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Guiney, Hayley; Lucas, Samuel; Cotter, J. D.; Machado, Liana

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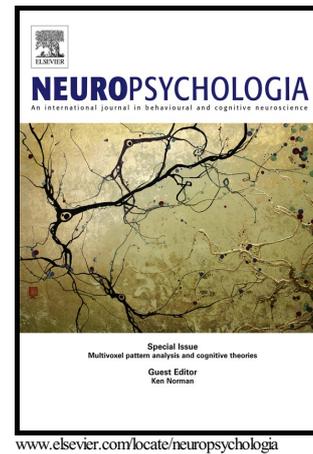
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Investigating links between habitual physical activity, cerebrovascular function, and cognitive control in healthy older adults*

Hayley Guiney^{1,2*}, Samuel J.E. Lucas^{1,3}, James D. Cotter¹, Liana Machado^{1,2}

¹University of Otago

²Brain Research New Zealand

³University of Birmingham

*Corresponding author. Hayley Guiney, Department of Psychology, University of Otago, William James Building, 275 Leith Walk, Dunedin 9054, New Zealand.

hayley.guiney@psy.otago.ac.nz

Abstract

A growing body of evidence indicates regular physical activity benefits older adults' cognitive functioning, particularly when a high level of cognitive control is required. Recent research has pointed to improved cerebrovascular function as one mechanism through which such benefits might arise. This study built on previous research by investigating in 51 healthy older adults aged 60 to 72 years relationships between habitual physical activity, cerebrovascular function (indicated by resting cerebral blood flow velocity in the middle cerebral artery [$n = 42$], and its responsiveness to hypercapnia [$n = 26$] and hypocapnia [$n = 25$]), and cognitive control (inhibition and switching). Linear regression analyses showed moderate positive associations between physical activity and inhibitory control, but not

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cerebrovascular function. There were also no significant relationships between the cerebrovascular measures and cognitive control. These results indicate that regular engagement in physical activity is associated with superior inhibitory control in older adulthood, but cerebrovascular function was not found to explain those relationships. Taken together, the current findings reinforce reports of positive links between habitual physical activity and cognition in healthy older adults, but also signal that interrelationships with cerebrovascular function may be more complex than currently indicated by the literature, necessitating further research to elucidate the role cerebrovascular function might play in accounting for physical activity-cognition links in healthy older adults.

Keywords: ageing; blood flow; cognition; exercise; transcranial Doppler

A large body of research points to physical activity as a simple lifestyle behaviour that might help to promote older adults' brain health and functioning. For example, cross-sectional, longitudinal, and intervention evidence shows that habitual physical activity can benefit older adults' cognitive functioning and the underlying neural structures that support such functioning (for reviews, see Bherer, Erickson, & Liu-Ambrose, 2013; Carvalho, Rea, Parimon, & Cusack, 2014; Guiney & Machado, 2013; Jedrzejewski, Lee, & Trojanowski, 2007; Smith, Potter, McLaren, & Blumenthal, 2013). Some studies also indicate that habitual physical activity might have greater benefits for higher-level cognitive functions that decline disproportionately with age (Benedict et al., 2013; Bixby et al., 2007; Clark, Parisi, Kuo, & Carlson, 2016; Colcombe & Kramer, 2003; Frederiksen et al., 2015). These promising findings have led to the identification of several putative mechanisms that may underlie the benefits of physical activity for cognition, including improved cerebrovascular functioning (for reviews, see Barnes, 2015; Hötting & Röder, 2013; Stillman, Cohen, Lehman, & Erickson, 2016). Research indicates that habitual physical activity could benefit

cerebrovascular functioning through a range of physiological pathways (Bolduc, Thorin-Trescases, & Thorin, 2013; Jackson et al., 2016), and superior cerebrovascular functioning is in turn likely to benefit cognitive functioning as it supports more efficient delivery of oxygen and nutrients to the brain via the regulation of cerebral blood flow (CBF; discussed in Leithner & Royle, 2014). Thus, the purpose of the current study was to consider the interrelationship between physical activity habits, cerebrovascular functioning, and cognition in older adults, in an effort to shed further light on whether cerebrovascular functioning could be an important factor underlying physical activity-cognition links in this age group. Note that, in this article, ‘habitual physical activity’ refers to the broad concept of engaging in physical activity or exercise on a regular basis, which researchers can measure several ways but often index with aerobic fitness, self-reported physical activity, or both.

Evidence that habitual physical activity benefits cerebrovascular functioning comes from both animal and human research. In middle-aged animals, aerobic exercise increases production of vascular growth factors (Latimer et al., 2011) and promotes angiogenesis, both of which support optimal cerebrovascular functioning (reviewed in Barnes, 2015). In healthy older adult humans, researchers have found positive associations between indices of habitual physical activity (aerobic fitness, self-reported physical activity, or both) and cerebrovascular function. Compared to their less fit and inactive counterparts, aerobically fit and highly active older adults had higher resting CBF velocity (Ainslie et al., 2008; Bailey et al., 2013; Brown et al., 2010) and greater hypercapnic responsiveness (Bailey et al., 2013; Brown et al., 2010). Other CBF regulatory mechanisms have also been linked to fitness. For example, older adults with higher fitness were better able to maintain cerebral perfusion during a physiological challenge designed to lower brain perfusion pressure (via graded lower body negative pressure), indicating that a physically active lifestyle may be associated with better cerebral autoregulation (Formes, Zhang, Tierney, Schaller, & Shi, 2010). Importantly, these cross-sectional findings converge with intervention studies showing that engagement in aerobic

exercise programmes can increase hypercapnic responsiveness in healthy older adults (Murrell et al., 2013) and stroke patients (Ivey, Ryan, Hafer-Macko, & Macko, 2011).

