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Executive function mediates effects of white matter hyperintensities on episodic memory

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ABSTRACT

This study examined the relationship between white matter hyperintensities (WMH) and executive functioning on episodic memory in a group of older adults who were cognitively normal or diagnosed with MCI or dementia. Volumetric magnetic resonance imaging (MRI) measures of total brain volume, white matter hyperintensity volume, and hippocampal volume along with age, education, and gender were evaluated as predictors of episodic memory. WMH were found to influence both episodic memory and executive functioning independently of other variables. The influence WMH on episodic memory was mediated by executive functioning and was completely eliminated when the interaction between executive functioning and hippocampal volume was entered in the regression model. The results indicate that executive functioning mediates the effects of WMH on episodic memory but that executive functioning and hippocampal volume can also interact such that executive functioning can exacerbate or ameliorate the influence of hippocampal volume on episodic memory.

1. Introduction

White matter hyperintensities (WMH) are areas of hyperintense signal on T2-weighted magnetic resonance images (MRI) of the brain and are thought to be due to ischemic demylination, neuronal loss, and gliosis (Fazekas et al., 1993; Pantoni, 2002). WMH burden increases in healthy aging but is also related to risk factors such as hypertension, heart disease, and diabetes (Breteler et al., 1994; Debette et al., 2010; DeCarli et al., 1995). WMHs are typically greater in older adults with mild cognitive impairment (MCI) and dementia than in healthy older adults (Wolf, Ecke, Bettin, Dietrich, & Gertz, 2000; Wu et al., 2002), and have been related to cognition in all three groups (DeCarli, Massaro, et al., 2005; Elias et al., 2004; Gunning-Dixon & Raz, 2000; Lopez, Jagust, & Dulberg, 2003; Wu et al., 2002). Longitudinal data have supported the cross-sectional findings and have indicated a relationship between WMH burden and cognitive performance, with increasing WMH burden associated with decreasing cognitive functioning, particularly with regard to executive function and processing speed (de Groot et al., 2001; Gunning-Dixon & Raz, 2000; Kramer, Reed, Mungas, Weiner, Chui, 2002; Prins, Van Dijk, & den Heijer, 2005; Vannorsdall, Waldstein, Kraut, Pearlson, & Schretlen, 2009). Longitudinal reports have also shown that WMH can predict declines in global functioning (e.g., daily living activities such as housekeeping; Inzitari et al., 2007), motor performance, and the onset of dementia (Prins et al., 2004). Although early studies suggested that WMH may not be relevant to understanding cognition in older adults, the past 10 years of research have revealed a relationship between white matter integrity and cognitive function that plays an important role in age-related changes in cognition.

Older individuals commonly complain of impaired memory performance. Neuroimaging and neuropsychological research has shown that interactions between prefrontal cortex and medial temporal lobe structures are important for normal memory function (Dickerson, Miller, Greve, Dale, Albert, Schacter, & Sperling, 2007; Shimamura, Janowsky, & Squire, 1990; Simons et al., 2002a, 2002b; Simons & Spiers, 2003) and that the frontal lobes and hippocampus are particularly vulnerable to effects of aging and age-related disease processes, respectively (Moscovitch & Winocur, 1995; Troyer, Graves, & Cullum, 1994; West, 1996; Wu et al., 2008). Neuroimaging studies of memory in young adults and neuropsychological tests in older adults have demonstrated that both frontally mediated executive function and medial-temporal function are important predictors of memory and of age-related memory declines (e.g., Dickerson et al., 2007; Ferrer-Caja, Crawford, Bryan, 2002; Glisky, Polster, Routhieaux, 1995; Troyer et al., 1994).

