Cerebrovascular function associated with fluid not crystallised abilities in older adults: a transcranial Doppler study

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Abstract

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 crystallised abilities. We sought to investigate the relationships between cerebrovascular function and cognitive domains. Fifty individuals between 60 and 75 years (31 female, 19 male) underwent cognitive testing: Wechsler Vocabulary and Matrix Reasoning subtests (crystalised and fluid ability measures respectively), and the Addenbrooke's Cognitive Examination Revised/ACE-R (general cognitive ability). Transcranial Doppler (TCD) measures were also collected at rest and during a cognitive word generation task, from which a lateralisation index was calculated. Lower pulsatility index at rest, and greater left lateralisation during the TCD cognitive task were associated with better performance on the Matrix Reasoning but not Vocabulary task; and these effects were independent from each other and vascular comorbidity burden. These functional findings confirm previous structural studies, where fluid abilities are more vulnerable to cerebrovascular dysfunction than crystallised abilities, and identify two (likely related) mechanisms: degraded cerebrovascular integrity (indexed by pulsatility index) and a de-lateralisation 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.

Key words: aging, cerebrovascular, cognition, transcranial doppler

Introduction

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 crystallised 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 is 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., 2007; Salarirad et al., 2011) and longitudinally (Elias, Elias, Robbins, & Budge, 2004; Raz, Rodrigue, Kennedy, & Acker, 2007). However, these studies have assessed 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.

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, 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 crystallised abilities, especially in those aging without dementia. It is critical to determine these relationships, and how associations vary relative to 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 older samples 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 non-invasive, well-tolerated technique in older samples (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), where 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-lateralisation to language tasks is consistently reported (Badcock, Nye, & Bishop, 2012; Bracco, et al., 2011; Rosch, Bishop, & Badcock, 2012). The word generation task, where participants are asked 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 shown to be reliable (Knecht, Deppe, Ringelstein, et al., 1998) and comparable to language lateralisation 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). 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 lateralisation relative to aging could not be made (Sorond, et al., 2008). There have been reports of dementia being associated with a reduced lateralisation 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 crystallised abilities (Elias, et al., 2004; Raz, Lindenberger, et al., 2007; 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., 2007). 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).

We aimed to investigate associations between TCD/fTCD measures and cognitive performance, focusing on reasoning (related to fluid ability) and vocabulary (related to crystalised 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 lateralisation and degree of fTCD response (Asil & Uzuner, 2005; Gucuyener, et al., 2010; Matteis, et al., 1998; Rosengarten, Molnar, Trautmann, & Kaps, 2006). Therefore, we hypothesised that lower pulsatility index at rest, along with a larger degree of cerebral blood flow velocity response and left-lateralisation during cognitive operations, would be associated with better fluid cognitive performance (WASI-II Matrix

Reasoning), but not significantly associated with crystallised performance (WASI-II Vocabulary).

Methods

Participants

We obtained TCD measures successfully from 50 right-handed (Nicholls, Thomas, Loetscher, & Grimshaw, 2013) individuals (62% females) between 60 and 75 years of age. Participants were recruited from Magill and surrounding areas, South Australia. Exclusion criteria included 1) not a native English speaker; 2) not predominantly right handed according to Flinders Handedness Survey (Nicholls, Thomas, Loetscher, & Grimshaw, 2013); 3) uncorrected hearing or visual impairment; 4) uncontrolled high blood pressure; 5) history of cancer within past 5 years (excluding skin or prostate); 6) taking medications targeting the central nervous system within past month; 7) alcohol or substance abuse within past year, or use of recreational drugs within past month; 8) history of psychiatric disorder within past 5 years; 9) any brain disease; or 10) 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 ACER cut-off of 82 (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006) and a 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) is also computed from ACE-R questions, with a total score of 30.

WASI-II Matrix Reasoning and Vocabulary. The Wechsler Abbreviated Scale of Intelligence – Second edition (WASI-II) Full Scale IQ – 2 subtest (FSIQ-2) was used to measure general cognitive ability (Wechsler, WASI-II: Manual). 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 crystalised 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 a DWL Doppler-BoxTM 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 centimetres per second (cm/s) at 100Hz. 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 one minute 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, 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 over one cardiac cycle], were time-averaged over this one minute period for both the left and right middle cerebral arteries.

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, i.e. all letters in alphabet except z and x. Each trial lasted for 60 seconds: initially participants were instructed to 'relax' (displayed for 20 seconds) followed by instructions to 'clear mind' (displayed for 5 seconds) before the target letter appeared for 2.5 seconds, they were then given 12.5 seconds to silently think of words starting with that letter, then another 5 seconds to say as many as they could, and then they relaxed (15 seconds). A brief auditory tone was heard at the 'clear mind', 'say' and 'relax' prompts for each trial. We used the DopOSCCI program to analyse the fTCD data, which normalises the data across hemisphere to reduce measurement artefacts such as probe angle, excludes heart cycle variation and excludes trials based on pre-defined range and signal separation boundaries; each trial is then

baseline-corrected and averaged (Badcock, Holt, Holden, & Bishop, 2012). This average is termed an evoked-flow response plot.

