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Cerebrovascular Function Associated With Fluid, Not Crystallized, Abilities in Older Adults: A Transcranial Doppler Study

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The brain is dependent on the cerebrovascular system, particularly microvasculature, for a consistent blood supply; however, age-related changes in this system affect neuronal and therefore cognitive function. Structural vascular markers and vascular disease appear to preferentially affect fluid cognitive abilities, sparing crystallized abilities. We sought to investigate the relationships between cerebrovascular function and cognitive domains. Fifty individuals between 60 and 75 years of age (31 women, 19 men) underwent cognitive testing: Wechsler Vocabulary and Matrix Reasoning subtests (crystallized and fluid ability measures, respectively Wechsler, 2011), and the Addenbrooke's Cognitive Examination–Revised (ACE-R; general cognitive ability; Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006). Transcranial Doppler (TCD) measures were also collected at rest and during a cognitive word-generation task, from which a lateralization index was calculated. Lower pulsatility index at rest, and greater left lateralization during the TCD cognitive task were associated with better performance on the Matrix Reasoning but not the Vocabulary test; these effects were independent from each other and from any vascular comorbidity burden. These functional findings confirm previous structural studies, which revealed that fluid abilities are more vulnerable to cerebrovascular dysfunction than crystallized abilities, and identify two (likely related) mechanisms: degraded cerebrovascular integrity (indexed by pulsatility index) and a delateralization of function. Cerebrovascular dysfunction is a key contributor to cognitive aging that deserves further attention, particularly in relation to early diagnostic markers of impairment and monitoring of vascular (e.g., physical activity) interventions.

Keywords: aging, cerebrovascular, cognition, transcranial doppler

Aging is associated with declines in cognitive abilities. However, the pattern varies across domains (Ardila, 2007; Ryan, Sattler, & Lopez, 2000). Fluid abilities such as problem solving decline from the 20s, whereas crystallized abilities such as vocabulary remain stable or increase between the 20s and 60s, with slow declines thereafter (Ryan et al., 2000; Salthouse, 2003, 2009). Vascular function declines through adulthood and vascular comorbidities increase (Kalaria, 2010), and it has been established that these vascular factors impact cognitive function and dementia in late life (Breteler, 2000; Hachinski et al., 2006; Keage et al., 2012; Savva, Stephan, & Group, 2010; Sharp et al., 2011). Vascular health in late adulthood appears to preferentially affect fluid ability cross-sectionally (Raz et al., 2008; Salarirad et al., 2011) and longitudinally (Elias, Elias, Robbins, & Budge, 2004; Raz, Rodrigue, Kennedy, & Acker, 2007). However, these studies have assessed either structural brain indices (white-matter hyperintensities, correlates of small-vessel disease) or vascular disease, rather than the functioning of the cerebrovascular system and its relationship with cognitive abilities.

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Cerebrovascular dysfunction is a significant cause of age-related cognitive impairment (Hachinski et al., 2006), and has been proposed to drive the accumulation of neuropathologies characteristic of dementias such as Alzheimer's disease (Ajmani et al., 2000; Crawford, 1996, 1998; de la Torre, 2000a, 2000b; Kalaria, 2010). Normal aging is associated with increased vascular resistance, and decreased cerebral blood flow and cerebral blood-flow velocities (Ajmani et al., 2000; Bracco et al., 2011; Fabiani et al., 2014; Martin, Friston, Colebatch, & Frackowiak, 1991; Scheel, Ruge, Petruch, & Schöning, 2000; Zimmerman et al., 2014). Reductions in cerebral blood flow have been linked to age-related memory impairment (Celsis et al., 1997) and conversion from a normal or mild cognitive impairment state to a dementia diagnosis (Hirao et al., 2005; Ruitenberg et al., 2005; Tanaka et al., 2002).

Despite links between cerebral blood flow and cerebral blood-flow velocity to cognitive impairment in late life, it is unclear how cerebrovascular function relates to cognitive performance such as fluid and crystallized abilities, especially in those aging without dementia. It is critical to determine how associations vary relative to the cognitive domain, to understand the path from healthy to cognitively impaired states including mild cognitive impairment and dementia. There are major feasibility issues in undertaking this research in samples of older adults using equipment such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), including mobility (ability to get to the scanner, and then into scanner), tolerability (noise and invasive nature), acceptable experimental parameters (excessive muscle movement), and medical contraindications (metal implants, pacemakers etc.). Transcranial Doppler (TCD) sonography is a noninvasive, well-tolerated technique in samples of older adults (Keage et al., 2012), and is relatively inexpensive. Cerebral blood-flow velocity is measured bilaterally, usually through the temporal windows within major cerebral arteries such as the middle, anterior, and posterior; the middle cerebral arteries are typically assessed, as they supply approximately 70% of the blood supply to the cerebral hemispheres (Lindegaard et al., 1987). Recordings can be taken during rest or a cognitive task (referred to as functional TCD/fTCD) when cognitive stimuli are presented and an average is calculated over multiple trials to estimate the evoked response.

