

Midlife Arterial Stiffness and Brain Activation During Working Memory Task

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Abstract: *Objective:* Arterial stiffness is associated with cognitive decline and may serve as an early marker of brain vulnerability. In search of potential early intervention targets, the present study examined the neural correlates of working memory in relation to arterial stiffness in middle-aged, cognitively healthy adults. *Methods:* Twenty-eight adults, ages 40-60 years, completed a 2-Back verbal working memory task during fMRI. Arterial stiffness was measured using the β -stiffness index via simultaneous ultrasound and applanation tonometry on the carotid artery. Mean task-related activation intensity was determined for 12 *a priori* regions of interest (ROI). Statistical analyses included partial correlations, controlling for hypertension status and antihypertensive medication. *Results:* Arterial stiffness was correlated negatively with task-related activation in 3 ROIs: left precentral gyrus/BA 6 ($r=-0.64$, $p<0.001$), left precentral/middle frontal gyrus ($r=-0.62$, $p=0.001$) and left superior parietal lobule/BA 7 ($r=-0.48$, $p=0.013$). There was also a negative association between arterial stiffness and task-related activation in the right superior frontal gyrus/BA 6 ($r=-0.45$, $p=0.023$). *Conclusions:* Greater arterial stiffness was significantly associated with decreased task-related brain activation during a verbal working memory task, possibly reflecting increased vulnerability for cognitive impairment. Arterial stiffness should be investigated further as an early marker of cognitive risk and a potential target for early intervention.

Keywords: Arterial stiffness, β -stiffness index, working memory, fMRI, BOLD, middle-aged adults, aging.

INTRODUCTION

Cognitive functioning is one of the most important determinants of functional ability, and quality of life [1]. Dementia currently affects approximately 24 million people worldwide and is estimated to reach 42 million by 2020 [2]. Accordingly, it is becoming increasingly important to understand the pathogenesis of dementia and identify early risk factors that can be targeted for primary prevention. Accumulating evidence points to vascular risk factors as key players in the development of dementia [3].

Arterial stiffness, which is characteristic of the aging process, is an independent risk factor for coronary heart disease, renal disease, stroke, and total mortality [4]. Arterial stiffening results from changes in both the structure and cellular elements of the vessel wall and subsequent deterioration of elastic fibers [5]. Recent studies have associated arterial stiffness with global cognitive decline [6-9], suggesting that arterial stiffness may be a target for early intervention for cognitive decline and dementia. Most previous studies to date have focused on elderly populations, [6-9] yet in order to develop effective early interventions it is critical to identify markers of cognitive vulnerability in younger samples, particularly in middle-aged adults. This poses a problem with traditional neuropsychological measures, which may lack the sensitivity to detect early, subtle changes in

functioning in cognitively healthy individuals. Neuroimaging is a uniquely sensitive and robust measure that could potentially detect changes in cerebrovascular functioning before behavioral decline manifests [10].

In the present study, we determined the relationship between arterial stiffness and cerebrovascular response to cognition in an apparently and cognitively healthy, middle-aged sample. To address this aim, we utilized blood-oxygen-level-dependent functional magnetic resonance imaging (BOLD fMRI) to assess brain activation during a verbal working memory (VWM) task. Based on previous findings of diminished cerebral blood flow in task-related areas during working memory (WM) in a sample with vascular risk, [11] we hypothesized that increased arterial stiffness would relate to decreased BOLD response in task-related brain regions.

METHODS

Participants

Thirty-seven right-handed participants aged 40 to 60 years were recruited from Austin, TX with flyers and newspaper advertisements. In an effort to recruit participants with varying levels of arterial stiffness, we chose to target individuals with varying risk for cardiovascular disease. We used hypertension status as a convenient marker for cardiovascular risk [12], targeting participants who were hypertensive, normotensive with genetic risk of hypertension, and normotensive with no genetic risk. Consistent with previous studies, family history of hypertension, defined as hypertension before age 60 years in a first-degree relative, was used

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as a surrogate marker of genetic risk for hypertension [13]. Family history of hypertension was confirmed using the Ohio Blood Pressure History Survey, which has a sensitivity of 95.4%, specificity of 92.4%, and accuracy of 94.2% [14]. Hypertension was defined as a diagnosis from a physician, use of antihypertensive medication or meeting The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) hypertension guidelines: systolic pressure ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg [15].

