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Cerebral blood flow is not modulated following acute aerobic exercise in preadolescent children

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ABSTRACT

Cognitive enhancements following a single bout of exercise are frequently attributed to increases in cerebral blood flow, however to date we have little understanding of the extent to which such bouts of exercise actually even influence cerebral blood flow following the cessation of exercise. To gain such insight, both regional and global changes in cerebral blood flow were assessed using 3D pseudo-continuous arterial spin-labeled magnetic resonance imaging in a sample of 41 preadolescent children. Using a within-participants randomized crossover design, cerebral blood flow as assessed prior to and following 20-min of either aerobic exercise or an active-control condition during two separate, counterbalanced sessions. The aerobic exercise condition consisted of walking/jogging on a motor driven treadmill at an intensity of approximately 70% of age-predicted maximum heart rate (HR = 136.1 ± 11.1 bpm). The active control condition consisted of walking on the treadmill at the lowest possible intensity (0.5 mph and 0% grade; HR = 92.0 ± 12.2 bpm). Findings revealed no differences in cerebral blood flow following the cessation of exercise relative to the active control condition. These findings demonstrate that cerebral blood flow may not be altered in preadolescent children following the termination of the exercise stimulus during the period when cognitive enhancements have previously been observed.

Over the past decade, there has been a growing focus on examining the effects of single bouts of exercise on cognition, with evidence generally observing enhancements in cognition following the cessation of the bout of exercise (Chang et al., 2012; Lambourne and Tomporowski, 2010; Verburgh et al., 2014). In particular, cognitive processes generally clustered within the construct referred to as cognitive control appear to be disproportionately influenced following these single bouts of exercise. During the period 5 to 48 min following a 20–30 min moderate intensity bout of aerobic exercise, enhancements in cognitive control operations have exhibited moderate-to-large effect sizes (0.4 to 0.9) in both preadolescent and young-adult populations (Drollette et al., 2012; Pontifex et al., 2009; Sandroff et al., 2016; Tomporowski et al., 2005; Weng et al., 2015). Similarly, acute bouts of exercise have been observed to alter neural responses to reward (Crabtree et al., 2014; Masterson et al., 2018) and affect (Petruzzello and Tate, 1997). However, while the evidence base demonstrating the beneficial after effects of these single bouts of exercise continues to grow, we still have limited understanding of the neurobiological mechanisms that underlie this relationship.

One mechanism that has been attributed to underlie these post-exercise induced enhancements in cognition is increased cerebral blood flow (Pontifex et al., 2009). Given that cerebral blood flow at rest is regulated through a cascade of reflexive responses sensitive to neurogenic activity, metabolic processes, arterial blood gas concentration, as well as cardiac output (Smith and Ainslie, 2017), the supposition is that exercise might elicit — potentially through increased cardiac output and changes in the partial pressure of blood gasses —an increase in cerebral blood flow independent of the brain actually requiring additional blood flow. Thus, such exercise-induced increases in cerebral blood flow would thereby result in greater metabolic resource availability and waste clearing, which in turn might induce facilitations in cognitive processing and alter neural responses (Delp et al., 2001; Pereira et al., 2007; Vingerhoets and Stroobant, 1999). Indeed, a growing body of evidence using techniques such as Doppler ultrasonography and near infrared spectroscopy has demonstrated that exercise results in a curvilinear increase in cerebral blood flow in an intensity dependent fashion (Ogoh and Ainslie, 2009; Rooks et al., 2010; Smith and Ainslie, 2017). In adult populations, the greatest

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enhancements in cerebral blood volume and cerebral oxygenation occur during moderate to vigorous exercise intensities occurring around 60% of maximal oxygen uptake (Rooks et al., 2010; Smith and Ainslie, 2017), however children appear to exhibit a more muted response with similar increases in cerebral blood volume being elicited across a wider range of exercise intensities (Ellis et al., 2017). However, while the vast majority of work has focused on changes in cerebral blood flow *during* exercise, relatively little work has investigated the extent to which these increases in cerebral blood flow persist *following* the bout of exercise during the period associated with cognitive enhancements.

Although the measurement of cerebral blood flow during exercise has largely relied upon the use of measurement techniques such as Doppler ultrasonography and near infrared spectroscopy, the "gold standard" measurement technique for non-invasive assessments of whole-brain cerebral blood flow is arterial spin-labeled (ASL) MRI (Buckley et al., 2014; Goff et al., 2010). Arterial spin-labeling bypasses the need for intravascular contrast agents or radioactive labeled tracers by using electromagnetically tagged arterial blood flowing towards the brain as an endogenous contrast agent to determine where blood perfuses in the brain (Goff et al., 2010). This approach therefore enables measurement of both global and regional modulations in cerebral blood flow, and has been found to be particularly effective in pediatric populations which exhibit greater cerebral blood flow than adult populations (Wang et al., 2003). In an initial proof of concept investigation, Smith and colleagues (Smith et al., 2010) examined the extent to which cerebral blood flow was modulated following a single bout of exercise in a sample of 5 college-aged adults. Following a 30 min bout of moderately-intense aerobic exercise, resting-state cerebral blood flow was increased globally relative to pre-exercise. Yet regional analysis specifically focusing on the motor cortex revealed no exercise-induced modulations (Smith et al., 2010). Utilizing a larger sample size, MacIntosh et al. (2014) failed to observe any global changes in cerebral blood flow following a 20 min bout of moderately-intense aerobic exercise in a sample of 16 college-aged adults. However, planned contrasts observed reductions in cerebral blood flow in gray matter 10 min following exercise relative to pretest (MacIntosh et al., 2014).