TCD is gaining popularity as a method to assess cerebrovascular function (at rest and during cognitive operations) and relationships with diagnoses or cognitive performance in difficult or frail populations such as infants and children (Bakker et al., 2014; Bishop, Watt, & Papadatou-Pastou, 2009; Lohmann, Dräger, Müller-Ehrenberg, Deppe, & Knecht, 2005) and older adults (Bracco et al., 2011; Keage et al., 2012; Sorond, Schnyer, Serrador, Milberg, & Lipsitz, 2008). A systematic review has reported that, in studies using TCD, cerebral blood-flow velocity slows in old age and the integrity of cerebral vasculature deteriorates (as measured via pulsatility or resistance indices, which reflect distal cerebrovascular resistance, cerebral perfusion pressure, pulse amplitude of arterial pressure, and compliance of the cerebral arterial bed, as well as heart rate; de Riva et al., 2012) in those with dementia (Keage et al., 2012).

FTCD studies have assessed cerebral blood-flow velocity change within the left and right middle cerebral arteries relative to a cognitive operation (Deppe, Knecht, Lohmann, & Ringelstein, 2004; Knecht et al., 2001), and left-lateralization to language tasks is consistently reported (Badcock, Nye, & Bishop, 2012; Bracco et al., 2011; Rosch, Bishop, & Badcock, 2012). The word-generation task, which asks participants to generate words relative to one letter of the alphabet (an alternative is a word-stem task, e.g., words starting with "Luc" or "Cor"), is commonly employed as an experimental fTCD language paradigm (Badcock, Nye et al., 2012) and has been shown to be reliable (Knecht, Deppe, Ringelstein, et al., 1998) and comparable to language lateralization indexed by fMRI (Schmidt et al., 1999; Somers et al., 2011) and the Wada test (Knecht, Deppe, Ebner, et al., 1998). For fTCD, participants are typically asked to generate words silently, to avoid excessive muscle movement, and then, to ensure task compliance, are asked to provide overt responses after this silence period; there is then a period of rest to ensure cerebral blood-flow velocity returns to baseline. These trials to single letters are averaged to create an evoked-flow plot, which represents the average cerebral blood-flow velocity increase within the left and right middle cerebral arteries relative to the word generation (see Figure 1).

Sorond et al. (2008) investigated changes in cerebral blood-flow velocity associated with aging in a group of 15 healthy older adults (74 ± 1.4 years), as compared to a group of 14 younger adults (30 ± 1.4 years) using three fTCD experimental paradigms (word stem completion, visual search and basic choice reaction time (RT)). They reported that the older group displayed larger increases in cerebral blood-flow velocity to cognitive stimuli relative to the younger group regardless of cognitive task, however, measures were unilateral and therefore conclusions about lateralization relative to aging could not be made (Sorond et al., 2008). There have been reports of dementia being associated with a reduced lateralization fTCD response (Matteis et al., 1998) and also a reduction in the average cerebral blood-flow velocity increase during a cognitive operation (Asil & Uzuner, 2005; Gucuyener et al., 2010; Rosengarten, Paulsen, Burr, & Kaps, 2010).

Few aging and dementia studies have examined the relationship between resting TCD or fTCD indices and cognitive performance (Keage et al., 2012; Silvestrini et al., 2006), and within younger healthy samples, the correlations reported are typically poor or inconsistent (Badcock, Nye et al., 2012; Bakker et al., 2014). However, these null and inconsistent results may be due to inappropriate cognitive test selection. As introduced above, vascular disease and brain imaging correlates (e.g., white matter hyperintensities) are associated with impairments and declines in fluid not crystallized abilities (Elias et al., 2004; Raz, Lindenberger, et al., 2008; Raz, Rodrigue, et al., 2007; Salarirad et al., 2011). Similarly, those with cognitive impairment (but not dementia) due to vascular causes present with primary impairments in attention and executive function, with relatively intact performance on naming and verbal fluency (Garrett et al., 2004; Hachinski et al., 2006; Nyenhuis et al., 2004). Fluid abilities and attention primarily rely on frontal lobe function (Blair, Kertesz, McMonagle, Davidson, & Bodi, 2006), and these frontal regions appear to be most vulnerable to changes in cerebral blood supply (Raz, Lindenberger, et al., 2008). Together, it appears that vascular dysfunction and performance on fluid ability and attentional tasks cluster together. Previous attempts of assessing associations between TCD measures and cognitive performance have focused on general performance or memory function, which is not a key cognitive deficit in those with vascular-related cognitive impairment (Hachinski et al., 2006).