Participants were excluded from the study if they were smokers or had a history of neurological disease (i.e., large vessel stroke, seizure disorder, Parkinson's disease, clinically significant traumatic brain injury, multiple sclerosis, or brain infection/meningitis), major psychiatric illness (e.g. schizophrenia, bipolar disorder), substance abuse (i.e., diagnosed abuse and/or previous hospitalization for substance abuse), or MRI contraindications.

Of the thirty-seven participants recruited, two were unable to complete the imaging visit, one due to anxiety and another due to being overweight. Three more participants exhibited below chance performance on the fMRI task and were removed from the analyses. Arterial stiffness could not be assessed on four additional participants. The final sample included 28 participants.

The local Institutional Review Board approved the study, and all volunteers provided written informed consent before enrollment. Participants completed a medical history interview with one of the team members. Medical conditions and treatments were coded as either present or absent according to participants' self-report. Handedness was confirmed using the Edinburgh Handedness Questionnaire [16].

Working Memory Paradigm

Working memory was assessed using a verbal n-Back task [17], which consisted of a series of single consonants presented visually for 500 ms each and a 2500 ms inter-stimulus interval. Consonants were arranged in random order from a list of all consonants except "L" due to ambiguity in the lowercase form. Participants were asked to determine whether each stimulus was a target letter. Responses were collected using a two-button MR-compatible response box. Participants used their right index finger to indicate an affirmative response and their right middle finger to indicate a negative response. A 0-Back control condition was alternated with a 2-Back condition in a block design. An imaging run consisted of three blocks of the 0-Back, three blocks of the 2-Back, and three blocks of rest presented in alternating order. The task lasted approximately 6 minutes. Each session included two runs of the task. The 0-Back condition consisted of three blocks of 12 consonants of random case and order, 33% of which were targets. Targets were defined as an uppercase or lowercase letter "H." The 2-Back condition consisted of three blocks, each containing 15 consonants of random case and order, 33% of which were targets. A letter was a target if it was the same as the letter presented two stimuli earlier regardless of the case (e.g., s, G, S, d, V, D ...). Task performance was assessed by measuring accuracy rates and mean reaction time for all correct trials. Dur-

ing the rest condition participants rested for 30 seconds while focusing on a fixation cross in the middle of the screen.

Procedures

Brachial blood pressure was measured using an automatic blood pressure device (VP-2000, Colin Medical, San Antonio, TX) that uses the modified oscillometric pressure sensor method [18].

Arterial stiffness of the common carotid artery was assessed with the β -stiffness index [19]. Common carotid artery diameter was measured from the images derived from an ultrasound machine (iE 33, Philips, Bothell, WA) equipped with a high-resolution linear-array transducer. Simultaneously, contralateral carotid artery pressure was acquired via applanation tonometry (Millar TCB-500, Millar Instruments, Houston, TX) under quiet conditions with participants in the supine position. All ultrasound images were analyzed by the same investigator using automated edge-detection software (Vascular Research Tool Carotid Analyzer, Medical Imaging Applications, Coralville, IA) that allowed the investigator to find maximal systolic expansion and basal (minimum) diastolic diameters of the carotid artery. Carotid blood pressure signal obtained by applanation tonometer was calibrated by equating the carotid mean and diastolic blood pressure to the brachial artery value because the baseline levels of carotid blood pressure are subjected to hold-down force. β -stiffness index is calculated from the ratio of the natural logarithm of SBP/DBP to the relative change in arterial diameter.

All participants completed standard clinical neuropsychological instruments with established reliability and validity [20]. These measures assessed global cognitive functioning (Mini Mental Status Exam [21]; Wechsler Abbreviated Scale of Intelligence [22]) and emotional functioning (Beck Depression Inventory-II [23]; State Trait Anxiety Inventory [24]). Tests were administered and scored by a trained research assistant using standard administration and scoring criteria.

