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Functional imaging of working memory and peripheral endothelial function in middle-aged adults

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ABSTRACT

The current study examined the relationship between a prognostic indicator of vascular health, flow-mediated dilation (FMD), and working memory-related brain activation in healthy middle-aged adults. Forty-two participants underwent functional magnetic resonance imaging while completing a 2-Back working memory task. Brachial artery endothelial-dependent flow-mediated dilation (FMD) was assessed using B-mode ultrasound. The relationship between FMD and task-related brain activation in *a priori* regions of interest was modeled using hierarchical linear regression. Brachial FMD, was significantly related to reduced working memory-related activation in the right superior parietal lobule ($\beta = 0.338$, $p = 0.027$), independent of age, sex, systolic blood pressure, and full scale IQ ($F(5, 36) = 2.66$, $p = 0.038$). These data provide preliminary support for the association between a preclinical marker of endothelial dysfunction and cerebral hemodynamic alterations in healthy middle-aged adults. Considering the modifiable nature of endothelial function, additional investigations on the prognostic significance of FMD on future cognitive impairment are warranted.

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1. Introduction

Dementia currently affects over 24 million people and its prevalence is anticipated to double over the next 20 years (Qiu, De Ronchi, & Fratiglioni, 2007), making it one of the most significant and prevalent emerging public health issues. As successful treatments for dementia are lacking, identification and management of modifiable risk factors are essential. Recent reports suggest that vascular etiology contributes to over 50% of all dementia cases (Breteler, 2000). Atherosclerotic processes have been implicated in the pathogenesis of Alzheimer's disease (Roher et al., 2003) and greater arterial stiffness has been recorded in individuals with dementia than in age-matched healthy controls (Hanon et al., 2005). Given that vascular risk factors for dementia are potentially modifiable, it is of utmost importance to find an efficacious method for identifying the early signs of vascular deterioration and their impact on cognition.

One promising approach has been to examine cardiac factors in relation to cognitive performance and brain structure integrity in non-demented older adults with cardiovascular disease (Gunstad et al., 2005; Haley, Forman et al., 2007a; Hoth et al., 2007; Moser et al., 2008; Paul et al., 2005). Using this approach, clinically significant levels of atherosclerosis and peripheral endothelial dysfunction have been associated with poorer attention-executive-psychomotor performance and greater white matter damage (Forman et al., 2008; Haley, Sweet et al., 2007b; Hoth et al., 2007). While these studies have helped to elucidate the relationship between vascular health and brain function, their findings were limited to elderly adults already suffering from cardiovascular disease and exhibiting signs of vascular cognitive impairment. Considering that our best defense against dementia is prevention, it would be ideal to identify vascular markers that are associated with cerebral alterations in younger, healthier individuals.

The key challenge was to identify a vascular marker with prognostic significance for future vascular dysfunction. We chose to focus on endothelial function since it is considered an overall indicator of vascular health (Vita & Keaney, 2002). Vascular endothelium plays an important role in the maintenance of vascular tone and prevention of atherosclerosis by inhibiting leukocyte and platelet adhesion to the arterial wall (Brunner et al., 2005). More importantly, endothelial dysfunction is evident before the development of clinically-defined atherosclerosis (Vita & Keaney, 2002) and is considered a pathogenic factor in the development and progression of cardiovascular disease (Perticone et al., 2001).

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The aim of the present study was to determine if initial signs of vascular dysfunction as indicated by poorer endothelial function are associated with the cerebral hemodynamic response during cognition among middle-aged adults free of cardiovascular disease. To accomplish our goal, we conducted functional magnetic resonance imaging (fMRI) and brachial artery flow mediated vasodilatation (FMD) measurements on cognitively normal middle-aged adults. FMRI is unique in its sensitivity to detect early alterations in brain function in individuals at risk for cognitive impairment (Bondi, Houston, Eyler, & Brown, 2005; Bookheimer et al., 2000; Haley et al., 2008) and FMD provides an overall indicator of endothelial function throughout the vasculature (Vita & Keaney, 2002). Based on previous research on elderly subjects with cardiovascular disease (Haley, Sweet et al., 2007b; Irani et al., 2009), we hypothesized that decreased endothelial function would be associated with lower functional response to working memory and that lower activations would be related to lower task performance.

2. Methods

2.1. Subjects

Right-handed adults between the ages of 40 and 60 were recruited through flyers and newspaper advertisements posted in Austin, Texas. Handedness was assessed using the Edinburgh Handedness Questionnaire (Oldfield, 1971). Individuals with a history of coronary artery disease, angina pectoris, myocardial infarctions, heart failure, and cardiac surgery were excluded. Additional exclusion criteria included history of neurological disease (e.g., stroke, Parkinson's disease, clinically significant traumatic brain injury), major psychiatric illness (e.g. schizophrenia, bipolar disorder), substance abuse (i.e., diagnosed abuse and/or previous hospitalization for substance abuse), metabolic disorder (i.e., diabetes, thyroid disorder), smoking (within the last 2 years) or MRI contraindications. The study was in accordance with the Second Declaration of Helsinki and was approved by the local institutional review committee. Forty-two adults participated in the study, providing written informed consent before enrollment. Participants characteristics are presented in Table 1.