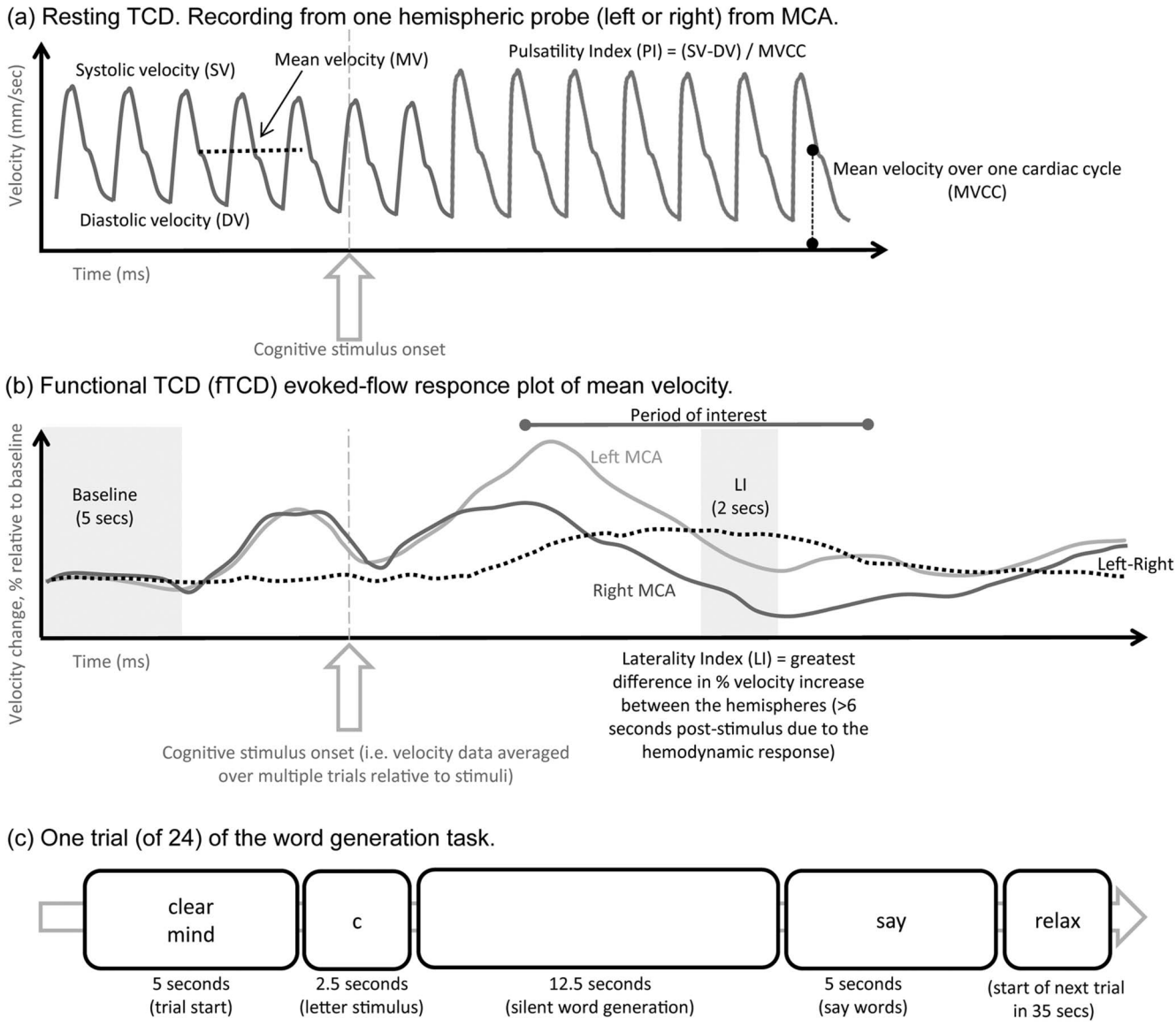

Figure 1. (a) Illustration of a transcranial Doppler (TCD) recording of blood-flow velocity within the middle cerebral arteries. Key measures include maximum/systolic velocity, minimum/diastolic velocity, mean flow velocity, and pulsatility index which includes mean velocity over one cardiac cycle (MVCC). (b) A functional TCD evoked-flow response, which is an average of mean flow velocity over trials, relative to the onset of a cognitive stimulus. The lateralization index (LI) is calculated as the average mean flow velocity centered at the point of maximal difference between left and right channels within the period of interest (5–15 s poststimulus). The timing of the LI and the standard deviation of the LI were also measured; further the average velocity (split into 1-s intervals) within the period of interest for both left and right middle cerebral artery channels, to measure the flow change relative to baseline. (c) Illustration of one word-generation task trial.

We aimed to investigate associations between TCD/fTCD measures and cognitive performance, focusing on reasoning (related to fluid ability) and vocabulary (related to crystallized ability), in a sample of older healthy adults. Further, given vascular risk factors (such as diabetes, hypertension, high cholesterol) are associated with cognitive impairment in those without dementia (Di Carlo et al., 2000), which have large effects within the cerebrovascular system (de la Torre, 2013; Richardson et al., 2012), we aimed assess if TCD-cognitive associations were independent of cardiovascular comorbidity. Pulsatility index but not flow velocities appear to relate to cognitive impairment and dementia (Keage et al., 2012), as do reduced lateralization and degree of fTCD response (Asil & Uzuner, 2005; Gucuyener et al., 2010; Matteis et al., 1998; Rosengarten, Molnar, Trautmann, & Kaps, 2006). Therefore, we hypothesized that lower pulsatility index at rest, along with a larger degree of cerebral blood-flow velocity response and

left-lateralization during cognitive operations, would be associated with better fluid cognitive performance (WASI-II Matrix Reasoning), but not significantly associated with crystallized performance (WASI-II Vocabulary).