Some caution is warranted in interpreting the results of these previous investigations as neither study utilized a control condition or group to ensure that the effects were the result of exercise rather than the result of repeated exposure to the assessment. Although much of the acute-exercise and cognition literature has utilized passive control experimental conditions such as seated rest or reading (Drollette et al., 2012; Hillman et al., 2003; Pontifex et al., 2009; Pontifex et al., 2015; Pontifex et al., 2013), even postural changes have been demonstrated to impact cerebral blood flow (Olufsen et al., 2004). Accordingly, the present investigation utilized a within-subjects repeated measures crossover design to examine resting-state cerebral blood flow prior to and following moderate intensity aerobic exercise relative to an active-control condition during two separate, counterbalanced sessions using an arterial spin labeled MRI approach.

Beyond the assessment of global or regional changes in cerebral blood flow on a structure-by-structure basis; the present investigation additionally sought to determine to what extent acute exercise might induce modulations in cerebral blood flow within functionally connected neural structures or networks proposed to be involved in cognitive control such as the left frontoparietal network, right fronto-parietal network, and executive control network. Given the dynamic state of these neural networks, it may be that the conflicting modulations in cerebral blood flow observed within the present literature are the result of summating cerebral blood flow across neural networks that are differentially modulated in response to exercise. By directly evaluating modulations in cerebral blood flow within empirically derived neural networks, and in response to both exercise and control conditions, a more precise understanding of the after-effects of single bouts of exercise on cerebral blood flow may be obtained.

Given the preliminary nature of the present investigation, the potential to detect the after-effects of single bouts of exercise on cerebral blood flow was maximized by utilizing a preadolescent population who demonstrate less intensity-related variation in their exercise induced cerebral blood flow response (Ellis et al., 2017) and in whom the arterial spin-labeled MRI technique has been demonstrated to be particularly robust (Wang et al., 2003), relative to adult populations. Given the acute exercise and cognition literature, it was hypothesized that cerebral blood flow would be increased following a 20 min bout of moderate-intensity aerobic exercise within neural networks underling aspects of high-level cognitive operations, with no such changes observed for neural networks involved in motor control given the use of the active-control condition involving walking at the slowest intensity possible on a motor-driven treadmill.

1. Method

1.1. Participants

Forty-one typically developing preadolescent children (18 female; 10.2 ± 1.0 years) from the greater-Lansing, Michigan region participated in this investigation. An original sample of 49 participants were assessed for eligibility, with 4 participants not meeting the inclusionary criteria (i.e., presence of ADHD, braces, or uncomfortable in small spaces) and 4 participants declining to participate in the MRI portion of the experiment. All participants provided written assent and their legal guardians provided written informed consent in accordance with the Institutional Review Board at Michigan State University. Further, all participants were reported as being free of any neurological disorder, psychological condition, previous history of head trauma, cardiovascular disease, physical disabilities, and indicated normal or corrected to normal vision. Demographic data is provided in Table 1.

1.2. Imaging data acquisition

The MRI data acquisition was conducted using a GE 3T Signa® HDx MR scanner (GE Healthcare, Waukesha, WI) with an 8-channel head coil. During each scan session, higher-order shimming procedures were first carried out to improve magnetic field homogeneity. Then, a commercial 3D pseudo-continuous arterial spin-labeled (3D PCASL; Alsop et al., 2015) pulse sequence implemented as a product in the GE

Table 1
Mean (SD) values for participant demographics.

Measure	All participants
N	41 (18 females)
Age (years)	10.2 ± 1.0
Tanner scale	1.5 ± 0.6
IQ	112.6 ± 13.1
Percent identifying as a race other than white	19.5%
Percent identifying as American Indian or Alaska native	0%
Percent identifying as Asian	2.4%
Percent identifying as black or African American	7.3%
Percent identifying as native Hawaiian or other pacific Islander	0%
Percent identifying as white or Caucasian	75.6%
Percent identifying as more than one race	9.8%
Socioeconomic status	0.8 ± 0.2
Percent participating in free or reduced-price lunch	14.6%
Household income as a percent of the federal poverty level (%)	364.6 ± 130.8
Age predicted heart rate max (bpm)	198.8 ± 0.7
Lowest observed heart rate (bpm)	58.5 ± 10.5

Note: Socioeconomic status (ranging from 0 [lowest] to 1 [highest]) was computed as the mean across financial capital, human capital, and social capital domains based upon parental employment, participation in free or reduced price lunch, parental education, and family structure (Ensminger et al., 2000). Federal poverty level was computed using the U.S. Department of Health and Human Services 2016 poverty guidelines.