There is also evidence from ageing and dementia studies that better cerebrovascular functioning supports more effective cognitive functioning. Those studies often utilise Transcranial Doppler ultrasound, which is a noninvasive and inexpensive technique that has high temporal resolution and indexes cerebrovascular function by estimating resting CBF velocity and/or changes in CBF velocity in response to changes in arterial CO₂ (Keage et al., 2012; Willie et al., 2011). Higher resting CBF velocity and greater responsiveness to increases in CO₂ ('hypercapnic responsiveness') reflect better functioning (Barnes, 2015; Davenport, Hogan, Eskes, Longman, & Poulin, 2012), and both indicators decline with age (Bailey et al., 2013; Flück et al., 2014; Lu et al., 2011) and neurological disease (den Abeelen, Lagro, van Beek, & Claassen, 2014; Vicenzini et al., 2007). In addition, low CBF velocity and hypercapnic responsiveness are associated with increased risk for future cognitive decline (Viticchi et al., 2012). Greater responsiveness to decreased arterial CO₂ ('hypocapnic responsiveness') could also be considered an indicator of superior cerebrovascular functioning, but the balance of research to date indicates that hypocapnic responsiveness is not adversely affected by adult ageing (Jaruchart, Suwanwela, Tanaka, & Suksom, 2016) or neurological disease (den Abeelen et al., 2014; Hanby, Panerai, Robinson, & Haunton, 2017; Vicenzini et al., 2007).

In sum, research to date indicates three relevant links: (i) habitual physical activity is linked to superior cognitive functioning; (ii) habitual physical activity is linked to superior cerebrovascular functioning; and (iii) cerebrovascular functioning supports cognition, at least as evidenced by ageing and dementia research (for a summary of the theoretical links, see dashed arrows in Figure 1). Together, these interrelationships support the hypothesis that improved cerebrovascular functioning could be one mechanism through which habitual physical activity benefits cognitive functioning. However, only a handful of studies have

examined all three links in the same sample with the aim of testing that hypothesis. Two of those studies, which were conducted with older adults, reported significant interrelationships between aerobic fitness, aspects of cerebrovascular function, and overall cognitive functioning (Brown et al., 2010; Gill et al., 2015). Brown et al. (2010) also found that some indicators of cerebrovascular function at least partially mediated the relationship between fitness and cognition. Alongside their fitness analyses, Gill et al. (2015) assessed interrelationships with self-reported past-year and lifetime physical activity, but found no significant links with cerebrovascular function. These findings indicate that while some indices of cerebrovascular function help explain the positive link between fitness and cognition, they might not account for the link between physical activity and cognition. However, this conclusion contrasts with a recent young adult study, which found that cerebrovascular responsiveness mediated the link between self-reported physical activity and cognitive control (Guiney, Lucas, Cotter, & Machado, 2015).

These apparently contrasting results could be attributed to the inclusion of different populations (young versus older adults) or to the use of different measures to represent the constructs of interest. To address this issue, we sought to repeat our previous young adult study (Guiney et al., 2015) in older adults using the same method and procedures. In line with that earlier work, habitual physical activity was indexed as the number of days per week engaged in at least 30 min moderate or 15 min vigorous activity. Cognitive functioning was indexed with the same battery of computerised cognitive tests, which were designed to assess cognitive control (inhibition and switching). We focused on specific cognitive processes rather than a global measure of cognitive functioning as evidence indicates that habitual physical activity confers the greatest benefits for processes disproportionately affected by age (e.g., Benedict et al., 2013). Importantly, the tests used in the current study have been shown to be sensitive to healthy ageing (Bierre, Lucas, Guiney, Cotter, & Machado, 2017; Brett & Machado, 2017). As in our previous young adult study, cerebrovascular function was indexed

by resting CBF velocity and hypercapnic and hypocapnic responsiveness, with all three indices measured via transcranial Doppler ultrasound. Based on previous physical activity-cognition research (e.g., Bixby et al., 2007; Clark et al., 2016), we expected to find positive associations between habitual physical activity and performance on tasks that tap cognitive control. The main novel question investigated here was whether, as in young adults, indices of cerebrovascular function underlie those links.

Method

Participants

Fifty-two community-dwelling older adults were recruited through notices in a community newspaper in Dunedin, New Zealand. Participants were included if they: were aged at least 60 years; had no history of, and were not taking any medications for, psychiatric, neurological, or central nervous system conditions; had no history of cerebrovascular disease; were non-smokers; and had normal to corrected-to-normal vision. After attending the laboratory session, participants were excluded from analysis if they scored below 24 on the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), indicating possible dementia ($n = 1$). Table 1 summarises the descriptive statistics for the final sample of 51 participants (31 females).

Procedure

Summary

The University of Otago Human Ethics Committee approved this study (reference: 10/242). All participants provided informed written consent and reported their sex, date of birth, and years of education before completing paper-based versions of the MMSE, Beck Depression Inventory (BDI-II; Beck, Steer, & Brown, 1996), Pittsburgh Sleep Quality Index

(PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), and New Zealand Physical Activities Questionnaire - Short Form (NZPAQ-SF; McLean & Tobias, 2004), which is the New Zealand version of the reliable and widely used International Physical Activities Questionnaire (IPAQ-SF; Craig et al., 2003). Height and mass were then measured, followed by cognitive and cerebrovascular testing. Cognitive testing always preceded cerebrovascular testing since hypercapnia can affect neural activity (Xu et al., 2011), and therefore could influence cognitive functioning. The procedure (summarised in Figure 2) lasted between 1.5 and 2 hours, and participants were reimbursed NZ\$20–25.