Each imaging session included at least six blocks of 0-Back/2-Back practice, two imaging runs of the 2-Back task, and T_1 -weighted imaging for anatomical reference. If necessary, more practice blocks were administered. E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA) was used to present the 2-Back task, which was back-projected onto a screen positioned at the participant's head and viewed through a double-mirror attached to the head coil. An MR-compatible response box collected participants' responses.

MRI Data Acquisition

MRI data for each participant were acquired in a single session on a 3T GE Signa Excite MRI scanner equipped with a standard head coil. A whole brain echo-planar imaging (EPI) sequence (TR = 3000 ms, TE = 30 ms, FOV = 24 cm², 64 x 64 matrix, 42 axial slices, 3 mm slice thickness, 0.3 mm gap) was used for functional imaging. Structural imaging included a high-resolution Spoiled Gradient Echo (SPGR) sequence (256 x 256 matrix, FOV = 24 cm², 1 mm slice thickness, 0 gap) anatomical scan of the entire brain in the sagittal plane.

Data Preprocessing

All EPI images were processed using Analysis of Neuro-Images (AFNI) software [25]. Each time series was spatially registered to the sixth volume of the session to reduce the effects of head movement. This AFNI 3-dimensional registration program also provides information on displacement and rotation for each volume that was used later to further correct motion. Data pre-processing also included adjustment for differences in adjacent slice timing due to interleaved slice acquisition, temporal smoothing, spatial filtering, and transformation to standard stereotaxic space [26]. Task-related brain activation was determined using voxel-wise multiple regression analyses with the following parameters: a 0-Back/2-Back reference waveform convolved with a gamma function and covariates accounting for instruction screens, head movement, and linear trends.

A priori regions of interest (ROIs) were created from areas associated with a verbal 2-Back task in a healthy sample [17]. Coordinates from identified ROIs [17] were used to create spherical *a priori* ROIs, each with a conservative five-millimeter radius used to minimize inclusion of white matter. The coordinates and their cortical areas are presented in (Table 2). The ROIs were applied to individual data to determine mean task-related activation intensity in each region.

Statistical Analyses

All variable distributions were examined using the Shapiro-Wilk test of normality recommended for small samples. Descriptive statistics were calculated for all demographic and clinical variables (Table 1).

The relationship between β -stiffness index and task-related brain activation was assessed for each ROI using partial correlations controlling for use of antihypertensive medication and hypertension status (normotension, normotension with family history of hypertension, or hypertension). Both hypertension [11] and genetic risk of hypertension [27] have been related to subclinical dysfunction in the neural systems supporting WM. A Sidak-corrected α level of 0.015 was used as the criterion of statistical significance to account for multiple comparisons and preserve the 5% Type I error rate. Exploratory correlations ($\alpha=0.05$) between activation and task accuracy and activation and reaction time were performed in the three areas in which activation significantly correlated with β -stiffness index. Data were analyzed using SPSS 16.0 computer software (SPSS Inc., Chicago, IL).

RESULTS

Descriptive statistics regarding the clinical and demographic variables are presented in (Table 1). β -stiffness index did not significantly correlate with age, body mass index, brachial blood pressure, IQ, global cognitive performance, memory, or emotional functioning (current level of depressive symptoms, state and trait anxiety). β -stiffness index was not different between men and women or between hypertension status groups.

Mean accuracy on the verbal 2-Back task was $80\pm 10\%$, and mean reaction time was 1124 ± 304 ms. β -stiffness index did not significantly correlate with task accuracy or reaction

time. All participants moved less than 1.5 mm per imaging run.