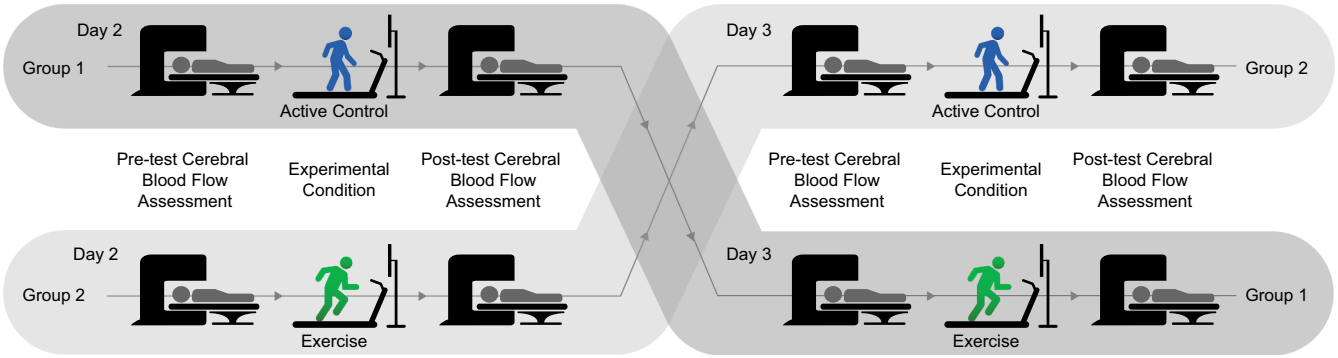

Fig. 1. Diagram of the experimental procedure.

scanner was used to quantify regional cerebral blood flow. This pulse sequence and the recommended parameters have been demonstrated to be reliable in both patients and healthy volunteers and are optimized to the GE scanner (Huang et al., 2013; Zeng et al., 2017). The sequence parameters were: fast spiral acquisition, 30 4-mm axial slices, time of echo (TE) = 9.83 ms, time of repetition (TR) = 4.52 s, 8 spiral arms with 512 sampling points per arm, effective resolution = 3.22 mm × 3.22 mm, reconstructed matrix size = 128 × 128, number of excitation (number of label-control pairs) = 3, field of view (FOV) = 22 cm × 22 cm, receiver bandwidth = ± 62.5 kHz, labeling duration = 1.45 s, saturation time = 2 s, and post labeling delay time = 1.525 s. A set of 180 T_1-weighted 1-mm^3 isotropic volumetric inversion recovery fast spoiled gradient-recalled sagittal images (10 min scan time), with cerebrospinal fluid (CSF) suppressed, was obtained to cover the whole brain with the following parameters: TE = 3.8 ms, TR of acquisition = 8.6 ms, time of inversion (TI) = 831 ms, TR of inversion = 2332 ms, flip angle = 8°, FOV = 25.6 cm × 25.6 cm, matrix size = 256 × 256, slice thickness = 1 mm, and receiver bandwidth = ± 20.8 kHz.

1.3. Imaging data processing

Cerebral blood flow maps were generated in the unit of ml of blood/100 g of tissue/min based on the equation recommended by Alsop and colleagues (Alsop et al., 2015) with the necessary scaling corrections recommended by the manufacturer (GE Healthcare) on the partial saturation of reference images, inversion efficiency, background suppression efficiency and the number of excitation. First, to account for any slight motion during the scan, the control-label perfusion weighted difference images were aligned linearly to the proton-density weighted images via the "3dvolreg" software in AFNI (Cox, 1996). The proton-density weighted images were then co-registered to the subject- and session specific T1-weighted images using asl_reg in FSL's BASIL toolset, which is optimized for co-registration of CBF images to structural images with more anatomical detail (Chappell et al., 2009). The resulting transformation was used to co-register the CBF maps to the T1-weighted image for each subject- and session using asl_reg. The global gray matter mask was in standard MNI152 space provided through the Harvard-Oxford atlas available within FSL. The network masks were also provided in standard MNI152 space through NITRC (www.nitrc.org/projects/genr/). Multiplication of the masks and each cerebral blood flow image then allowed for the computation of mean cerebral blood flow within the global gray matter and within each network mask for each session and condition. For whole-brain voxelwise analyses, asl_reg was used to warp each cerebral blood flow image into standard MNI152 space, and resulting images were masked using the MNI brain mask to remove non-brain tissues. Spatial smoothing of FWHM 5 mm was then applied to cerebral blood flow images using FSL's SUSAN (Smith and Brady, 1997) replicating the methods of MacIntosh et al. (2014). Smoothing was done to improve the signal to noise ratio of the spatially transformed images for between-subject analyses that assume each voxel was aligned across participants.

1.4. Procedure

Using a within-participants design, participants visited the laboratory on three separate days. The first day consisted of a paperwork and screening session where, following provision of informed assent/consent, participants were administered the two subtest Wechsler Abbreviated Scale of Intelligence, Second Edition (Wechsler, 2011) to estimate IQ and completed the Edinburgh Handedness Inventory (Oldfield, 1971) to determine hand dominance. Participants, in collaboration with their legal guardian, then completed the Tanner Staging System questionnaire (Taylor et al., 2001), a magnetic resonance screening form, and a health history and demographics questionnaire. Following completion of all paperwork, participants were given a 15-min exposure in a high-fidelity mock-MRI, mimicking the bore size and sounds occurring during scanning.