Initial measures

The MMSE was used to screen participants for possible dementia. The BDI-II was included as a validated measure of depressive symptoms (Beck et al., 1996) and the PSQI of sleep quality (Beaudreau et al., 2012; Spira et al., 2012). BMI was calculated in kg/m^2 , and assessed according to the World Health Organization guidelines (World Health Organization, 2016). Habitual physical activity, derived from the NZPAQ-SF, was calculated as the number of days per week participants reported engaging in at least 30 min of moderate-equivalent physical activity (30 min moderate activity, including brisk walking, or 15 min vigorous activity). To assist recall, the NZPAQ-SF prompts participants to separately report the number of days (out of the past 7) and amount of time per day spent engaged in brisk walking, moderate intensity and vigorous intensity activity for at least 10 min at a time. Showcards with examples of moderate and vigorous activities were used to assist with the categorisation of physical activity intensity.

Cognitive testing

Participants sat in a dimly lit room while completing three computer-based reaction time (RT) tests of incremental difficulty: Pro, Anti, and then Pro/Anti. A chin rest (Applied Science Laboratories, Bedford, MA) maintained a screen viewing distance of 57 cm. All stimuli were presented against a black background using MATLAB (The Mathworks, Natick,

MA) and the Psychophysics Toolbox (Brainard, 1997; Pelli, 1997). At the beginning of each trial, a 0.3° white fixation dot appeared in the centre of the screen. Following a variable interval of 400, 600, 800, 1,000, or 1,200 ms, a 2° square, which was either red or green, appeared 8° to the left or right of the fixation dot (measured centre to centre). Using a DirectIN two-button response box (Empirisoft, New York, NY), the task was to press the button on the same side as green squares and the opposite side of red squares as quickly as possible without compromising accuracy. In the Pro task, only green squares appeared. In the Anti task, only red squares appeared. In the Pro/Anti task, the square could be either red or green, thus successful performance required participants to switch unpredictably between pressing the button on the same or opposite side of the square. Responses were correct if the appropriate button was pressed between 100 and 1,500 ms after the square appeared, otherwise a 900 Hz error tone sounded for 300 ms. Practice trials (four for Pro; six for Anti and Pro/Anti) always preceded the test trials (20 for Pro and Anti; 40 for Pro/Anti). Fixation duration, square side, and square colour (Pro/Anti only) were randomly selected at the start of each trial, with the constraint that each combination of conditions had to occur an equal number of times across the test trials for each task. For Pro/Anti, these global probability controls did not adjust for the number of switch trials (a Pro trial preceded by an Anti trial, or vice versa) in each participant's randomly-generated sequence, thus some participants would have had more switch trials than others, potentially influencing performance. To address this issue, we included the number of switch trials a participant received as a possible covariate when considering Pro/Anti performance.

Cerebrovascular testing

All cardiorespiratory equipment was calibrated before data collection in each session. To assess cerebrovascular function, transcranial Doppler ultrasound measured blood flow velocity through the middle cerebral artery (MCAv; for a review of this technique see Willie et al., 2011). To insonate the MCA, the experimenter secured a 2-MHz transcranial Doppler

ultrasound probe (DWL, Compumedics, Singen, Germany) to the right-hand side of the participant's head, just above the zygomatic arch, using a plastic headband. Insonation of the MCA was confirmed using established criteria, including the position and orientation of the probe, insonation depth, and direction of blood flow in relation to the probe (Lupetin, Davis, Beckman, & Dash, 1995; Willie et al., 2011). Following insonation, participants were fitted with a leak-free face mask attached to a two-way non-rebreathing valve (Hans Rudolph 7900 series, Kansas City, MO). A rapidly responding gas analyser (Model CD-3A, AEI Technologies, Pittsburgh, PA) sampled the partial pressures of end-tidal CO₂ (P_{ET}CO₂, a robust proxy for arterial CO₂; McSwain et al., 2010) and O₂ (P_{ET}O₂; mm Hg) from the face mask. A heated pneumotachograph (Hans Rudolph 3813 series, Kansas City, MO), which measured ventilation, was attached to the outflow of the non-rebreathing valve. All data were recorded continuously at 200 Hz by an analogue-to-digital converter (Powerlab/16SP ML795, ADInstruments, Dunedin, New Zealand) linked with a computer running physiological data analysis software (Chart 7.1; ADInstruments, Dunedin, New Zealand). The recording of data for analysis commenced only once the cerebrovascular and respiratory measures were stable and displayed the expected pattern and magnitude for each variable (as viewed in Chart 7.1).

Participants sat quietly while MCAv was measured during normocapnia (i.e., normal breathing of room air), hypercapnia, and then hypocapnia (volitional hyperventilation). The normocapnic phase lasted 2 min, after which participants breathed a hypercapnic gas mixture (5% CO₂, 21% O₂, and a balance of N₂) for 4 min from a Douglas bag attached to the intake of the non-rebreathing valve. At the end of the hypercapnia period, participants resumed breathing room air for 2 min to allow all respiratory and cerebrovascular measures to return to normal levels. Finally, to induce hypocapnia, participants were instructed to breathe faster and more deeply, with the goal being to achieve and then maintain for 2 min a reduction in P_{ET}CO₂ of the same magnitude as the increase observed during hypercapnia. To this end, the

experimenter periodically provided feedback about breathing rate and depth, based on real-time $P_{ET}CO_2$ measures (see Figure 2). Steady-state values for each phase (normocapnia, hypercapnia, hypocapnia) were calculated by averaging across the last minute of each phase.

Analysis

All analyses were conducted using STATA/IC 14.1 (STATA Corp LP, Texas).