Method

Participants

We obtained TCD measures successfully from 50 right-handed (Nicholls, Thomas, Loetscher, & Grimshaw, 2013) individuals (62% women) between 60 and 75 years of age. Participants were recruited from Magill and surrounding areas, South Australia. Exclusion criteria included (a) not a native English speaker; (b) not predominantly right-handed according to Flinders Handedness Survey (Nicholls, Thomas, Loetscher, & Grimshaw, 2013); (c) uncorrected hearing or visual impairment; (d) uncontrolled high blood pressure; (e) history of cancer within past 5 years (excluding skin or prostate); (f) taking medications targeting the central nervous system within past month; (g) alcohol or substance abuse within past year, or use of recreational drugs within past month; (h) history of psychiatric disorder within past 5 years; (i) any brain disease; or (j) diagnosis of learning disability.

Due to equipment issues, we were unable to collect fTCD data from one participant, who therefore only contributed resting TCD data to analyses. Full participant characteristics are presented in Table 1. According to an ACE-R cut-off of 82 (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006) and an MMSE cut-off of 24 (O'Bryant, Humphreys, Smith, & et al., 2008) reflecting the presence of dementia, all participants in this sample were either healthy or fell within Mild Cognitive Impairment ranges.

Cognitive Measures

ACE-R including MMSE. The Addenbrooke's Cognitive Examination—Revised (ACE-R) was designed as a dementia screening tool (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006), and has shown high sensitivity and specificity in detecting Mild Cognitive Impairment, unlike other similar tools (Lonie, Tierney, & Ebmeier, 2009). The ACE-R includes five subscales of attention/orientation, memory, verbal fluency, language, and visuospatial ability, from which a total score out of 100 is calculated. A Mini-Mental State Examination (MMSE) score (Folstein, Folstein, & McHugh, 1975) was also computed from ACE-R questions, with a total score of 30.

WASI-II Matrix Reasoning and Vocabulary. The Wechsler Abbreviated Scale of Intelligence (2nd ed.; WASI-II; Wechsler,) Full Scale IQ–2 subtest (FSIQ-2) was used to measure general cognitive ability. This short version of the WASI-II consists of the Vocabulary task, with 31 items requiring participants to provide definitions of words; and the Matrix Reasoning task, with 30 items where participants complete a series of matrices by selecting correct response options. The Vocabulary task is reported to be a measure of crystalized cognitive ability, and the Matrix task a measure of fluid ability, with distinct patterns of age-related decline (Salthouse, Pink, & Tucker-Drob, 2008).

TCD Recordings and Experimental Paradigm

Bilateral cerebral blood-flow velocity recordings were made using DWL Doppler-Box hardware and QL 2.8 software, a DiaMon head fixation, and 2 MHz ultrasound probes (Compumedics DWL, Singen, Germany). TCD velocity recordings were made in centimeters per second (cm/s) at 100 Hz. The left and right middle cerebral artery M1 segments (confirmed by locating the anterior cerebral bifurcation) were insonated from the transtemporal window. Participants sat upright in a supportive chair, and experimenters conducting the TCD acquisition were blinded to the cognitive test scores. Figure 1 displays resting and functional TCD output.

Resting TCD measures were taken for 1 min with the eyes open. Maximum/systolic, mean and minimum/diastolic blood-flow velocities, along with the pulsatility index (reflecting distal cerebrovascular resistance, cerebral perfusion pressure, pulse amplitude of arterial pressure, and compliance of the cerebral arterial bed and heart rate; Czosnyka, Richards, Whitehouse, & Pickard, 1996; de Riva et al., 2012). Systolic velocity–diastolic velocity/mean-flow velocity for one cardiac cycle were time-averaged over this 1-min period to calculate pulsatility indexes for both the left and right middle cerebral arteries.

Table 1
Participant Characteristics Including Age, Sex, Years of Formal Education Completed, Cognitive Performance, and Cardiovascular Risk Factors

Variable	Male (n = 19)	Female (n = 31)	Total (n = 50)
Age range (years)	64–74	60–75	60–75
Mean age ± *SD*	68.89 ± 3.03	65.77 ± 4.57	66.96 ± 4.30
Number of years of education ± *SD*	14.12 ± 3.70	14.69 ± 3.89	14.47 ± 3.79
MMSE range (0–30)	25–30	27–30	25–30
Mean MMSE ± *SD*	28.58 ± 1.46	29.19 ± .87	28.96 ± 1.16
ACE-R range (0–100)	82–99	88–99	82–99
Mean ACE-R ± *SD*	91.16 ± 5.26	93.74 ± 3.53	92.76 ± 4.01
BMI	26.67 ± 5.44	24.02 ± 4.69	25.66 ± 5.00
Current hypertension treated	32%	23%	26%
Current smoker	5%	3%	4%
Type 2 diabetes	0%	3%	2%
High cholesterol untreated	5%	13%	10%

Note. MMSE = Mini-Mental State Examination; ACE-R = Addenbrooke's Clinical Examination–Revised (Australian Version); BMI = body-mass index.

Cognitive fTCD measures were taken during a word-generation paradigm (see Figure 1). Participants were seated in front of a computer screen for the task. There were a total of 24 trials, that is, all letters in alphabet except z and x. Each trial lasted for 60 s: Initially participants were instructed to "relax" (displayed for 20 s) followed by instructions to "clear mind" (displayed for 5 s) before the target letter appeared for 2.5 s; they were then given 12.5 s to silently think of words starting with that letter, then another 5 s to say as many as they could, and then they relaxed (15 s). A brief auditory tone was heard at the clear-mind, say, and relax prompts for each trial. We used the DopOSCCI program (Badcock, Holt, Holden, & Bishop, 2012) to analyze the fTCD data, which normalizes the data across hemisphere to reduce measurement artifacts such as probe angle, excludes heart-cycle variation, and excludes trials based on predefined range and signal separation boundaries; each trial is then baseline-corrected and averaged (Badcock et al., 2012). This average is termed an evoked-flow response plot.