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The patterns found thus far between age, WMH, executive function and episodic memory parallel findings from recent investigations of frontal and medial temporal lobe functioning and age-related declines in memory and cognition. Specifically, age-related WMH are more prevalent in the frontal lobes than in posterior regions of the brain in cognitively normal older adults, and are more extensive throughout the brain in MCI and dementia patients (Fazekas et al., 1996; Wen & Sachdev, 2004; Yoshita et al., 2006). Moreover, WMH, irrespective of location, are associated with reduced frontal lobe metabolism (DeCarli et al., 1995; Tullberg et al., 2004) and recent work with cognitively normal individuals suggests that WMH are associated with disconnection of frontal lobe from functionally linked cortical areas (Nordahl et al., 2006). These findings converge with the frontal aging hypothesis (Buckner, 2004; West, 1996) and point to the possibility that frontal lobe dysfunction caused by WMH may lead to executive function impairment that is sufficient to affect episodic memory performance.

The relationship between WMH and executive functioning, however, appears to be more robust than that between WMH and episodic memory. Although a relationship between WMH burden and executive functioning is typically observed, a relationship between WMH and memory has not always been found (e.g., Parks, DeCarli, Jacoby, & Yonelinas, 2010). It may be the case, therefore, that multiple brain regions and types of cognition need to be considered in order to understand relationships between WMH and episodic memory. For instance, Brickman et al. (2006) and Brickman, Habeck, Zarahn, Flynn, and Stern (2007) found that frontal lobe white matter volume mediated the relationship between age and executive functioning as well as the relationship between age and memory, and Charlton, Barrick, Markus, and Morris (2010) found that executive functioning partially mediated the effect of white matter integrity on memory performance in high-functioning healthy older controls.

To evaluate the hypothesis that WMH influence on episodic memory is mediated by impairments of executive function we examined the relationships between age, WMH volume, executive functioning and hippocampal volume. In addition, we specifically tested whether the effects of hippocampal volume and executive functioning on memory performance are interactive or additive.

2. Methods

2.1. Subjects

All participants were evaluated at the University of California, Davis Alzheimer's Disease Center. Participants included 422 individuals (264 women and 158 men; see Table 1 for demographic variables). The sample was fairly representative of the local population: 29.6% were African American, 26.1% were Hispanic, 40% were Caucasian, and 4.3% reported other ethnicities.

Participants received a thorough multidisciplinary clinical evaluation through the University of California, Davis Alzheimer's Disease Center. Exams included medical history, a neurological exam, appropriate laboratory tests and neuropsychological testing with a standardized test battery. A bilingual physician examined Spanish speaking patients. Diagnosis of cognitive status (normal, MCI, or dementia) was made according to standard criteria. Mild cognitive impairment was diagnosed if a person did not meet the criteria for dementia but had a clinically significant impairment in at least one cognitive domain. Dementias were diagnosed using Diagnostic and Statistical Manual of Mental Disorders (Third Edition Revised) criteria for dementia, modified to exclude the requirement of memory impairment. Alzheimer's disease was diagnosed using National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria (McKhann, Drachman, & Folstein, 1984). Underlying etiology of dementias were diagnosed but were not used for the current study. Of our 69 participants diagnosed as demented 61 met clinical diagnostic criteria for probable or possible Alzheimer's Disease (AD), two met clinical criteria for possible or probable ischemic vascular disease, one met clinical criteria for probable dementia with lewy bodies, two met clinical criteria for frontal temporal dementia and a final two had a dementia with etiologic diagnosis deferred. Repeat analysis of our data excluding individuals with AD did not substantially change the main findings presented below.

2.2. Neuropsychological Measures

The Spanish and English Neuropsychological Assessment Scales (SENAS) were used to measure cognitive functioning. The SENAS tests are the result of an extensive process to develop English and Spanish measures of cognitive functioning in domains relevant to neuropsychological assessment of older adults and have been validated in several studies (e.g., Mungas, Reed, Crane, Haan, González, 2004; Mungas, Reed, Farias, & DeCarli, 2005, 2009). This study used a subset of the SENAS tests that were averaged within domains to create composite measures of executive function and episodic memory. The executive function composite was created from a set of fluency and working memory measures. The episodic memory composite was created from Word List Learning I and Word List Learning II.