Physical activity frequency (the number of days per week of ≥ 30 min of moderate-equivalent intensity activity) represented habitual physical activity. The four measures of cognitive control were based on accuracy-adjusted RTs ('acc-adj RTs'), calculated by dividing median RTs on correct trials by the proportion of correct responses (Chambers, Stokes, & Mattingley, 2004; Townsend & Ashby, 1983): Anti and Pro/Anti acc-adj RTs, inhibition cost (Anti minus Pro acc-adj RT, to remove visuomotor components of the task to help isolate inhibitory performance) and switching cost (Pro/Anti minus Anti acc-adj RT to remove visuomotor and inhibitory components of the task to help isolate switching performance). Note that errors increase the value of acc-adj RTs, which can be interpreted in the same way as RTs (i.e., larger values indicate poorer performance). There were three measures of cerebrovascular function: MCAv under normocapnic resting conditions ($MCAv_{normocapnia}$); change in blood flow velocity in response to increased CO_2 , induced by inspiration of the gas mixture (hypercapnic responsiveness); and change in blood flow velocity in response to decreased CO_2 , induced by hyperventilation (hypocapnic responsiveness). As per Murrell et al. (2013) and Guiney et al. (2015), hypercapnic and hypocapnic responsiveness were calculated as the percentage change in MCAv from $MCAv_{normocapnia}$ per unit (mm Hg) change in $P_{ET}CO_2$ observed under each condition:

$$\frac{[(MCAv_{[condition]} - MCAv_{normocapnia}) / MCAv_{normocapnia}] * 100}{P_{ET}CO_{2[condition]} - P_{ET}CO_{2normocapnia}}$$

Pairwise Pearson correlations were computed first to test for associations between habitual physical activity, cognitive control, and cerebrovascular function, and to identify significant covariates. Age, sex, education, depressive symptoms, sleep quality, and body mass index (BMI) were considered potential covariates, given past evidence of interrelationships with habitual physical activity and cognitive performance (Lindwall, Larsman, & Hagger, 2011; Rock, Roiser, Riedel, & Blackwell, 2014; Sutter, Zollig, Allemand, & Martin, 2012). As discussed in the ‘Cognitive testing’ subsection, when assessing relationships with Pro/Anti performance the number of switch trials a person received was also considered a possible covariate. Significant correlations ($p < .05$) were then subjected to separate linear regression analyses to further examine the interrelationships, after adjusting for any identified covariates. Given that cerebrovascular data could not be obtained from all participants, t tests (for continuous variables) and chi-squared tests (for categorical variables) were used to assess potential differences in participant characteristics, physical activity levels, and cognitive performance between those with missing compared to non-missing cerebrovascular data (see Table S1 in the supplementary materials).

Calculations in G*Power (Faul, Erdfelder, Buchner, & Lang, 2009) indicated that the current study had 80% power to detect moderate-sized correlations ($r \geq .39$) between habitual physical activity and cognitive performance. This expected effect size is comparable to those observed in our previous young adult study that used the same methods and procedures (Guiney et al., 2015). Missing cerebrovascular data for some participants meant 80% power to detect correlations with resting MCAv of $r \geq .42$ and responsiveness of $r \geq .53$, indicating adequate power if one could expect effect sizes of the magnitude reported in similar cerebrovascular studies with older adults (e.g., Bailey et al., 2013; Barnes, Taylor, Kluck, Johnson, & Joyner, 2013; Gill et al., 2015).

Results

Descriptive statistics

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Table 1 summarises the descriptive statistics for each measure. BDI-II scores indicated that 94% of participants had minimal depressive symptoms (scores 0–13) and 6% had mild symptoms (scores 14–19; Beck et al., 1996). PSQI scores indicated that 63% of the sample had good sleep quality (score ≤ 5); BMI values indicated that 29% of participants were normal weight (18.5–24.99 kg/m²), 41% were overweight (25.0–29.99 kg/m²), and 29% were obese (> 30 kg/m²). One participant was excluded from the Pro/Anti analyses as their accuracy on that task (43%) was below chance. Nine participants did not contribute any cerebrovascular data due to inability to insonate the MCA ($n = 8$) or participant refusal ($n = 1$). A further 16 did not complete the hypercapnia condition due to unavailability of the hypercapnic gas mixture ($n = 10$) or technical problems ($n = 6$), and one further participant declined participation in the hypocapnia condition. Importantly, there were no significant differences between those who had missing versus non-missing responsiveness data, except that those with missing data tended to be older (see Table S1).

For the cognitive tasks, t tests confirmed the expected slowing of RTs and reduction in accuracy as task difficulty increased. Compared to Pro, Anti performance was slower, $t(50) = -12.02$, $d = -1.81$, $p < .001$, and less accurate, $t(50) = 3.90$, $d = 0.75$, $p < .001$; compared to Anti, Pro/Anti performance was slower, $t(49) = -19.27$, $d = -2.82$, $p < .001$, and less accurate, $t(49) = 4.29$, $d = 0.79$, $p < .001$. Analysis of the randomly generated Pro/Anti task trial sequences showed considerable variation in the number of switch trials across participants (14 to 28 switches), but since the number of switch trials was not significantly associated with Pro/Anti performance ($r = .21$, $p = .152$) or switching costs ($r = -.01$, $p = .963$), it was excluded from further analysis.

Physical activity and cognitive control

The initial correlation analyses indicated that habitual physical activity was moderately associated with better Anti performance and smaller inhibition costs ($r = -.38$ and $p = .006$ in both cases), but there were no relationships evident with Pro/Anti performance (p

= .183) or switching costs ($p = .665$). Worse sleep quality was, as expected, associated with poorer inhibitory control (Anti performance, $r = .28$, $p = .044$; inhibition costs, $r = .28$, $p = .050$), but PSQI scores were not considered potential confounders as they were not related to physical activity ($p = .934$). No other covariates were identified (but note that alternative analysis approaches using grouped physical activity levels and/or forced entry of all covariates produced the same pattern of results). In follow-up regression analyses, habitual physical activity explained 15% of the variance in Anti performance and 14% in inhibition costs (see Figure 1). The residuals for both regressions were not normally distributed, but subsequent analyses with normalised (via square root transformations) data produced similar results, albeit with a slightly weaker relationship between physical activity and inhibition costs ($p = .012$).