Table 1. Sample Characteristics

Characteristic	# or Mean
Males, %	64.3%
Age, year	50 \pm 6
Education, year	16 \pm 3
Race, %	
Caucasian, non-Hispanic	64.3%
Hispanic	17.9%
African American, non-Hispanic	7.1%
Asian American	3.6%
Other	3.6%
No response	3.6%
Beta-Stiffness Index, U	5.9 \pm 1.6
Body Mass Index, kg/m ²	27.3 \pm 5.0
Brachial SBP, mmHg	127 \pm 19
Brachial DBP, mmHg	77 \pm 10
Brachial MAP, mmHg	96 \pm 14
Family History of Hypertension, %	39%
Hypertension, %	25%
Antihypertensive Medication, %	
ACE Inhibitors	21.4%
Beta Blockers	10.7%
Calcium Blocker	3.6%
FSIQ	113 \pm 13
Mini Mental Status Exam	28.3 \pm 1.5
Beck Depression Inventory-II	6.1 \pm 5.5
State Trait Anxiety Inventory-State	45.0 \pm 6.1
State Trait Anxiety-Trait	49.3 \pm 8.6

β -stiffness index was significantly correlated with task-related activation in three of the twelve ROIs: left precentral gyrus/BA 6 ($r=-0.64$, $p<0.001$), left precentral/middle frontal gyrus ($r=-0.62$, $p=0.001$), and left superior parietal lobule/BA 7 ($r=-0.48$, $p=0.013$) (Figs. 1-3). In addition, there was a strong trend between increased β -stiffness index and decreased task-related activation in the right superior frontal gyrus/BA 6 ($r=-0.45$, $p=0.023$).

Exploratory analyses revealed significant correlations between accuracy on the 0-Back task blocks and activation in the left precentral gyrus/BA 6 ($r=0.49$, $p=0.009$) and in the left superior parietal lobule/BA 7 ($r=0.44$, $p=0.021$), as well

Table 2. Coordinates of *a Priori* Regions of Interest and their Cortical Areas

Region of Interest	x	y	z
Right Superior Frontal Gyrus, BA 6	13	8	54
Left Middle Frontal Gyrus, BA 9	-42	23	39
Right Middle Frontal Gyrus, BA 9	37	37	33
Left Inferior Frontal Gyrus	-47	6	15
Right Inferior Frontal Gyrus	43	6	31
Left Insula	-32	20	8
Left Precentral Gyrus, BA 6	-39	-1	29
Left Precentral Gyrus, BA 6	-47	-2	43
Left Precentral/Middle Frontal Gyrus	-30	-6	57
Left Superior Parietal Lobule, BA 7	-26	-60	45
Right Inf/Sup Parietal Lobule, BA 7	32	-56	43
Right Caudate Nucleus	18	1	23



Left Precentral Gyrus/BA 6
-39 -1 29

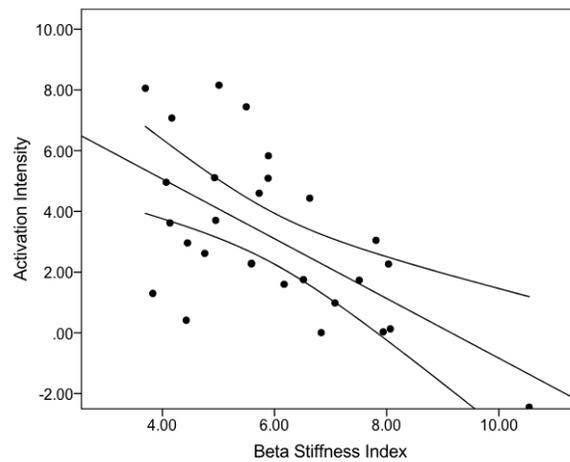
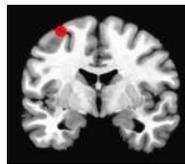


Fig. (1). Activation intensity versus BSI in the left precentral gyrus/BA 6.