From these evoked-flow plots we obtained four measures: (a) the lateralization index, which is defined as mean difference between the left and right mean flow velocity increase relative to baseline, over a 2 s period centered on the absolute maximum peak difference, within a predefined period of interest (in this study, 5–15 s post-presentation of the letter stimulus); (b) the timing of the lateralization index within the period of interest (i.e., the time at which an individual reached their peak lateralized state); (c) the standard deviation of lateralization indices across trials; and (d) the average increase in cerebral blood-flow velocity within the period of interest (per second, 5–15 s poststimulus presentation).

Procedure

Data collection occurred over two sessions as part a larger cognitive aging study at the University of South Australia Cognitive Neuroscience Laboratory in Adelaide, Australia and was approved by the University of South Australia Human Ethics Committee. In the first session, demographic, health, and cognitive measures were taken, i.e., the ACE-R (Mioshi et al., 2006), the MMSE (Folstein et al., 1975) and the WASI-II (Wechsler, 2011). In the second session, TCD recordings were taken. Within the sample, there was on average 22.76 days (SD = 12.93) between testing sessions.

Analysis

BMI was trichotomized according to World Health Organisation guidelines: (a) underweight and normal, (b) overweight and (c) obese. There were only two underweight individuals, so we could not include this category independently. To determine the burden of vascular conditions for each individual, we summed the presence of the following four conditions: current hypertension, current smoker, Type 2 diabetes, and untreated high cholesterol, giving a possible score range of 0 (*no vascular conditions*) to 4 (*all vascular conditions present*), with scores in the sample ranging from 0 to 3. WASI-II Matrix Reasoning and Vocabulary (Wechsler, 2011) raw scores (unscaled or converted to an intelligence estimate) were used. Scores derived from ACE-R (Mioshi et al., 2006, including the MMSE, Folstein et al., 1975) are not subject to scaling.

Pearson correlations and linear regressions were used to assess associations between (a) demographic factors (age and sex), vascular comorbidity burden (possible 0–4), and cognitive performance (WASI-II Matrix Reasoning and Vocabulary, ACE-R, and MMSE); (b) resting TCD measures (systolic, diastolic, and mean flow velocity, along with pulsatility index) with cognition and vascular comorbidities; and (c) fTCD measures (lateralization index and its SD, time to peak lateralized state; and the degree of increase relative to baseline) with cognition and vascular comorbidities. In the group of 49 individuals with fTCD data in this study, the number of word-generation trials accepted for analysis ranged from 10 to 24, with a median of 22.

Results

Relationships Between Cognitive Measures

Table 2 displays correlations between the cognitive measures: WASI-II Matrix Reasoning and Vocabulary subtests (Wechsler, 2011), the MMSE (Folstein et al., 1975) and ACE-R Fluency (including five subtests; Mioshi et al., 2006). There was a moderate correlation between the WASI-II Matrix and Vocabulary subtests of r = .435, p = .002.

Table 2
Pearson's Correlations Between Cognitive Measures for N = 50 Participants

	WASI-II Matrix		MMSE		ACE-R total		ACE-R Attention and Orientation		ACE-R Memory		ACE-R Language		ACE-R Visuospatial		ACE-R Fluency	
Measure	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
WASI-II Vocabulary	**.425**	**.002**	**.365**	**.009**	**.591**	**<.001**	.082	.572	**.450**	**<.001**	**.431**	.002	.198	.169	**.436**	**<.002**
WASI-II Matrix			**.331**	**.019**	**.351**	**.012**	.108	.456	.233	.104	**.398**	**.004**	**.282**	**.047**	.171	.236
MMSE					**.541**	**<.001**	**.603**	**<.001**	**.477**	**<.001**	**.452**	**<.001**	.097	.504	.231	.106
ACE-R total							**.312**	**.027**	**.773**	**<.001**	**.615**	**<.001**	**.439**	**.001**	**.635**	**<.001**
ACE-R Attention and Orientation									.204	.156	.170	.237	−.068	.637	.181	.209
ACE-R Memory											**.337**	**.017**	.034	.812	**.400**	**.004**
ACE-R Language													**.369**	**.008**	.241	.091
ACE-R Visuospatial															.166	.249

Note. WASI-II = Wechsler Abbreviated Scale of Intelligence (2nd ed.); MMSE = Mini-Mental State Examination; ACE-R = Addenbrooke's Clinical Examination–Revised (Australian Version). Boldface indicates $p < .05$.

Relationships Between Demographic Factors, Vascular Comorbidities, and Cognitive Performance

Participants who were women, $r = -.40$, $p = .004$ and younger, $r = -.36$, $p = .01$ performed better than those who were men and older on the ACE-R Memory subscale; and those who were younger also performed better on the MMSE, $r = -.33$, $p = .019$. Increasing vascular comorbidity was associated with poorer performance on the WASI-II Matrix Reasoning test, $r = -.33$, $p = .018$, with the effect for ACE-R Fluency failing to reach conventional significance levels, $r = -.27$, $p = .056$. BMI was unrelated to cognitive measures in this sample.