Other relationships

Contrary to expectations, habitual physical activity was not significantly related to any of the cerebrovascular measures (MCAv, $p = .916$; hypercapnic responsiveness, $p = .614$; hypocapnic responsiveness, $p = .988$), and there were no significant relationships between the cerebrovascular measures and cognitive performance (all $ps > .1$; see Table S2). Alternative analyses with grouped independent variables and/or forced entry of all covariates again produced the same pattern of results.

Discussion

The current study investigated in healthy older adults the relationships between habitual physical activity, cerebrovascular function, and cognitive control, with the aim of shedding light on whether cerebrovascular function plays a role in explaining physical activity-cognition links in that age group. The basic pattern of cognitive performance aligned with past older adult studies that used the same tasks (Bierre et al., 2017; Brett & Machado,

2017), and although there were some missing cerebrovascular data, the values for $MCA_{V_{normocapnia}}$, hypercapnic responsiveness, and hypocapnic responsiveness were similar to those observed in comparable studies (Ainslie et al., 2008; Lucas et al., 2012; Murrell et al., 2013). Importantly, the only difference between participants with missing versus non-missing cerebrovascular data was that they tended to be older, which is consistent with the fact that the temporal window narrows with age, making insonation of the MCA more difficult (discussed in Willie et al., 2011). The main regression results showed that the more days per week older adults performed at least 30 minutes of moderate-equivalent intensity physical activity, the more effective their inhibitory control. However, there were no significant links observed between habitual physical activity and cerebrovascular function, or between cerebrovascular and cognitive functioning. These findings show the expected modest positive links between habitual physical activity and aspects of higher-order cognitive functioning in older adulthood, but in contrast to previous findings in young adults (Guiney et al., 2015), those benefits were not reliably explained by better cerebrovascular function. The following sections discuss each of the investigated links separately before integrating the findings and making recommendations for future research.

Physical activity and cognitive control

The current study assessed two aspects of cognitive control: inhibition and switching. Consistent with previous research in older adults (for a review, see Guiney & Machado, 2013), more frequent physical activity was associated with superior inhibitory control. In contrast, the association between physical activity and switching costs was very weak ($r = .06$) and not significant, indicating little or no meaningful link between the two – a finding that aligns with Fanning et al. (2016), but not others (Dupuy et al., 2015; Johnson et al., 2016). However, those latter studies did not isolate the specific effect of switching from other components of the task, leaving open the possibility that the benefits reflected functions other than switching ability. Importantly, our finding that physical activity was associated with

benefits for inhibitory control but not switching aligns with our previous work in young adults (Cameron, Lucas, & Machado, 2015; Guiney et al., 2015).

The physical activity-cognition links reported here are important as they indicate that more frequent physical activity may help support more effective performance on everyday tasks that require inhibiting a prepotent response and instead performing a goal-directed action (e.g., exercising self-control, ignoring distractors; Diamond, 2013). Although the cross-sectional design of the current study means that neither causation nor the direction of the effects can be inferred, the observation of a positive link between physical activity and cognition aligns with intervention studies showing that exercise engagement improves older adults' cognitive performance (e.g., Colcombe et al., 2006; Fanning et al., 2016). Regarding the direction of the effect, longitudinal evidence shows that better cognitive functioning leads people to be more physically active (Belsky et al., 2015), but also that relationships between habitual physical activity and cognition are bidirectional (Daly, McMinn, & Allan, 2014).

Physical activity and cerebrovascular function

Only very weak nonsignificant associations between physical activity and cerebrovascular function were observed in the current study ($r < .1$ for all measures). These findings align with Gill et al. (2015), who reported no significant links with self-reported current and lifetime physical activity, but they appear to be inconsistent with other work in older adults (Ainslie et al., 2008; Bailey et al., 2013; Tarumi et al., 2015). Note though that those studies tested groups of participants at either end of the physical activity scale (e.g., endurance athletes versus sedentary individuals in Ainslie et al., 2008), and it may be that significant differences in cerebrovascular function emerge only when comparing highly active older adults to their sedentary counterparts due to threshold effects or the higher statistical power associated with more homogeneous groups. Moreover, as indicated by a recent study in young adults, it may be that evidence of superior cerebrovascular function in

more moderately-active individuals emerges only when the cerebrovascular system is challenged (e.g., during aerobic exercise; Brugniaux, Marley, Hodson, New, & Bailey, 2014).

Having said that, the absence of any notable habitual physical activity-cerebrovascular function links also contrasts with previous research in older adults that found positive linear relationships between aerobic fitness and measures of resting CBF velocity (Bailey et al., 2013; Gill et al., 2015) or cerebrovascular responsiveness (Bailey et al., 2013; Barnes et al., 2013; Gauthier et al., 2015). One explanation for these apparent discrepancies arises from the notion that aerobic fitness and physical activity represent only partially overlapping constructs that may influence cerebrovascular function through different pathways. Both measures generally reflect physical activity engagement, but aerobic fitness is also influenced by other factors. For example, genetic factors can account for up to 50% of the variation in fitness (Bouchard et al., 1998), and there is wide inter-individual variation in the degree to which fitness responds to changes in physical activity (Bouchard & Rankinen, 2001). Thus, it is possible that the fitness-cerebrovascular links observed in previous research were driven by genetic or other individual-level factors, rather than activity engagement per se. Alternatively, it may be that objective indicators of habitual physical activity (of which aerobic fitness is one) produce more valid results than self-reported data (Tucker, Welk, & Beyler, 2011), particularly in older adults whose recall abilities may have declined with age (Khan, Martin-Montanez, Navarro-Lobato, & Muly, 2014). While the observation of significant physical activity-cognition relationships in this study bolsters confidence in the self-report measure used, it is nevertheless possible that reporting inaccuracies introduced sufficient error to mask physical activity-cerebrovascular links. Future research could improve on the current design by including objective measures of habitual physical activity (e.g., via accelerometers).