Participants were then randomly counterbalanced into two different session orders (day 2: control, day 3: exercise or day 2: exercise, day 3: control; see Fig. 1) to ensure that any observed effects were unrelated to the specific order in which participants received the exercise and control conditions. The exercise and control sessions occurred approximately 16.3 ± 17.8 days apart and at approximately the same time of day (1.8 ± 1.9 h different between sessions) with all tests occurring between 9 am and 5 pm given evidence suggesting that differences in neural activation can occur as a function of time of day (Hasler et al., 2014; Masterson et al., 2016). Each session occurred on a day in which the participant had not participated in physical education or other structured physical activity. Of the 41 participants that were randomized, three participants discontinued participation after the second session (2 following the control condition, 1 following the exercise condition; see Fig. 2). Consistent with previous investigations demonstrating exercise induced enhancements in cognition in this population (Hillman et al., 2009; Pontifex et al., 2013), the exercise experimental condition consisted of 20 min on a motor-driven treadmill at an aerobic exercise intensity of approximately 70% of age-predicted (205.8 − (0.685 ∗ Age); Robergs and Landwehr, 2002) maximum heart rate (HR = 136.1 ± 11.1 bpm). This intensity was equivalent to a fast walk or slow jog for the majority of participants. Given that cerebral blood flow is impacted by postural changes (Bode, 1991; Olufsen et al., 2004) and to maximize internal validity, an active-control experimental condition was used to reduce confounds related to body position, demand characteristics/expectancy, and locomotion patterns. This active-control condition consisted of 20 min on a motor-driven treadmill at the lowest possible intensity (0.5 mph and 0% grade; HR = 92.0 ± 12.2 bpm; see Table 2). A polar HR monitor (Model H7, Polar Electro, Finland) was used to measure HR throughout the test alongside OMNI ratings of perceived exertion (Robertson et al., 2000). To ensure that any observed effects were unrelated to experimenter interaction or non-

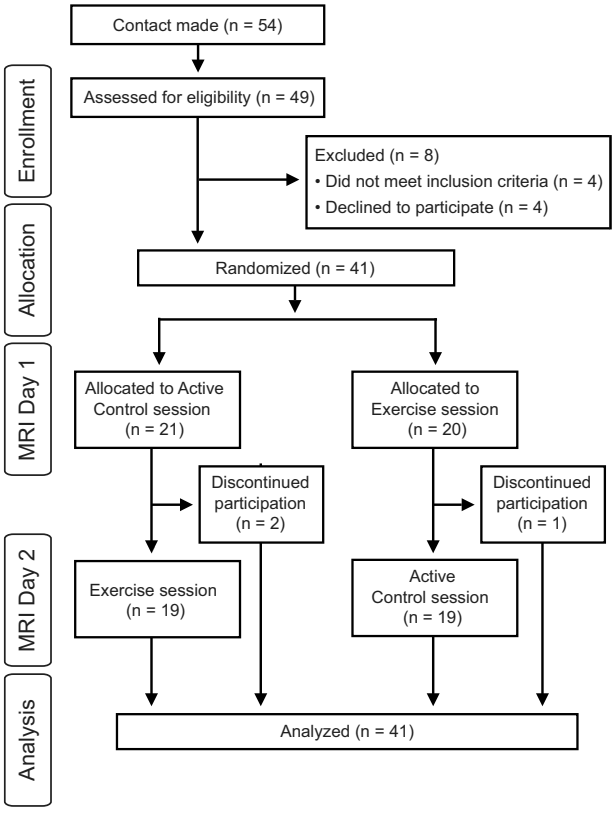

Fig. 2. Consort flowchart.

exercise related stimuli, participants watched an emotionally neutral video (minutes 65–85 and 85–105 from Wonders of the Universe; Wonders of the Universe, 2011) during the entire 20 min experimental period for both the exercise and active-control conditions. Regional cerebral blood flow was assessed prior to each experimental condition (pre-test) and again as soon as possible following termination of the experimental condition and completion of all MRI localizer procedures (post-test; approximately 25 min following each experimental condition; see Table 2), with structural MRI scans conducted at the very end of post-test scanning. Prior to entry into the MRI, participants' blood pressure was assessed in a seated position using an electronic blood pressure cuff (Omron, Kyoto, Japan). Heart rate and respiratory rate were assessed in a supine position at the start of each cerebral blood flow assessment using the peripheral gating and respiratory straps of the GE 3T Signa® HDx MR scanner (GE Healthcare, Waukesha, WI).