From these evoked-flow plots we obtained four measures: (1) the lateralisation index, which is defined as mean difference between the left and right mean flow velocity increase relative to baseline, over a 2 second period centred on the absolute maximum peak difference, within a predefined period of interest (in this study, 5-15 seconds post-presentation of the letter stimulus), (2) the timing of the lateralisation index within the period of interest (i.e. the time at which an individual reached their peak lateralised state), (3) the standard deviation of lateralisation indices across trials, and (4) the average increase in cerebral blood flow velocity within the period of interest (per second, 5-15 seconds post-stimulus 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; approved by the University of South Australia Human Ethics Committee. In the first session, demographic, health and cognitive (ACE-R including the MMSE, along with WASI-II) measures were taken. In the second session, TCD recordings were taken. Within the sample, there was on average 22.76 days (standard deviation/SD=12.93) between testing sessions.

Analysis

BMI was trichotomised according to World Health Organisation guidelines: (1) underweight and normal, (2) overweight and (3) 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, as well as NART (i.e. number of correct pronunciations), raw scores (un-scaled or converted to an intelligence estimate) were used. Scores derived from ACE-R (including MMSE) are not subject to scaling.

Pearson correlations and linear regressions were used to assess associations between (1) demographic factors (age and sex), vascular comorbidity burden (possible 0-4) and cognitive performance (WASI-II Matrix Reasoning and Vocabulary, ACE-R and MMSE), (2) resting TCD measures (systolic, diastolic and mean flow velocity, along with pulsatility index) with cognition and vascular comorbidities, and (3) fTCD measures (lateralisation index and its SD, and time to peak lateralised state; and the degree of increase relative to baseline) and 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 four cognitive measures: WASI-II Matrix Reasoning and Vocabulary subtests, MMSE and ACE-R Fluency (including five subtests). There was a moderate correlation between the WASI-II Matrix and Vocabulary subtests of r=.435, p=.002.

Relationships between demographic factors, vascular comorbidities and cognitive performance

Participants who were female (r=-.40, p=.004) and younger (r=-.36, p=.010) performed better than those who were male 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), where females had higher velocities than males. 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 Matrix Reasoning (r=-.385, p=.006), where those with lower pulsatility index had better performance. To ensure the associations between pulsatility index and WASI-II Matrix Reasoning performance was not the product of age, we ran partial correlations, and found the effects did not change (r=-.34, p=.017). The correlation between pulsatility index and WASI-II Vocabulary was r=.141,

p=.330, which was statistically significantly different to the correlation with 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-lateralisation to the word generation task as indexed by the lateralisation index (r=-.31, p=.029; Figure 2a). The lateralisation index was positively related to WASI-II Matrix Reasoning (r=.40, p=.005 Figure 2b), MMSE score (r=.38, p=.005) and ACE-R total score (r=.32, p=.025); where the ACE-R Attention and Orientation sub-scale was the only sub-scale to also show this effect (r=.36, p=.012). Correlation results did not change when partialling out pulsatility index, a theoretical cause of reduced lateralisation index. The correlation between lateralisation index and WASI-II Vocabulary was r=.239, p=.098, which was not significantly different to 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 seconds post-stimulus), there was no relationship with age, vascular comorbidity or cognitive performance when looking over the entire 10-second period, or breaking this period up into 1-second intervals. We assessed the left and right channels separately and also 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 lateralisation of TCD response during a cognitive

task, and the pulsatility index to a smaller (non-significant) degree; and vascular comorbidities also appeared to associate with crystalised 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), and pulsatility index, lateralisation 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 lateralisation index were significantly related to the WASI-II Matrix Reasoning performance, but unrelated to WASI-II Vocabulary performance.

Discussion

This study demonstrated that fluid cognitive abilities are preferentially vulnerable to cerebrovascular dysfunction in late life. Further, that increasing age (in this cross-sectional study) is associated with an attenuation of lateralisation during a cognitive task, as measured with TCD. This study demonstrates 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, as opposed to vascular structure of disease (Elias, et al., 2004; Raz, Lindenberger, et al., 2007; Raz, Rodrigue, et al., 2007; Salarirad, et al., 2011), identified specific associations with fluid abilities, and a relative sparing of crystallised abilities. We found that cerebrovascular integrity (indexed by pulsatility index) and lateralisation of the TCD response during a cognitive task were associated with fluid abilities (WASI-II Matrix Reasoning); the effect for pulsatility index was particularly strong, with a

statistically significant dissociation between crystalised 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 crystallised ability (Colom et al., 2013), crystallised 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., 2007).