Resting TCD (Eyes Open): Associations With Cognition and Vascular Comorbidities

Resting TCD effects did not vary between hemisphere (i.e., left and right middle cerebral arteries), therefore correlations presented here are averaged between the left and right. Sex was significantly associated with resting, eyes-open mean flow velocity, $r = -.37$, $p = .004$: Women had higher velocities than men. The association between age and pulsatility index failed to reach conventional significance levels, $r = .26$, $p = .066$. There were no associations between resting TCD measures and vascular comorbidities.

Pulsatility index was significantly associated with WASI-II (Wechsler, 2011) Matrix Reasoning, $r = -.385$, $p = .006$: Those with lower pulsatility index had better performance. To ensure that the associations between pulsatility index and WASI-II Matrix Reasoning performance was not a product of age, we ran partial correlations, and found that the effect did not change, $r = -.34$, $p = .017$. The correlation between pulsatility index and WASI-II Vocabulary was $r = .141$, $p = .330$, which was significantly different from the correlation between pulsatility index and WASI-II Matrix Reasoning: $t(47) = 3.909$, $p < .001$ (Steiger, 1980).

FTCD: Associations With Cognitive Performance and Vascular Comorbidities

Age was associated with a reduced left-lateralization to the word-generation task as indexed by the lateralization index, $r = -.31$, $p = .029$; Figure 2a. The lateralization index was

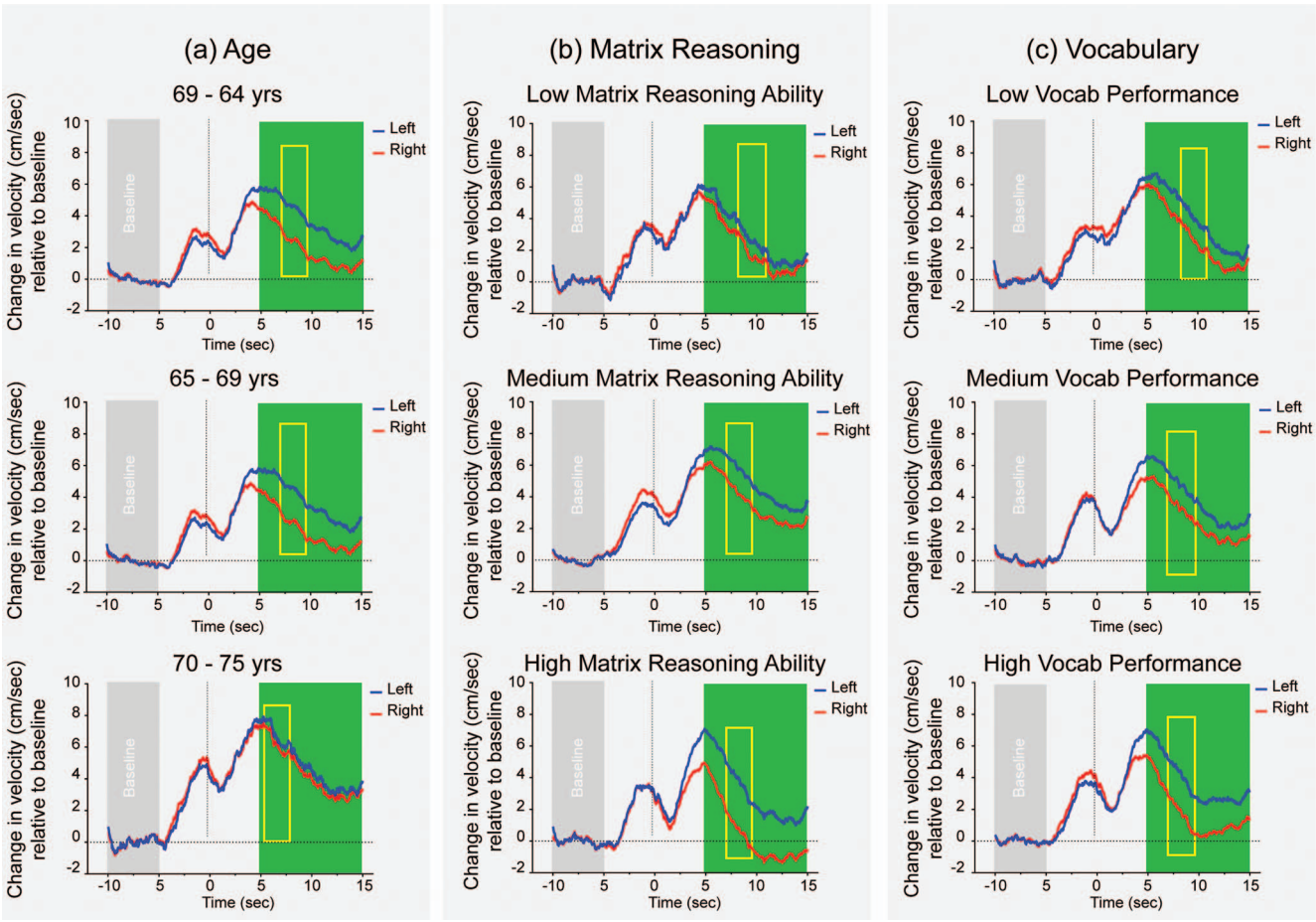

Figure 2. Stratified groups displaying key results: (a) lateralization index decreases with age between 60 and 75 years, (b) lateralization index increases with fluid abilities as indexed by Wechsler Abbreviated Scale of Intelligence, 2nd ed. (WASI-II) (Wechsler, 2011) Matrix Reasoning subtest, and (c), lateralization index does not associate with crystallized abilities as indexed by the WASI-II Vocabulary test. Green shaded area indicates period of interest, during which the peak lateralization index (yellow box) is taken.

