mm; slice thickness = 5 mm; 24 slices. This sequence provided 240 time points of time series data.