In our sample, there was a left-lateralisation 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 left hemisphere (Friedman et al., 1998; Gaillard et al., 2000). We found that the magnitude of fTCD lateralisation decreased over age, between 60 and 75 years, as assessed cross-sectionally. Consistently, fMRI studies have identified an age-related reduction in lateralised 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 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, the result of aging, oxidative stress as well as amyloid accumulation (Ajmani, et al., 2000).

Importantly, it was the lateralisation 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 decrease in the mean increase in flow velocity during three fTCD experimental paradigms, including a word stem completion task (very similar to the word generation task), however 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 crystalised measures in linear regression models, taking into account age and sex, as well as pulsatility index and lateralisation index. Memory performance (not fluid ability) appears the best cognitive predictor of conversion from vascular cognitive impairment to dementia over five 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, non-invasive and cost-effective measurement tools for screening, diagnostics and ongoing monitoring; and 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 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) and one measure of crystalised 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). Lastly, 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, where back transition to a normal cognitive state is very common over a number of years (Marioni et al., 2011; Matthews, Stephan, McKeith, Bond, & Brayne, 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 the old (Hachinski, et al., 2006). Aging is associated with changes to the cerebrovascular system, either directly (haemorrhage 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 the age-related lateralisation 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 lateralisation 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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Table 1. Participant characteristics including age, sex, years of formal education completed, cognitive performance and cardiovascular risk factors.

	Male	Female	Total
	n=19	n=31	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
MMSE±SD	28.58±1.46	29.19±0.87	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%

MMSE=Mini Mental State Examination, ACE-R=Addenbrooke's Clinical Examination Revised Australian Version, BMI=Body Mass Index

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	
	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

Bold indicates p<.05

Table 3. Results from two linear regressions illustrating associations between fluid and crystalised cognitive measures with age, sex, vascular comorbidity, pulsability index and lateralisation index.

	WASI-II Matrix Reasoning		WASI-II Vocabulary	
	Stand.Beta	*p*	Stand.Beta	*p*
Sex (1 female/2 male)	-.016	.911	-.086	.571
Age	-.020	.893	-.103	.523
Vascular comorbidity (0-3)	**-.275**	**.037**	**-.310**	**.032**
Pulsatility index	**-.285**	**.040**	.224	.135
Lateralisation index	**.353**	**.010**	.223	.129