Left Precentral/Middle Frontal Gyrus
-30 -6 57

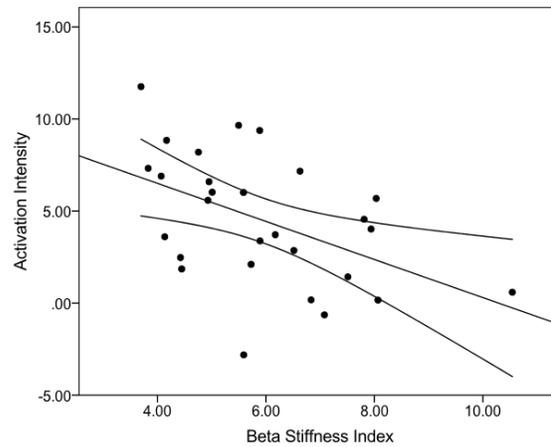


Fig. (2). Activation intensity versus BSI in the left precentral/middle frontal gyrus.

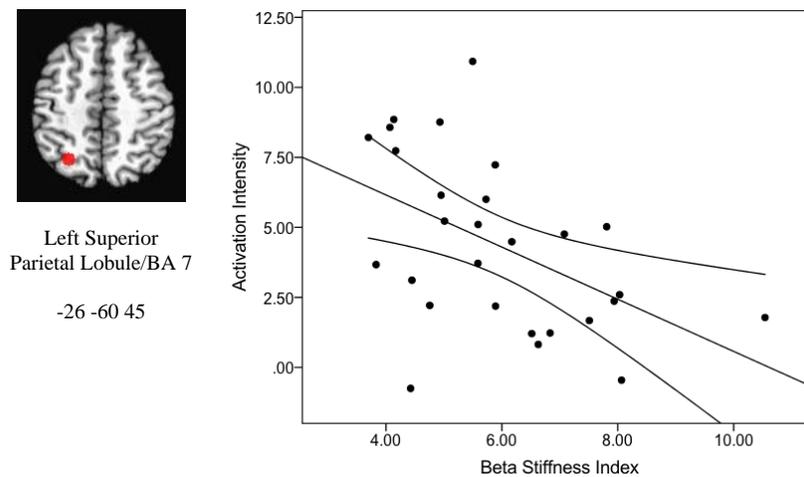


Fig. (3). Activation intensity versus BSI in the left superior parietal lobule/BA 7.

as between on 2-Back task blocks and task-related activation in the left precentral gyrus/BA 6 ($r=0.40$, $p=0.039$) and in the left precentral/middle frontal gyrus ($r=0.41$, $p=0.036$).

DISCUSSION

The present study investigated the relationship between arterial stiffness and brain activation during a VWM task in a middle-aged sample with varying vascular risk. We chose a WM task based on previous research showing WM to be susceptible to vascular dysfunction [11]. We found significant negative correlations between β -stiffness index and task-related activation in the left precentral gyrus/BA 6, left precentral/middle frontal gyrus, and left superior parietal lobule/BA 7, as well as a strong trend between increased β -stiffness index and decreased task-related activation in the right superior frontal gyrus/BA 6. These relationships were independent of antihypertensive medication and hypertension status. Our results suggest that increased arterial stiffness is associated with subclinical alterations in the neural support of VWM systems.

Decreased task-related activation at comparable levels of performance is often interpreted as more efficient processing in a young healthy population. However, decreased task-related activation in our middle-aged population more likely reflects less efficient, an interpretation supported by previous research [11]. Indeed, an fMRI investigation of cortical activity during a VWM task in healthy adults varying in age found that while decreased activity corresponded to faster reaction time in the young group, increased activity corresponded to faster reaction time in the older group [28]. This study suggests that in middle-aged and older cohorts decreased brain activation during cognitive demand is likely associated with less efficient functioning. We found significant positive correlations between 0-Back block accuracy and activation in the left precentral gyrus/BA 6 and the left superior parietal lobule/BA 7 and between 2-Back block accuracy and activation in the left precentral gyrus/BA 6 and left precentral/middle frontal gyrus. These findings support our interpretation that decreased activation in task-related areas reflects subclinical dysfunction in the cerebrovascular response to cognitive demands associated with VWM.