Composite scores on the cognitive domains were *z*-transformed. Thus, scores of 0 indicate average performance, negative scores indicate below average performance and scores greater than zero indicate above average performance.

2.3. Vasular risk factors

The presence or absence of six cerebro-vascular risk factors (stroke, diabetes, hperlipidema, TIA, hypertension, and coronary heart disease) was reviewed for each participant and, in combination with a review of relevant medical records, was used to create a composite score that was the sum of factors present. Vascular risk scores range from 0 to 6 and are reported here as percentages.

2.4. Image acquisition

All brain imaging was obtained at the University of California at Davis Imaging Research Center on a 1.5 T GE Signa Horizon LX Echospeed system. Two sequences were employed: a T1 weighted coronal 3D spoiled gradient recalled echo (SPGR) acquisition and a fluid attenuated inversion recovery (FLAIR) sequence designed to enhance WMH segmentation (Jack et al., 2001). The exact sequence parameters for the FLAIR imaging are as follows: axial-oblique 2D Fluid Attenuated Inversion Recovery (FLAIR) Fast Spin Echo sequence: TE: 144 ms, TR: 11000 ms, TI: 2250 ms, Flip Angle: 90°, slice thickness: 3 mm, slice spacing: 0.0 mm (Interleaved), FOV: 22 cm × 22 cm, NEX: 1, Matrix: 256 (freq) × 192 (phase), Bandwidth: 15.63 kHz, Phase FOV: 1.00, Freq Direction: A/P Options: Superior/Inferior saturation pulse On (80 mm thick).

2.4.1. WMH segmentation

WMH volumes were measured across entire brain volumes. Segmentation of WMH was performed by a semi-automated procedure using a set of in-house computer algorithms and programs previously described (DeCarli, Fletcher, Ramey, Harvey, & Jagust, 2005; DeCarli, Massaro, et al., 2005).

An analysis of regional WMH revealed that the distribution of WMH in participants in this study was similar to previous reports (DeCarli, Fletcher, et al., 2005; Tullberg et al., 2004), with average correlations between frontal, temporal, parietal, occipital and total WMH averaging about 0.9 with the exception of occipital to total WMH which was $r = 0.67$. In order to assess whether total WMH volume could account for the regional distribution of WMH, or whether WMH were distributed in a way that total volume could not account for, we performed a principle components analysis of the regional distribution of WMH that included total WMH volume. The results revealed a single eigenvector that explained 84.6% of the variance with weightings that were nearly balanced (total = 0.40, frontal = 0.45, occipital = 0.30, parietal = 0.64, temporal = 0.37) with the possible exception of the parietal weighting which was slightly higher. Given the strong relationship between regional and total WMH volumes, we use total WMH volume in our statistical analyses.

2.4.2. Hippocampal volume measurement

Manual segmentation of hippocampus was performed by trained analysts according to a precise anatomical protocol as previously described (DeCarli, Reed, Jagust, Martinez, Ortega, & Mungas, 2008). Interrater reliability using interclass correlation methods was extremely good ranging from 0.90 to 0.95.

2.4.3. MRI normalization method

All MRI measures were divided by total cranial volume to correct for differences in head size related to gender (DeCarli, Massaro, et al., 2005; Massaro et al., 2004).

2.5. Statistical analyses

One way analyses of variance (ANOVA) were conducted on demographic and brain variables to identify differences between diagnostic groups; Bonferonni corrections were used when testing pairwise group differences.

Relationships between brain measures and cognitive outcome measures were examined using multiple linear regression models. As a first step, episodic memory and executive function measures were regressed onto age, education, gender, ethnicity, brain volume, hippocampal volume, and log-transformed WMH volumes. (WMH volumes were log-transformed to obtain a normal distribution.) Brain volume was included as a control for non-specific atrophy. To test the hypothesis that executive functioning mediates the effects of WMH burden on episodic memory, we