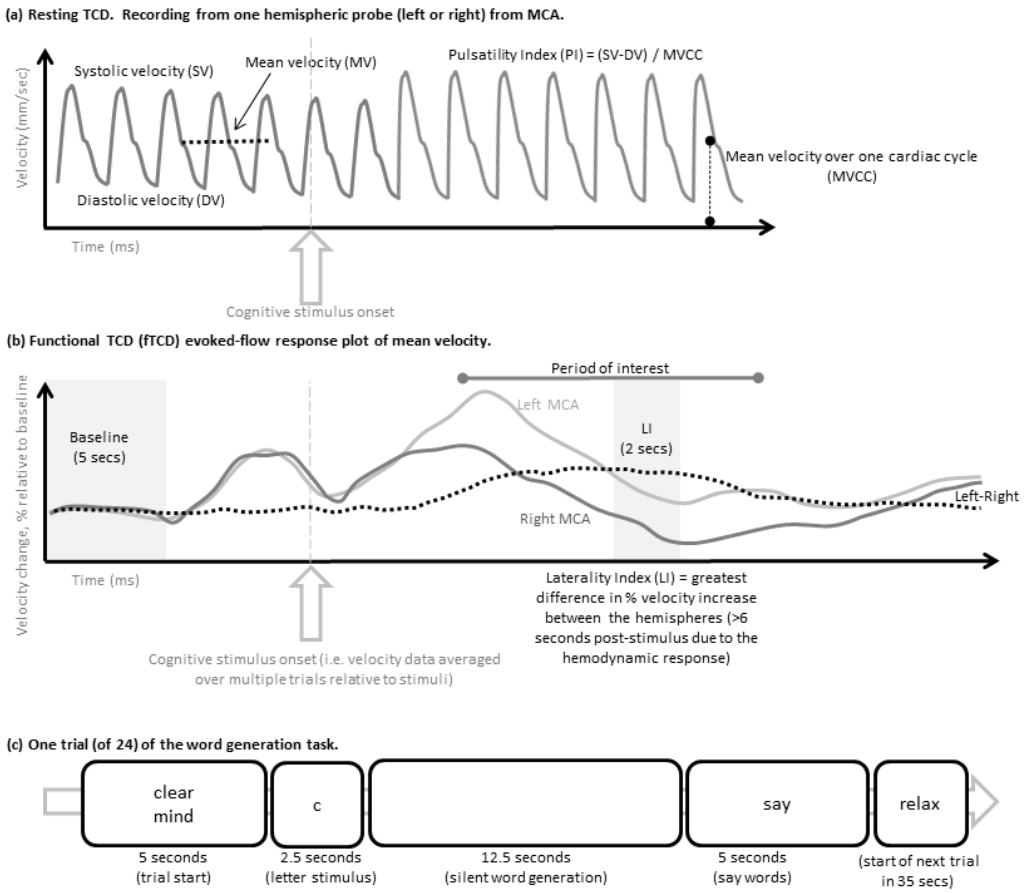

Figure 1. (a) Illustration of a TCD recording of blood flow velocity within the middle cerebral arteries. Key measures include maximum/systolic velocity, minimum/diastolic velocity, mean flow velocity, and pulsatility index which includes mean velocity over one cardiac cycle (MVCC). (b) A functional TCD evoked-flow response, which is an average of mean flow velocity over trials, relative to the onset of a cognitive stimulus. The lateralisation index (LI) is calculated as the average mean flow velocity centred at the point of maximal difference between left and right channels within the period of interest (5-15 seconds post-stimulus). The time LI and the standard deviation of LI was also measured; further the average velocity (split into 1 second 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.

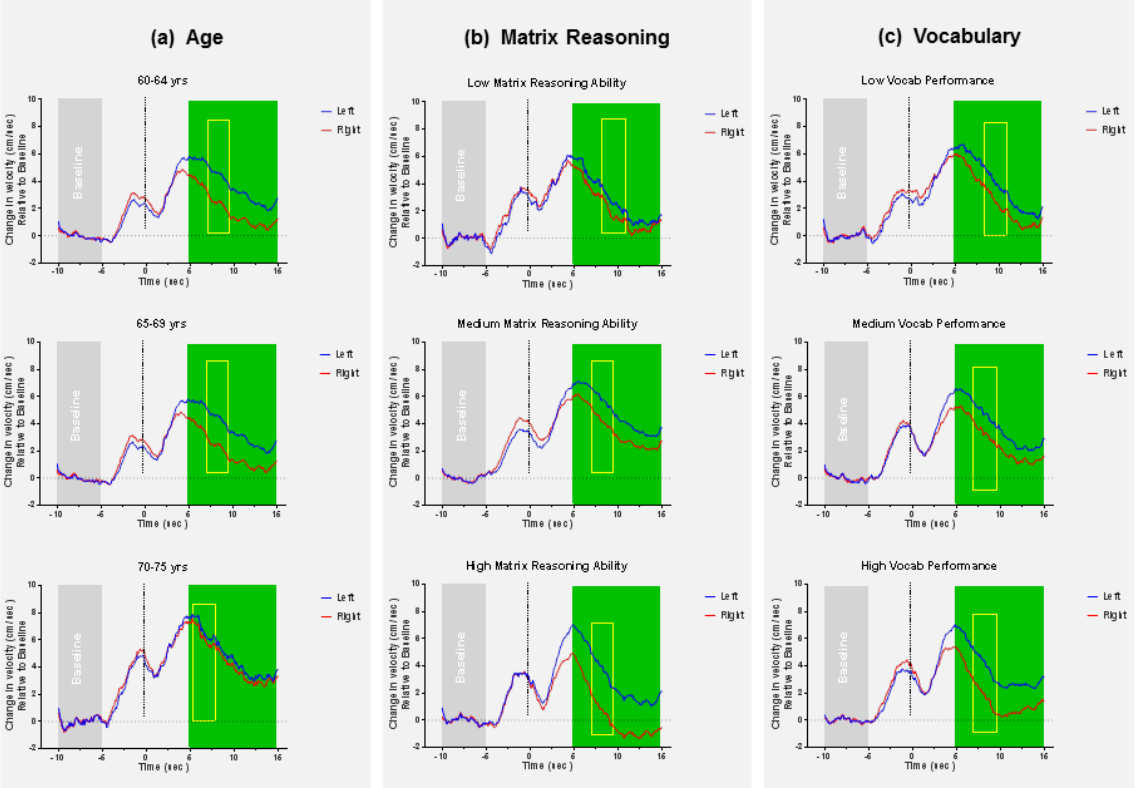

Figure 2. Stratified groups displaying key results: (a) lateralisation index decreases with age between 60 and 75 years, (b) lateralisation index increases with fluid abilities as indexed by WASI-II Matrix Reasoning test, and (c), lateralisation index does not associate with crystallised abilities as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