A further possible explanation for the notably weak links between physical activity and cerebrovascular function stems from the inability of transcranial Doppler to take into account changes in vessel diameter (discussed in Giller, 2003). With small changes in

diameter, changes in velocity approximate those in flow. However, as the change in diameter increases, changes in velocity begin to underestimate those in flow, with the discrepancy between the two measures becoming disproportionately greater (discussed in Hoiland & Ainslie, 2016). One might therefore hypothesise that we did not see relationships between physical activity and cerebrovascular responsiveness (as measured by changes in MCAv) because CO₂-induced changes in MCA diameter were greater in more active participants (possibly due to reduced arterial stiffness), which led to underestimation of responsiveness relative to less active participants. If so, these differential changes in vessel diameter could have masked physical activity-related differences in responsiveness when measured solely by MCAv.

However, this account seems less plausible in the context of several points. First, other studies that used the same transcranial Doppler techniques observed significant habitual physical activity-cerebrovascular relationships in the expected direction (e.g., Bailey et al., 2013; Barnes et al., 2013). Second, while transcranial Doppler has been shown to underestimate cerebrovascular responsiveness in young adults (Coverdale, Gati, Opalevych, Perrotta, & Shoemaker, 2014), recent work in older adults showed that estimates of responsiveness were similar when measured with and without adjustments for observed changes in vessel diameter (Coverdale, Badrov, & Shoemaker, 2017). Finally, despite some contention in the field regarding whether or not vessel diameter remains constant during tests of cerebrovascular responsiveness (Brothers & Zhang, 2016; Hoiland & Ainslie, 2016), there is broad agreement that in the context of relatively small changes in arterial CO₂ (as in the current study), transcranial Doppler provides valid estimates of cerebrovascular function (Ainslie & Hoiland, 2014). Nevertheless, further work is needed to better understand the impact of the limitations of transcranial Doppler. Specifically, research is needed to compare it with techniques that directly measure flow (e.g., Duplex Doppler or MRI arterial spin labelling) or index haemoglobin content in the microvasculature (e.g., near-infrared

spectroscopy or MRI-BOLD). Such multi-modal approaches will advance our understanding of how physical activity influences cerebrovascular health and the corresponding effect on brain function.

Cerebrovascular function and cognitive control

Expected links between cerebrovascular functioning and cognitive control were not statistically significant. These findings appear to contrast with previous research in healthy older adult populations (e.g., Brown et al., 2010; Davenport et al., 2012; Gill et al., 2015), but note that those findings related to global rather than domain-specific cognitive performance. Previous work that did assess links between cerebrovascular functioning and domain-specific performance has yielded inconsistent effects (Brown et al., 2010; Gauthier et al., 2015). For example, Brown et al. (2010) found links with some higher-order cognitive domains but not others, whereas Gauthier et al. (2015) reported no significant links. Gauthier et al. (2015) suggested that the absence of a cerebrovascular-cognition link in their study could in part be due to the recruitment of a sample of healthier-than-average older adults (as a result of strict exclusion criteria), and thus there may not have been sufficient variation in the measures for an observable effect to emerge. While the current sample is also likely to contain relatively healthy individuals, issues of restricted range do not appear to account for the lack of cerebrovascular-cognition links (see Table 1). An alternative account could be the limited sample size for the cerebrovascular measures, as some of the correlations between responsiveness and cognitive control were of a small to moderate-size ($r = -.28$ to $-.31$; see Table S2) and may have emerged as significant had a larger sample size been available. In addition, some of the limitations associated with transcranial Doppler discussed in the previous section (e.g., larger changes in vessel size as a result of less arterial stiffening in those with better cognitive functioning) might also help to explain the absence of cerebrovascular-cognition links in the current study.

Cerebrovascular function as an explanatory mechanism

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The current results indicate that cerebrovascular functioning did not measurably account for the physical activity-cognition relationships, as evidenced by the very weak relationships with physical activity. It could therefore be inferred that improved cerebrovascular function is not a key mechanism through which habitual physical activity benefits older adults' cognition, but there are alternative explanations for the current results that do not necessarily preclude cerebrovascular function as a potential mediator. For example, if the emergence of a significant interrelationship depends on the particular measures used, differences between this study and previous research with older adults could be attributed to the use of distinct measures to represent the constructs of interest. Indeed, even within studies, different indices of cerebrovascular function have revealed different patterns of effects (e.g., Brown et al., 2010; Gill et al., 2015; Tarumi et al., 2015).

However, other work in young adults that used the same method and procedures as the current study did show significant mediating effects of cerebrovascular responsiveness (Guiney et al., 2015), indicating that factors other than the particular measures used might account for the absence of such an effect in the current study. One possibility is that cerebrovascular functioning is just one of many mediators of physical activity-cognition relationships, and mediators not measured here were more important in terms of accounting for the observed physical activity-cognition links in the current sample. For example, research has revealed a wide range of potential mechanisms through which habitual physical activity could bring about cognitive benefits in older adults, including changes at molecular (e.g., increased production of neurotrophic factors), structural (e.g., increased neural connectivity and cortical volume), and psychological (e.g., improved mood; reviewed in Stillman et al., 2016) levels, as well as the interaction of those changes with genetic factors (Leckie, Weinstein, Hodzic, & Erickson, 2012). A second possibility is that some of the limitations associated with the current study made it harder to detect relationships with cerebrovascular functioning. For example, the sample sizes for the cerebrovascular

responsiveness measures were relatively small, but note that the relevant correlations were weak and thus low power does not appear to entirely explain the current findings.