1.5. Statistical analysis

As estimation of cerebral blood flow in white matter (i.e., myelinated axon tracts) has been shown to be unreliable (van Gelderen et al., 2008), all analysis were restricted to gray matter (i.e., neuronal cell bodies). Primary statistical analysis of cerebral blood flow was conducted on global gray matter as well as within previously identified pediatric resting-state fMRI networks (Muetzel et al., 2016). Specifically, analysis focused on networks (left frontoparietal network, right fronto-parietal network, and executive control network) underlying aspects of cognition previously observed to be enhanced following a single bout of exercise, with the motor network included in analysis as a control network. Analyses were conducted for global gray matter and in each of these specific regions with $\alpha = 0.05$ and Benjamini-Hochberg false discovery rate control ($d = 0.05$) for post-hoc decompositions. Each analysis was conducted separately using a 2 (Mode: control, exercise) × 2 (Time: pre-test, post-test) univariate multi-level model including the random effects of Participant, Participant × Mode interactions, and Participant × Time interactions with Kenward-Roger degrees of freedom approximations. Analysis were performed using the lme4 (Bates et al., 2015), lmerTest (Kuznetsova et al., 2017), and emmeans (Lenth et al., 2017) packages in R version 3.4.0. This approach maximized experimental power by allowing participants with missing data (either as a result of withdrawal or motion artifact) to be retained within the analysis (final $N = 41$; control pre-test: missing 6 cases; control post-test: missing 7 cases; exercise pre-test: missing 5 cases; exercise post-test: missing 6 cases). Statistical findings using this approach were consistent with analysis only including participants with complete data across all time points. Preliminary analysis were conducted to examine the Pearson product moment correlation between the change in cerebral blood flow and age, sex, pubertal status, IQ, change in heart rate or blood pressure from pre- to post-test for either the exercise or active control conditions. As no associations were observed ($p's \geq 0.09$), these factors were not included as covariates within the analysis. For each inferential finding, Cohen's d with 95% confidence intervals were computed as a standardized measure of effect size, using appropriate variance corrections for repeated-measures comparisons (d_{rm}; Lakens, 2013). Given a sample size of 41 participants and beta of 0.20 (i.e., 80% power), the present research design theoretically had sufficient sensitivity to detect t-test differences exceeding $d = 0.395$ (with a two-sided alpha) as computed using G*Power 3.1.2 (Faul et al., 2007).

Additionally, secondary voxel-wise analyses of cerebral blood flow across the whole brain gray matter were conducted using a series of non-parametric t-tests with FSL's randomise tool (Winkler et al., 2014).

Table 2
Mean (SD) values for the experimental sessions.

Measure	Active control	Exercise	t	p
Pre-test Cerebral Blood Flow assessment				
Systolic blood pressure (mm Hg)	105.0 ± 19.2	106.7 ± 17.5	0.4	0.68
Diastolic blood pressure (mm Hg)	71.5 ± 12.2	70.9 ± 17.9	0.2	0.85
Time prior to experimental condition (min)	42.1 ± 3.8	41.7 ± 5.9	0.3	0.77
Heart rate (bpm)	77.1 ± 11.4	76.2 ± 11.4	0.3	0.74
Respiratory frequency (breaths per minute)	20.5 ± 4.3	20.0 ± 4.3	0.5	0.60
Experimental condition				
Heart rate (bpm)	92.0 ± 12.2	136.1 ± 11.1	16.7	< 0.001
Heart rate reserve (%)	23.2 ± 8.1	54.5 ± 8.0	16.7	< 0.001
Heart rate percent of max (%)	45.7 ± 5.6	68.2 ± 5.5	17.4	< 0.001
Borg rating of perceived exertion	1.3 ± 1.7	4.0 ± 2.4	5.8	< 0.001
Treadmill speed (mph)	0.5	3.5 ± 0.4	47.0	< 0.001
Treadmill grade (%)	0	1.7 ± 1.1	9.9	< 0.001
Post-test Cerebral Blood Flow assessment				
Systolic blood pressure (mm Hg)	104.8 ± 18.8	101.2 ± 16.3	0.9	0.39
Diastolic blood pressure (mm Hg)	73.6 ± 17.1	71.0 ± 13.0	0.7	0.46
Time following experimental condition (min)	25.0 ± 3.6	25.3 ± 4.2	0.4	0.68
Heart rate (bpm)	75.2 ± 9.4	76.2 ± 9.8	0.5	0.63
Respiratory frequency (breaths per minute)	19.5 ± 3.0	19.9 ± 3.7	0.4	0.68

Note: t-tests reflect the difference between active control and exercise at each time point for each measure of interest. No statistical difference in blood pressure, heart rate, or respiratory frequency were observed between pre-test and post-test for either the active control or exercise conditions, $t's$ (37) ≤ 1.2, $p's \geq 0.2$, $d_{rm}'s \leq 0.16$ [95% CI: −0.29 to 0.49]. Similarly, no interactions of Mode × Time were observed, $F's$ (1, 37) ≤ 1.5, $p's \geq 0.2$, $f^2's \leq 0.46$ [95% CI: 0.0 to 1.06]. Heart rate during both the active control and exercise conditions (measured in an upright position) was statistically different from heart rate at pre-test and post-test (measured in a supine position), $t's$ (73) ≥ 4.1, $p's < 0.001$, $d_{rm}'s \geq 0.81$ [95% CI: 0.39 to 5.23].

Given the moderate sample size, variance images used to estimate the *t*-statistics were smoothed at 5 mm FWHM using the –v option in randomise. All models were run with 5000 permutations, and threshold-free cluster enhancement was used for voxel-based thresholding, with family-wise error corrected *p*-values of $p < 0.01$ considered statistically significant. As such models assume balanced designs, only participants without missing data (either as a result of withdrawal or motion artifact) could be included ($N = 25$). First, paired-samples non-parametric *t*-tests of the difference between Mode (control, exercise) in the change from pre- to post-test were conducted to test for a potential Mode × Time interaction. This was then followed by simple exploratory comparisons of time within each Mode, by running 1-sample *t*-tests to estimate where the change from pre- to post-test was greater than zero.