positively related to WASI-II Matrix Reasoning (Wechsler, 2011), $r = .40$, $p = .005$ (see Figure 2b); MMSE score (Folstein et al., 1975), $r = .38$, $p = .005$; and ACE-R total score (Mioshi et al., 2006), $r = .32$, $p = .025$. The ACE-R Attention and Orientation subscale was the only subscale to also show this effect, $r = .36$, $p = .012$. Correlation results did not change when partialling out the pulsatility index, a theoretical cause of reduced lateralization index. The correlation between the lateralization index and WASI-II Vocabulary was $r = .239$, $p = .098$, which was not significantly different from the correlation with WASI-II Matrix Reasoning: $t(47) = -1.105$, $p = .275$ (Steiger, 1980). Please see Figure 2 for evoked-flow plots relative to three stratified groups for age, WASI-II Matrix Reasoning performance, and WASI-II Vocabulary performance.

In terms of the mean increase in velocity relative to baseline within the period of interest (5–15 s poststimulus), there was no relationship with age, vascular comorbidity, or cognitive performance when looking over the entire 10-s period, or breaking this period up into 1-s intervals. We assessed the left and right channels separately, as well as the difference between the left and right.

Further Investigating the Association Between Cerebrovascular Function and Fluid Abilities

From the analyses above, it was apparent that three variables were related to fluid abilities: the presence of vascular comorbidities, the lateralization of TCD response during a cognitive task, and the pulsatility index to a smaller (nonsignificant) degree; and vascular comorbidities also appeared to associate with crystallized abilities. To further investigate these effects, we ran two linear regressions controlling for age and sex, with cognitive test results as the outcomes (WASI-II Vocabulary and Matrix Reasoning; Wechsler, 2011), and pulsatility index, lateralization index, and vascular comorbidity as the predictors. Results from these regressions are presented in Table 3, where it can be seen that, when controlling for age and sex, vascular comorbidities were consistently and significantly associated with poorer performance. The pulsatility index and lateralization index were significantly related to the WASI-II Matrix Reasoning performance, but not related to WASI-II Vocabulary performance.

Table 3
Results From Two Linear Regressions Illustrating Associations Between Fluid and Crystallized Cognitive Measures With Age, Sex, Vascular Comorbidity, Pulsatility Index and Lateralization Index

	WASI-II Matrix Reasoning		WASI-II Vocabulary	
Variable	Standard β	*p*	Standard β	*p*
Sex (1 woman/2 men)	−.016	.911	−.086	.571
Age	−.020	.893	−.103	.523
Vascular comorbidity (0–3)	**−.275**	**.037**	**−.310**	**.032**
Pulsatility index	**−.285**	**.040**	.224	.135
Lateralization index	**.353**	**.010**	.223	.129

Note. WASI-II = Wechsler Abbreviated Scale of Intelligence (2nd ed.); MMSE = Mini-Mental State Examination; ACE-R = Addenbrooke's Clinical Examination–Revised (Australian Version). Boldface indicates $p < .05$.

Discussion

This study demonstrated that fluid cognitive abilities are preferentially vulnerable to cerebrovascular dysfunction in late life. Further, we demonstrated that increasing age (in this cross-sectional study) is associated with an attenuation of lateralization during a cognitive task, as measured with TCD. This study has also shown the utility of TCD in the measurement of cerebral blood-flow velocity during rest and cognitive processing in older individuals.

This study of cerebrovascular function, supporting studies of vascular structure of disease (Elias et al., 2004; Raz, Lindenberger, et al., 2008; Raz, Rodrigue, et al., 2007; Salarirad et al., 2011), identified specific associations with fluid abilities, and a relative sparing of crystallized abilities. We found that cerebrovascular integrity (indexed by the pulsatility index) and lateralization of the TCD response during a cognitive task were associated with fluid abilities (WASI-II Matrix Reasoning; Wechsler, 2011); the effect for pulsatility was particularly strong, with a statistically significant dissociation between crystallized and fluid abilities. Fluid abilities primarily rely on frontal and parietal lobe function (Geake & Hansen, 2005; Perfetti et al., 2009; Prabhakaran, Smith, Desmond, Glover, & Gabrieli, 1997) and although there is some overlap within the middle frontal gyrus function between fluid and crystallized ability (Colom et al., 2013), crystallized abilities appear to primarily be associated with left temporal cortex structure (Choi et al., 2008). The frontal regions appear to be most vulnerable to disruptions in cerebral blood supply (Raz, Lindenberger, et al., 2008).