Nevertheless, it is important to acknowledge that the small sample sizes produced relatively wide confidence intervals, and the true effect sizes could be larger than indicated. Moreover, the current study did not account for the use of cardiovascular medications, or individual differences in blood pressure, diet, stress, or inflammatory markers, and it is possible that those factors influenced the cerebrovascular measures in such a way that links with the other variables were masked. Future research should seek to specifically investigate these effects to better understand their relationship to physical activity, cerebrovascular functioning, and cognition.

Conclusion

The main strength of this study is its examination of habitual physical activity, cerebrovascular function, and cognitive control in the same sample of healthy older adults. The results build on previous findings showing benefits of regular physical activity for higher-order cognitive functioning in older adulthood, but contrary to expectations, there were only weak, nonsignificant links between physical activity and cerebrovascular functioning. These findings could indicate that improved cerebrovascular functioning is not one of the mechanisms through which habitual physical activity brings about improvements in higher-order cognitive functioning in healthy older adults, but given supportive evidence from past studies and the fact that the use of different measures across studies has revealed different patterns of results, a more likely conclusion is that the interrelationships are more complex than indicated by the existing literature. More research will be needed to provide a clearer picture of the role cerebrovascular functioning might play in explaining the benefits of habitual physical activity for cognition in older adulthood. To this end, future research should

utilise longitudinal and intervention study designs and include objective measures of habitual physical activity as well as robust measures of cerebrovascular function.

Author Note

Hayley Guiney, Department of Psychology and Brain Health Research Centre, University of Otago, Dunedin, New Zealand, Brain Research New Zealand, Auckland, New Zealand; Samuel J.E. Lucas, Department of Physiology, University of Otago, Dunedin, New Zealand and School of Sport, Exercise, and Rehabilitation Sciences and Centre for Human Brain Health, University of Birmingham, Birmingham, England; James D. Cotter, School of Physical Education, Sport and Exercise Sciences, University of Otago, Dunedin, New Zealand; Liana Machado, Department of Psychology and Brain Health Research Centre, University of Otago, Dunedin, New Zealand, Brain Research New Zealand, Auckland, New Zealand.

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Fig 1. Relationships between physical activity, cerebrovascular function, and cognitive performance. Dashed arrows indicate the theoretical links between the three general constructs investigated. Solid arrows indicate the specific links found in the current study: more frequent physical activity was associated with better inhibitory control. Note that all cognitive control measures reflect accuracy-adjusted RTs (median RT/proportion correct). MCA_v = velocity of blood flow through the middle cerebral artery under normocapnic conditions.

Fig 2. Summary of the experimental procedure.

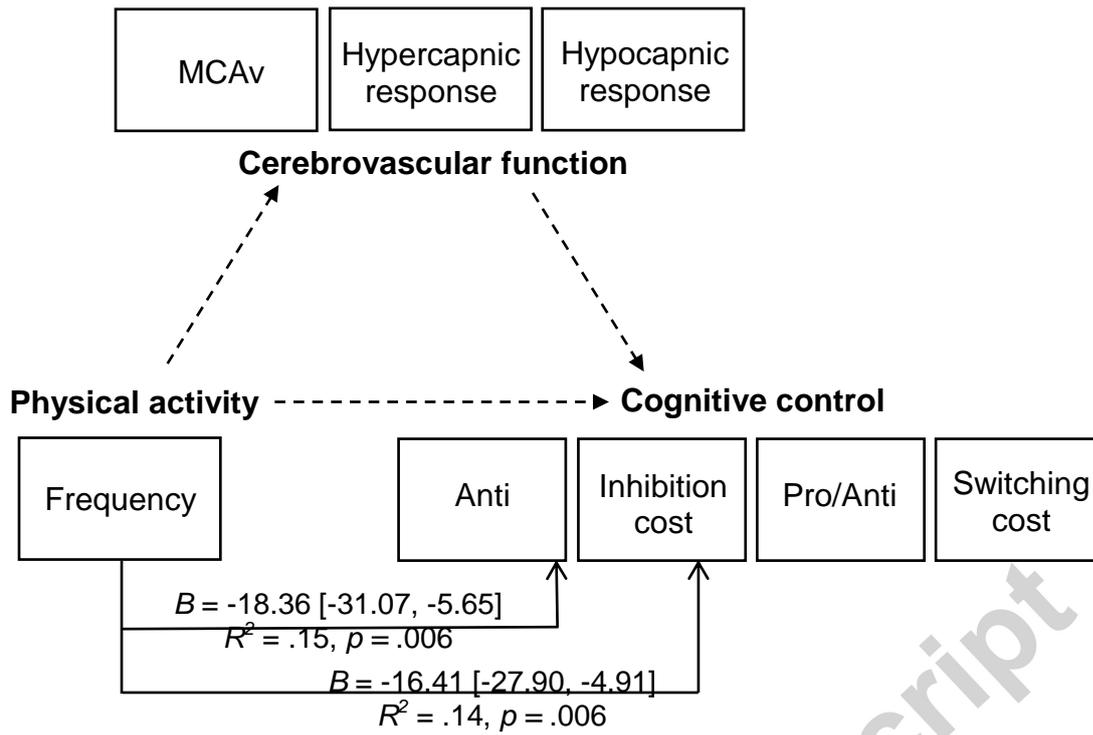


Figure 1.

