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Cerebral blood flow and arterial transit time responses to exercise training in older adults

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ABSTRACT

Brain vascular health worsens with age, as is made evident by resting grey matter cerebral blood flow (CBF_{GM}) reductions and lengthening arterial transit time (ATT_{GM}). Exercise training can improve aspects of brain health in older adults, yet its effects on CBF_{GM} and ATT_{GM} remain unclear. This randomised controlled trial assessed responses of CBF_{GM} and ATT_{GM} to a 26 week exercise intervention in 65 healthy older adults (control: n = 33, exercise: n = 32, aged 60–81 years), including whether changes in CBF_{GM} or ATT_{GM} were associated with changes in cognitive functions. Multiple-delay pseudo-continuous arterial spin labelling data were used to estimate resting global and regional CBF_{GM} and ATT_{GM}. Results showed no between-group differences in CBF_{GM} or ATT_{GM} following the intervention. However, exercise participants with the greatest cardiorespiratory gains (n = 17; ΔVO_{2peak} >2 mL/kg/min) experienced global CBF_{GM} reductions (-4.0 [-7.3, -0.8] mL/100 g/min). Cognitive functions did not change in either group and changes were not associated with changes in CBF_{GM} or ATT_{GM}. Our findings indicate that exercise training in older adults may induce global CBF_{GM} reductions when high cardiorespiratory fitness gains are induced, but this does not appear to affect cognitive functions.

1. Introduction

The global population is ageing rapidly (United Nations Department of Economic and Social Affairs, Population Division, 2022). With age, inevitably, comes cognitive decline, which can hinder the ability to live independently and maintain quality of life (Salthouse, 2012; Stites et al., 2018). Adverse age-related changes to cerebral haemodynamics, notably cerebral hypoperfusion (Damestani et al., 2023), may contribute to cognitive decline in older adults (De Vis et al., 2018; Ebenau et al., 2023; Wolters et al., 2017; van Dinther et al., 2023). Regular exercise is considered an essential strategy to maintain brain health in later life because it benefits cognitive functions (Barha et al., 2017; Northey et al., 2018) and dementia risk (Tari et al., 2019). Exercise-induced brain health benefits have been attributed to a multitude of factors, including neurogenesis, angiogenesis, neuroinflammation, and neural plasticity (Chen and Nakagawa, 2023; Lu et al., 2023). However, despite the observed associations between cerebral haemodynamics and cognitive functions, the effects of exercise training on cerebral haemodynamics in older adults remain poorly understood (Kleinloog et al., 2023).

Alongside grey matter cerebral blood flow (CBF_{GM}) reductions, arterial transit time (ATT_{GM}) also typically worsens (i.e., lengthens) with age (Damestani et al., 2023), though ATT_{GM} prolongation has been associated with greater cardiorespiratory fitness (Feron et al., 2024). ATT_{GM} is the time taken for blood to travel from large arteries in the neck to the cerebral tissue. Prolonged ATT_{GM} is associated with impaired cerebrovascular reactivity (Takata et al., 2023) and atherosclerotic risk

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(Hafdi et al., 2022), and is present in patients with Alzheimer's disease (Sun et al., 2022) or cerebral artery stenosis (Yu et al., 2022). Arterial spin labelling (ASL) is an MRI sequence that can estimate both CBF_{GM} and ATT_{GM} if data are acquired at multiple post-labelling delays. Using multiple post-labelling delays also improves CBF_{GM} estimation accuracy by enabling adjustment for regional and individual differences in ATT_{GM} (Dai et al., 2017). Despite this, compared with single-delay ASL, only a minority of ASL studies have utilised this technique due to increased data collection time and processing requirements, although shorter multiple-delay sequences are now available (Woods et al., 2024).

Exercise training induces favourable changes in arterial stiffness, endothelial function, blood pressure, body composition, and grey matter volume (Erickson et al., 2014; Hellsten and Nyberg, 2015; Slentz et al., 2005). Despite these variables being associated with higher resting volumetric CBF (Poels et al., 2008; Sabayan et al., 2014) or CBF_{GM} (Jefferson et al., 2018; Leidhin et al., 2021), and evidence that long-term exercise training may reduce age-related declines in regional (Tarumi et al., 2013; Thomas et al., 2013) and global (Sugawara et al., 2020) CBF_{GM}, there is limited data for training-induced CBF_{GM} increases in healthy older adults. For example, exercise training for eight or twelve weeks increased CBF_{GM} in small regions (Alfini et al., 2019; Chapman et al., 2013; Kleinloog et al., 2019; Maass et al., 2015); however, regional CBF_{GM} decreases were also present (Kleinloog et al., 2019; Maass et al., 2015). Furthermore, global effects in whole-brain CBF (Chapman et al., 2013) or CBF_{GM} (Flodin et al., 2017; Kleinloog et al., 2019; Maass et al., 2015) have not been observed. Interestingly, evidence that a one-year exercise intervention increased global volumetric CBF in older adults (Tomoto et al., 2023) and that a one-year weight loss intervention (diet and exercise) induced widespread CBF_{GM} increases in overweight/obese middle-aged adults (Stillman et al., 2021) indicates that longer interventions may be required to induce global effects. Differences in the exercise intervention, CBF measurement technique, or the regions investigated may explain discrepancies in results. All, except two (Maass et al., 2015; Tomoto et al., 2023), aforementioned studies measured CBF with ASL, but none used multiple post-labelling delays.