A prominent theory of VWM proposes a phonological loop consisting of a phonological short-term store and an articulatory subvocal rehearsal process [29]. The articulatory subvocal rehearsal process has been localized to areas in the frontal lobes, including the left precentral and left middle frontal gyri [30]. Presiding over the phonological loop is the central executive, which controls the processes of focusing, dividing, and switching attention [29]. One of the neural correlates proposed to subserve the central executive, specifically the control over focus of attention, is the superior parietal cortex/BA 7 [31]. Our finding of a negative correlation between β -stiffness index and activation in the left precentral gyrus/BA 6, the left precentral/middle frontal gyrus, and the left superior parietal lobule/BA 7 suggests that greater arterial stiffness is associated with impaired functioning of the articulatory rehearsal and attentional focus components of VWM.

Several mechanisms could explain the relationship between increased arterial stiffness and decreased brain activation in response to cognitive demand. Arterial stiffness results from structural and functional changes in the arterial wall. Structural alterations include decreased elastin and increased collagen in the vessel wall, which reduce vessel wall elasticity [5]. In addition, arterial stiffness is associated with endothelial dysfunction, which impairs arterial reactivity [5]. It is logical that this reduced arterial compliance and reactivity characteristic associated with arterial stiffening may account for the reduced BOLD signal observed in our participants with greater BSI. The BOLD signal results from the delivery of oxygenated hemoglobin to brain areas with increased neuronal activity. In healthy individuals, this delivery of oxygenated blood exceeds neuronal demand. Our finding that increased β -stiffness index related to diminished BOLD signal but not to task performance suggests that increased arterial stiffness is associated with delivery of a reduced, but adequate, supply of oxygenated blood to activated brain regions.

In addition to dysfunctional cerebrovascular response to neuronal activity, arterial stiffness may contribute, over time, to cognitive decline by damaging cerebral microvasculature. Large artery elasticity serves to absorb pulsatile energy,

thereby minimizing pulsatile load on microvasculature [32]. As elasticity decreases in large arteries, increased pulsatile energy is transmitted to the microcirculation, increasing the vulnerability of these vessels to pulse-induced damage [32]. Animal studies have demonstrated changes in cerebral microvascular structure and function resulting from increased pulse pressure [33]. This damage to the microvasculature may contribute to the pathogenesis of cerebral white matter lesions [34], which have been associated with decreased cognitive functioning [35] and dementia [36].

This is the first study to report a relationship between arterial stiffness and brain activation during performance of a cognitive task, indicating that BOLD fMRI may be a useful tool for identifying early markers of cognitive vulnerability in middle-aged, cognitively healthy individuals. Our results support previous research identifying arterial stiffness as a risk factor for cognitive decline and dementia [6-9]. A limitation of this study is the small sample size, which precluded examination of potential effects of ethnicity and sex. Similarly, the cross-sectional design of the study prevented us from assessing the relationship between arterial stiffness and brain functioning over time. Future studies should focus on arterial stiffness as an early marker of cognitive vulnerability and as a possible target for early intervention. Several studies focusing on the value of antihypertensive treatment for prevention of cognitive impairment have produced mixed results [37-40]. Although any antihypertensive agent that reduces mean arterial pressure can passively decrease arterial stiffness, not all of these treatments actively target arterial stiffness [41]. Further investigation of the effect of targeting arterial stiffness, either alone or with antihypertensive agents, on cognitive function and brain activation during cognitive demand may help identify more effective treatments of cognitive impairment associated with vascular risk. Finally, it is of note that there are a number of techniques available to measure arterial stiffness (e.g., pulse wave velocity, augmentation index, arterial compliance). Beta-stiffness index was chosen in the present study for several reasons. Beta-stiffness index is measured on the common carotid artery that leads to cerebral circulation downstream. As such, it is an ideal measure to assess relations between arterial stiffness and brain activation. Additionally, beta-stiffness index is much less affected by blood pressure [42] and can better tease out the relation between arterial stiffness and brain activation, both of which can be affected by blood pressure. However, future studies including multiple indexes of arterial stiffness in relation to brain function could be beneficial in determining which index may be most useful for studies of cognitive vulnerability.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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