2.2. Neuropsychological assessment

All participants completed standard clinical neuropsychological instruments with established reliability and validity (Lezak, Howieson, Loring, Hannay, & Fischer, 2004). These measures assessed global cognitive functioning (Mini Mental Status Exam, MMSE (Folstein, Folstein, & McHugh, 1975), full scale IQ (Wechsler Abbreviated Scale of Intelligence – Two Subtest, WASI (Wechsler, 1999), language (WASI Vocabulary Subtest; Category Fluency for Animals (Morris et al., 1989)) memory (California Verbal and Learning Test II, CVLT-II (Delis, Kramer, Kaplan, & Ober, 1987); Rey Complex Figure Test, RCF (Meyers & Meyers, 1995)), attention-executive functioning (Controlled Oral Word Association Test, COWAT (Ruff, Light, Parker, & Levin, 1996); Trail Making Test A & B (Reitan, 1958), Wechsler Adult Intelligence Scale-III, WAIS-III, Digit Span Subtest (Wechsler, 1997)), psychomotor speed (Grooved Pegboard (Ruff & Parker, 1993)) visual-spatial ability (RCF copy; WASI Matrix Reasoning Subtest) and emotional functioning (Beck Depression Inventory-II, BDI-II (Beck, Steer, & Brown, 1996); State Trait Anxiety Inventory, STAI (Spielberger & Gorsuch, 1970)). Tests were administered and scored by a trained research assistant using standard administration and scoring criteria.

Table 1
Participant characteristics ($n = 42$).

Participant characteristics	Mean ± SD
Age, y	49.0 ± 6.3
Sex (male/female)	16/26
Education, y	15.4 ± 2.7
Race, n, (%)	
Non-Hispanic white	21 (50.0%)
Hispanic	14 (33.3%)
Asian American	1 (2.4%)
African American	5 (11.9%)
Native American	1 (2.4%)
Body mass index, kg/m^2	28.5 ± 5.3
Systolic blood pressure, mm Hg	124 ± 15
Diastolic blood pressure, mm Hg	75 ± 8
Flow-mediated dilation,%	4.2 ± 4.8

2.3. Cardiovascular assessment

Participants abstained from caffeine and fasted for at least four hours prior to the assessment. After 15 min of rest in a supine position, brachial blood pressure was measured using a semi-automated device (Dinamap XL, Johnson & Johnson Medical Inc., Tampa, FL). Three separate recordings were made while participants sat upright in accordance with American Heart Association Guidelines (Perloff et al., 1993).

Endothelial function was assessed with brachial artery flow-mediated dilation. A B-mode Doppler ultrasound machine (iE 33 Ultrasound System, Philips, Bothell, WA) with a customized transducer holding device was used to measure brachial artery diameters and blood flow velocity. Brachial artery images were obtained in a longitudinal orientation located 5–10 cm proximal to the antecubital fossa. Baseline blood flow and diameter measurements were made after participants rested for at least 15 min in the supine position. After the acquisition of baseline measurements, a blood pressure cuff placed on the ipsilateral forearm distal to the elbow was inflated to 100 mm Hg above baseline systolic blood pressure for 5 min using a rapid cuff inflator (E20, Hokanson, Bellevue, WA). Ultrasound-derived blood velocity and diameter data were saved as DICOM format and transferred to a computer using a digital image viewing software (Access Point 2004, Freeland Systems; Westminster, CO) for later analyses. All ultrasound brachial images were subsequently analyzed by the same investigator using image analysis software (Vascular Research Tool Brachial Analyzer, Medical Imaging Applications, Coralville, IA).

FMD was expressed as the percent change in brachial artery diameters recorded during the pre and post occlusion phases and was calculated using the equation: (maximum diameter – baseline diameter)/baseline diameter $\times$ 100. The average of 10 end-diastolic brachial artery diameters before blood flow occlusion was used for baseline diameters and the average of three peak end-diastolic diameters during the reperfusion phase was used for maximum brachial artery diameter.

2.4. Working memory task paradigm

Working memory was assessed using a verbal n-Back task (Braver et al., 1997; Cohen et al., 1997; Walter et al., 2003), consisting of alternating blocks of 0-Back, 2-Back, and rest conditions. During each 0- and 2-Back block, a series of twelve individual consonants were visually presented in random order for 500 ms each with a 2500 ms inter-stimulus interval. Participants responded to target letters (33% in each block) using a two-button MR-compatible response box. In the 0-Back condition, the target was a prespecified letter (H) and in the 2-Back condition, the target was any letter that was identical to the one presented two stimuli earlier. Task performance was assessed by measuring mean accuracy

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