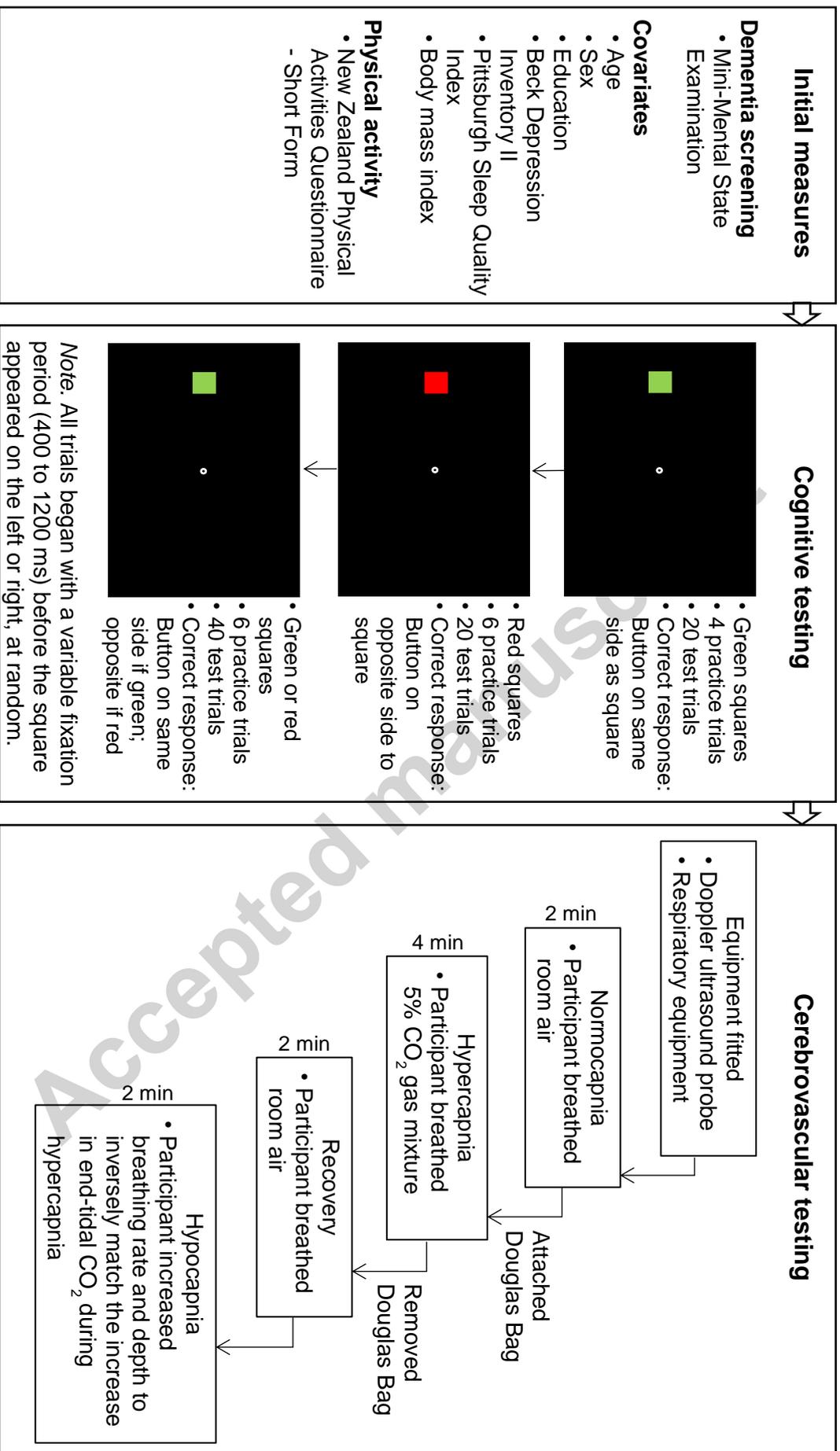


Figure 2.

Table 1 *Descriptive statistics for each measure*

	<i>n</i>	<i>M (SD)</i>	Range
Covariates			
Age (years)	51	66.8 (3.7)	60–72
Education (years)	51	13.6 (2.8)	8–18
Beck Depression Inventory-II score	51	4.9 (4.3)	0–16
Pittsburgh Sleep Quality Index score	51	4.9 (2.6)	1–11
Body mass index (kg/m ²)	51	27.9 (4.2)	18.8–38.8
Physical activity			
Frequency (days/week ≥ 30 min)	51	3.7 (2.5)	0–7
Cognitive measures			
RTs (ms)			
Pro	51	375 (48)	287–485
Anti	51	525 (107)	343–854
Pro/Anti	50	814 (96)	650–1083
Inhibition cost	51	150 (89)	-5–439
Switching cost	50	288 (106)	-30–497
Accuracy (% correct)			
Pro	51	98.7 (3.0)	85–100
Anti	51	95.3 (5.7)	80–100
Pro/Anti	50	88.6 (10.4)	58–100
Accuracy-adjusted RTs			
Pro	51	380 (47)	296–485
Anti	51	552 (117)	381–903
Pro/Anti	50	937 (188)	666–1511
Inhibition cost	51	173 (106)	-5–487
Switching cost	50	383 (186)	17–977
Cerebrovascular function			
MCAV _{normocapnia} (cm/s)	42	49.5 (12.4)	19.8–86.8
Hypercapnic responsiveness (%/mmHg)	26	3.2 (1.4)	0.6–6.6
Hypocapnic responsiveness (%/mmHg)	25	2.6 (0.9)	1.1–4.8

Note. MCAV = velocity of blood flow through the middle cerebral artery. Accuracy-adjusted RTs = median RT/proportion correct.

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Highlights

- Regular physical activity in older adults was linked to superior inhibitory control
- Cerebrovascular functioning was explored as a putative mechanism
- Cerebrovascular functioning did not explain the exercise-cognition relationship
- The mediating role of cerebrovascular functioning may change with age
- More research is needed to understand the role of cerebrovascular functioning

Accepted manuscript