2. Results

2.1. Global gray matter analysis

For analysis of global gray matter, a main effect of Time was observed, $F(1, 37) = 33.2$, $p < 0.001$, $d_{rm} = 0.39$ [95% CI: 0.23 to 0.55], with greater cerebral perfusion at pre-test (65.9 ± 6.8 ml/100 g/min) relative to post-test (63.5 ± 6.4 ml/100 g/min). No main effects of Mode or interactions of Mode × Time were observed, *F's* (1, 34) ≤ 0.1, *p's* ≥ 0.7, f^2*'s* < 0.01 [95% CI: 0.0 to 0.04] (see Table 3).

2.2. Network analysis

Across each of the networks examined (left frontoparietal network, right fronto-parietal network, executive control network, and motor network), analysis revealed a main effect of Time, *F's* (1, 37) ≥ 7.3, *p's* ≤ 0.01, d_{rm}*'s* = 0.25 [95% CI: 0.06 to 0.53], with greater cerebral perfusion at pre-test relative to post-test. However, for the motor network that main effect did not remain significant following false discovery rate control (Benjamini-Hochberg critical alpha = 0.01). No main effects of Mode or interactions of Mode × Time were observed, *F's* (1, 34) ≤ 0.9, *p's* ≥ 0.3, f^2*'s* ≤ 0.03 [95% CI: 0.0 to 0.14] (see Table 3).

2.3. Voxel-wise analysis

Voxel-wise analysis of the whole brain gray matter observed no differences between control and exercise in the change in cerebral blood flow from pre- to post-test, *p's* ≥ 0.1. Follow-up exploratory analysis of the change in cerebral blood from pre- to post-test following the control condition revealed six broad clusters demonstrating reductions in cerebral blood flow, with the strongest and most dispersed effects observed in the left inferior frontal gyrus, extending across lateral prefrontal cortex, superior temporal gyrus, planum temporale, insular cortex, angular gyrus, and inferior temporal cortex, and additional clusters in the anterior cingulate cortex and bilateral insular cortices, *t's* ≥ 3.03, *p's* ≤ 0.01 (see Table 4 and Fig. 3). Follow-up exploratory analysis of the change in cerebral blood from pre- to post-test following the exercise condition revealed nine broad clusters demonstrating reductions in cerebral blood flow, with the strongest and most dispersed effects observed in the right temporal pole extending into planum temporale, superior temporal gyrus, angular gyrus, insular cortex, and right lateral frontal cortex, with effects also observed in the anterior cingulate cortex and bilateral anterior insular cortices, *t's* ≥ 2.99, *p's* ≤ 0.01 (see Table 4 and Fig. 3).

3. Discussion

The aim of the present investigation was to provide greater insight into the extent to which a single bout of exercise might induce regional modulations in cerebral blood flow following the cessation of exercise — during the period that has been previously associated with cognitive enhancements in preadolescent children. In contrast to our a priori hypothesis that cerebral blood flow would be enhanced following the cessation of exercise in neural networks underlying aspects of high-level cognitive operations (left frontoparietal network, right fronto-parietal network, and executive control network); findings revealed that a single 20-min bout of moderate intensity aerobic exercise was not associated with any differences in cerebral blood flow following exercise relative to following an active control condition. Rather, cerebral blood flow was found to *decrease* from pre-test to post-test across each of the neural networks assessed — as well as for global gray matter — for both exercise and control conditions. Similarly, exploratory whole-brain voxel-wise analysis of changes in cerebral blood flow from pre- to post-test revealed reductions in cerebral blood flow within the insular cortex, superior temporal gyrus, angular gyrus, anterior cingulate cortex, and the bilateral insular cortices. Although the pattern of change in cerebral blood flow observed in the exploratory whole-brain voxel-wise analysis were not identical between the moderate intensity aerobic exercise and active control conditions, no statistical differences between these two conditions were observed.

Findings from the present investigation are in agreement with the reductions in gray matter cerebral blood flow 10 min following a bout of moderate intensity aerobic exercise observed by MacIntosh et al.

Table 3
Statistical summary of post-hoc comparisons of cerebral blood flow (ml/100 g/min) at pre-test relative to post-test for each region and mode.

	Pre-test	Post-test	*t*	*p*	d_{rm} [95% CI]
Global gray matter					
Active control	65.7 ± 6.8	63.4 ± 6.9	4.0	< 0.001	0.31 [0.15 to 0.47]
Exercise	66.0 ± 6.8	63.6 ± 6.2	4.1	< 0.001	0.39 [0.19 to 0.58]
Left frontoparietal network					
Active control	71.1 ± 7.6	68.3 ± 7.7	4.5	< 0.001	0.33 [0.17 to 0.48]
Exercise	71.3 ± 7.9	69.2 ± 7.6	3.3	0.001	0.29 [0.11 to 0.46]
Right frontoparietal network					
Active control	64.3 ± 7.3	61.9 ± 7.8	3.7	< 0.001	0.31 [0.14 to 0.48]
Exercise	64.8 ± 7.4	62.0 ± 7.3	4.3	< 0.001	0.38 [0.20 to 0.56]
Executive control network					
Active control	64.2 ± 7.3	62.4 ± 7.1	3.0	0.004	0.26 [0.08 to 0.43]
Exercise	64.2 ± 7.3	61.7 ± 7.5	4.3	< 0.001	0.33 [0.17 to 0.48]
Motor network					
Active control	53.2 ± 5.4	52.3 ± 5.7	1.5	0.1	0.16 [−0.06 to 0.38]
Exercise	53.7 ± 5.8	52.2 ± 5.0	2.4	0.02	0.25 [0.04 to 0.46]