In our sample, there was a left lateralization of function during the word-generation task. This is consistent with the fMRI literature, showing that silent word generation activates areas within the dorsolateral prefrontal, temporal, and extrastriate regions, particularly within the left hemisphere (Friedman et al., 1998; Gaillard et al., 2000). We found that the magnitude of fTCD lateralization decreased with age, as assessed cross-sectionally in adults between 60 and 75 years of age. Consistently, fMRI studies have identified an age-related reduction in lateralized function, which has been suggested to reflect compensatory strategies or "de-differentiation" of processing (Cabeza, 2002; Reuter-Lorenz & Cappell, 2008). There have been inconsistent reports as to whether cerebral blood-flow velocity (diastolic, systolic, and mean) decreases with age (Bracco et al., 2011; Keage et al., 2012); however, we did not find any relationships. The association between the pulsatility index and age failed to reach conventional significance levels in our sample. Deteriorated vessel integrity as indexed by the pulsatility index has been consistently reported in demented samples (Keage et al., 2012) due to increased rigidity in the aging vessels or changes in the viscosity of the blood, aging, oxidative stress, and amyloid accumulation (Ajmani et al., 2000).

It is important to note that it was the lateralization of the hemodynamic response to a cognitive operation and not the degree, variability, or timing of response that was associated with fluid ability. There was also no relationship between age and the degree of velocity increase (relative to baseline). Sorond et al. (2008) reported an age-related increase in the evoked response during three fTCD experimental paradigms, including a word-stem completion task (very similar to the word-generation task), but

they compared a group of younger adults around 30 years of age and older adults around 74 years of age. Our results suggest that the degree of hemodynamic response to a cognitive operation relative to baseline does not significantly change between 60 and 75 years of age; however longitudinal studies are needed to support this cross-sectional finding.

Vascular comorbidity lowers brain perfusion and places vulnerable aging neurons in a state of high-energy compromise, leading to a cascade of metabolic processes, neural damage, and pathology (de la Torre, 2002; de la Torre & Stefano, 2000), which is associated with cognitive impairment and dementia (de la Torre, 2012). Supporting this, cardiovascular disease has shown to relate to an increased burden of neuropathology, both vascular and Alzheimer's disease-related, in a large population-based cohort (Richardson et al., 2012). In our sample, vascular comorbidity burden was associated with poorer performance on both fluid and crystallized measures in linear regression models, taking into account age and sex, as well as the pulsatility and lateralization indexes. Memory performance (not fluid ability) appears the best cognitive predictor of conversion from vascular cognitive impairment to dementia over 5 years (Ingles, Wentzel, Fisk, & Rockwood, 2002), which could suggest that after a prolonged period of cerebrovascular dysfunction, areas outside the frontal lobes are affected, such as the hippocampus (Kalaria, 2010).

The technique of TCD employed in this study is both a strength and limitation. The technique is extremely well-tolerated by older (and sometimes frail) adults and although we had participants come to a laboratory for testing, there is no reason data could not be collected elsewhere (such as at the participant's residence), as the equipment is very portable. There has been a recent push within the aging and dementia community for simple, noninvasive and cost-effective measurement tools for screening, diagnostics, and ongoing monitoring; TCD certainly meets these criteria. The limitations of the technique relate to its lack of spatial resolution (velocity is measured within arteries, not tissue), which means that measures such as the pulsatility index reflect the summation of many cerebrovascular autoregulative mechanisms (Czosnyka et al., 1996; de Riva et al., 2012). We also only measured from the middle cerebral arteries. It would have been ideal to record from all major cerebral arteries (e.g., posterior, anterior, and basilar) to understand if they had associations with cognitive performance, especially the posterior arteries which supply the hippocampus (Tatu, Moulin, Bogousslavsky, & Duvernoy, 1998).

It is a limitation of this study that we only employed one measure of fluid ability (WASI-II Matrix Reasoning; Wechsler, 2011) and one measure of crystallized ability (WASI-II Vocabulary), and further, we only employed one fTCD cognitive task (the word-generation task). We also did not capture physical fitness, which has shown to be an important determinant of cerebrovascular function in older adults (Zimmerman et al., 2014). Last, within the sample there were no cases of dementia, according to the ACE-R cut-off (Mioshi et al., 2006), however, many individuals ($n = 23$) met the <94 cut-off for mild cognitive impairment (Pendlebury, Mariz, Bull, Mehta, & Rothwell, 2012). Mild cognitive impairment is a highly changeable state in which back transition to a normal cognitive state is very common over a number of years (Marioni et al., 2011; Matthews et al. 2008). There was no evidence of differences in effects when we assessed those with and without mild cognitive impairment; effects were in the same direction, but underpowered.

Structural change within the cerebral microvascular system is now established as a significant cause of cognitive impairment and dementia in older populations (Hachinski et al., 2006). Aging is associated with changes to the cerebrovascular system, either directly (hemorrhage or hypertension) or secondarily (through the effects of diabetes or obesity). In this study we have shown that cerebrovascular dysfunction associates with fluid cognitive abilities in older adults between 60 and 75 years of age. Further, we have replicated age-related lateralization attenuation using fTCD and have shown that it is not the product of contaminant changes in cerebrovascular integrity. Cerebrovascular measures such as the pulsatility index and lateralization may serve as clinical indicators of brain health in late life, and in the monitoring of the efficacy of vascular interventions.

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