Note: t-tests reflect the difference in cerebral blood flow between pre-test and post-test for each experimental condition for each neural region. The change in cerebral blood flow in the motor network in response to exercise did not remain significant following false discovery rate control (Benjamini-Hochberg critical alpha = 0.02). No statistical difference in cerebral blood flow was observed between the active control and exercise conditions for either pre-test or post-test, *t's* (34) ≤ 0.6, *p's* ≥ 0.5, d_{rm}*'s* ≤ 0.08 [95% CI: −0.21 to 0.32]. No interactions of Mode × Time were observed, *F's* (1, 37) ≤ 0.9, *p's* ≥ 0.3, f^2*'s* ≤ 0.03 [95% CI: 0.0 to 0.14].

Table 4
Statistical summary of whole-brain voxel-wise comparisons of cerebral blood flow (mL/100 g/min) at pre-test relative to post-test for each region and mode. Regions summarized below showed reduced cerebral blood flow from pre-to-post test.

Number of voxels	MNI coordinates (x,y,z) for peak	*t*-statistic cluster mean	Anatomical description of regions within cluster
Active control			
6345	−56,26,20	3.11	Left inferior frontal gyrus, extending across lateral prefrontal cortex, superior temporal gyrus, planum temporale, insular cortex, angular gyrus, and inferior temporal cortex
2821	68,−30,24	3.52	Right supramarginal gyrus, extending into middle and superior temporal gyrus and temporal pole
310	46,−8,6	3.03	Right posterior insular cortex
199	44,28,−2	3.52	Right frontal orbital cortex extending into anterior insula
197	8,46,2	3.66	Bilateral medial prefrontal cortex, paracingulate gyrus
40	−48,−46,48	3.05	Left supramarginal gyrus
Exercise			
8011	42,24,−24	3.04	Right temporal pole extending into planum temporale, superior temporal gyrus, angular gyrus, insular cortex, and right lateral frontal cortex
378	0,38,6	2.99	Bilateral anterior cingulate cortex
223	−60,6,−2	3.4	Left temporal pole extending into left insular cortex
223	−68,−26,2	3.54	Left superior temporal gyrus extending into planum temporale
199	10,−76,32	3.36	Right precuneus cortex extending into intracalcarine cortex
160	10,52,12	3.04	Right medial prefrontal cortex, paracingulate gyrus
77	44,−72,6	3.64	Right lateral occipital cortex
39	−34,18,2	3.4	Left anterior insula
33	−46,−12,4	3.46	Left posterior insula

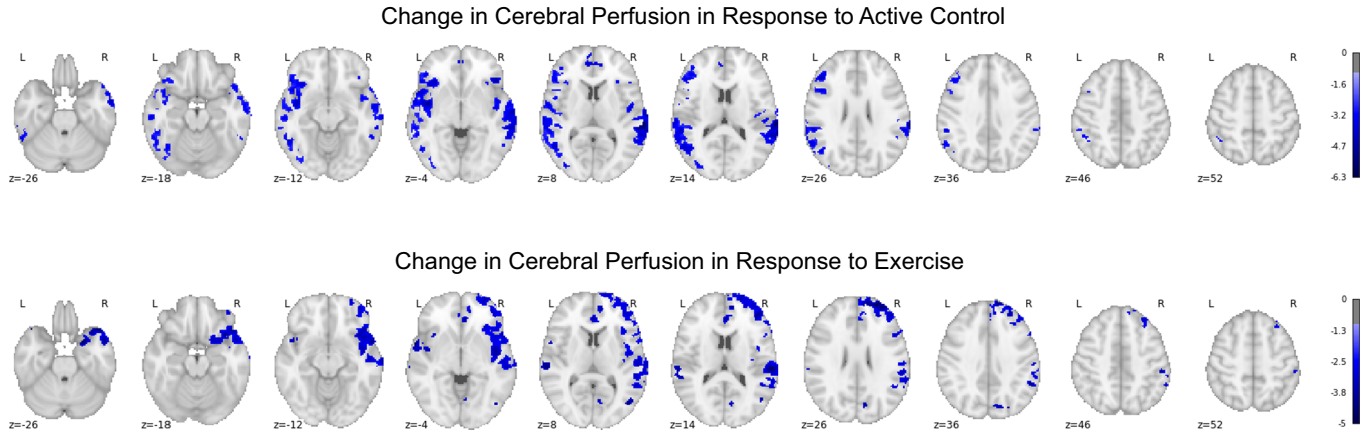

Fig. 3. Voxel-wise plot of the family-wise error corrected *t*-statistics for the difference in cerebral blood flow at post-test relative to pre-test overlayed onto the MNI152 template, in response to the active control and exercise conditions.

(2014). However, highlighting the importance of utilizing a control condition, findings from the present investigation demonstrate that such reductions in cerebral blood flow may not be the result of moderate intensity aerobic exercise in preadolescent children. It is important to note that the use of an active control experimental condition precludes ruling out 'physical activity' per se and/or locomotion as potentially inducing the reductions in cerebral blood flow observed within the present investigation. Nevertheless, as an active control condition, walking on the treadmill at the lowest-possible speed (0.5 mph) and grade (0%) satisfies two critical criteria: 1) it ensures that any differences were not the result of differences in body position between exercise and control conditions (Bode, 1991; Olufsen et al., 2004), and 2) it minimizes the potential influence of expectancy/demand characteristics whereby the outcome of the experiment may have been subconsciously altered by the participant to fit their hypothesized outcome given that they were recruited to take part in an exercise related study (Weber and Cook, 1972).

Although the physiological demands imposed by the active control condition (heart rate = 92 bpm [95% CI: 88.1 to 95.9]; heart rate reserve = 23.2% [95% CI: 20.5 to 25.8]) technically fall within the tail end of the light physical activity classification (20 to < 40% of heart rate reserve; American College of Sports Medicine, 2014), it is important to highlight that in this investigation resting heart rate was recorded in a supine rather than sitting position which may have artificially elevated the heart rate reserve calculations given the effect of body position on autonomic regulation (Watanabe et al., 2007). Accordingly, the physiological demands of the active control condition based upon the mean heart rate are more consistent with activities of daily living such as domestic or academic tasks than with what is typically construed as 'exercise' (Norton et al., 2010). Although previous research in both children and adults has demonstrated that increases in cerebral blood flow during exercise exhibit a curvilinear relationship with the greatest increases occurring during moderate intensity exercise (Ellis et al., 2017; Rooks et al., 2010; Smith and Ainslie, 2017), it is important to note that children exhibit a more generalized increase in cerebral blood flow across a wide range of exercise intensity (Ellis et al., 2017). Thus, future research is necessary to examine the extent to which modulations in cerebral blood flow may persist following the cessation of exercise when examined relative to other suitable control conditions as well as in response to a sedentary condition. Nevertheless, the finding that gray matter cerebral blood flow was reduced following both the active control and exercise conditions warrants further examination. That is, at present it is unclear if such findings are the result of the motor-control demands involved with physical activity engagement - regardless of the intensity of the physical activity - or are the result of repeated assessments/acclimation to the MRI during each

session. However, such an effect may be important to consider for investigations utilizing blood-oxygen-level dependent contrast imaging given that reductions in cerebral blood flow may alter background levels of activation.

Despite the methodological strength of the present investigation, there are a number of limitations that warrant further discussion. First and foremost is the timing of the cerebral blood flow assessment following exercise. Within the present investigation, cerebral blood flow was assessed during the period approximately 23 min following each experimental condition. Although this timing largely overlaps with previous investigations that have observed exercise-induced enhancements in cognition during this period (Drollette et al., 2012; Pontifex et al., 2009; Sandroff et al., 2016; Tomporowski et al., 2005; Weng et al., 2015), further research is necessary to determine how rapidly modulations in cerebral blood flow incurred during moderate intensity exercise return to baseline following the cessation of the exercise stimulus. It is important to point out, however, that the present investigation did not assess cerebral blood flow during exercise. Thus, while it is inferred that cerebral blood flow was enhanced during moderate-intensity exercise given this well-established finding (Rooks et al., 2010; Smith and Ainslie, 2017); further research is necessary to determine to what extent the magnitude of the cerebral blood flow enhancement during exercise as well as the intensity of the exercise bout impact upon how long after the cessation of exercise such modulations in cerebral blood flow persist.

Further research is also necessary in order to provide a greater understanding of the extent to which modulations in cerebral blood flow, both during and following exercise, are moderated by individual differences such as aerobic fitness. That is, a growing body of evidence in older adults has demonstrated that aerobic fitness is associated with greater resting-state cerebral blood flow (Ainslie et al., 2008; Brown et al., 2010). While such findings have not yet been demonstrated in preadolescent populations, such a higher baseline cerebral blood flow may influence the effects of a single bout of exercise. Although the research design of the present investigation largely mitigates the potential for other systematic bias to be introduced, further research should investigate the extent to which cerebral blood flow modulates in response to other factors such as sleep, caffeine consumption, and hydration status. Additionally, although the present investigation set the target exercise intensity based upon the percent of age-predicted maximal heart rate - consistent with methods employed previously in the acute exercise and cognition literature; further research is necessary to determine the extent to which modulations in cerebral blood flow may be observed by prescribing exercise intensity in relation to the percent of ventilatory threshold (Hall et al., 2010; Heck et al., 1985; Kashihara and Nakahara, 2005; McMorris, 2016). Such an approach would thus provide greater insight into the potential contribution of aerobic and anaerobic metabolism as they relate to modulations in cerebral blood flow.

Collectively, the present finding that cerebral blood flow may not be differentially modulated following the termination of the exercise stimulus exercise reduces the likelihood that cerebral blood flow may underlie post-exercise induced enhancements in cognition and alterations in neural activation. That is, speculatively, it may be that cognitive enhancements/neural alterations following exercise are more strongly related to modulations in cerebral blood flow that occur during the bout of exercise. Similarly, although the focus of the present investigation was on cerebral blood flow, modulations in cognition/neural activity following exercise could also relate to a cascade of other cerebral vascular responses (Ogoh and Ainslie, 2009). Clearly then, further research in this area is necessary to better understand those cerebral vascular factors that are influenced by acute bouts of exercise and to what extent such modulations relate to the cognitive enhancements and neural alterations following the cessation of the exercise bout.

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