Regarding ATT_{GM}, to our knowledge, no studies have investigated responses to exercise training. Two cross-sectional studies assessed the relationship between cardiorespiratory fitness and ATT_{GM} in older adults, with one reporting no correlation ($n = 14$) (Burley et al., 2021) and the other unexpectedly reporting higher cardiorespiratory fitness was associated with longer ATT_{GM} in parietal and occipital regions ($n = 77$) (Feron et al., 2024). Furthermore, exercise training-induced changes to cerebral blood velocity, which is inversely related to ATT_{GM} (Burley et al., 2021), are also unclear (Kleinloog et al., 2023; Smith et al., 2021). Exercise training studies are required to improve understanding of ATT_{GM} responses.

The present randomised controlled trial used multiple post-labelling delay ASL to investigate responses of resting CBF_{GM} and ATT_{GM} to home-based exercise training in older adults, and assessed if any changes were associated with training-induced cognitive improvements. High-intensity interval training was performed, hypothesised to induce superior cerebrovascular and cognitive benefits due to repeated lactate exposure (El Hayek et al., 2019; Morland et al., 2017). Exercise training was hypothesised to increase cardiorespiratory fitness and CBF_{GM}, lengthen ATT_{GM}, and improve cognitive functions. Furthermore, anticipated changes in CBF_{GM} and ATT_{GM} within the exercise group were hypothesised to be associated with improvements in cardiorespiratory fitness and cognitive functions.

2. Materials and methods

The data for the present study were collected as part of a larger study, The FAB Project (preregistration: https://osf.io/6fqg7, materials and data: https://osf.io/d7aw2/). The data in the present study are from a sub-group of a larger shared participant cohort, had unique outcome measures to other publications related to the project (Fernandes et al., 2024; Feron et al., 2024; Fosstveit et al., 2024; Rahman et al., 2023) and addressed *a priori* questions (as per preregistration). The study was approved by the STEM Ethical Review Committee at the University of Birmingham (ERN_20–1107). Before taking part in this study, participants were provided with a participant information sheet and provided their informed consent.

2.1. Study design

Participants were screened for eligibility before completing three experimental sessions (cognitive, MRI, and exercise sessions). Participants were randomised to control or exercise groups after the cognitive session. Participants then entered a 26 week intervention period, before returning to complete the same three experimental sessions, but in the reverse order. Post-intervention exercise and MRI sessions were conducted within a two week period, starting on the first day of the final intervention week, achieved for 53 % and 88 % of the control and exercise group, respectively. Pre-intervention sessions were completed within 5.4 ± 3.2 and 4.5 ± 2.5 weeks and post-intervention sessions were completed within 2.8 ± 2.3 and 1.8 ± 1.3 weeks for control and exercise groups, respectively. Mean duration between the start of the intervention period and the start of post-intervention experimental sessions were 26.3 ± 1.9 and 27.8 ± 2.9 weeks for the control and exercise groups, respectively. Participants were asked to refrain from vigorous physical activity for 24 h prior to the MRI session and obtained from caffeine for 1.5 h prior to the ASL measures, because these can acutely alter CBF (Clement et al., 2018).

2.2. Participants

Ninety-four healthy older adults entered the study, participant flow is shown in Fig. 1. Participants were aged 60–81 years, cognitively normal, without historic or current diagnosis of serious health conditions, non-smokers, and self-reported to not meet recommended global activity guidelines (Bull et al., 2020). Of these, 77 had pre-intervention ASL data, nine dropped out of the intervention, and post-intervention ASL data was unusable for a further three, leaving a sample of 65 older adults (characteristics in Table 1). Full inclusion criteria and health screening procedure (resting electrocardiogram, blood pressure, and cognitive assessment) can be found in Section 1 of the Supplemental Material.

2.3. 26 week intervention

Control participants were asked to continue living their normal life (i.e., avoid making significant changes to their physical activity and dietary habits).

Exercise participants completed a 26 week unsupervised home-based high-intensity interval training programme involving two interval and one circuit training sessions each week (Fosstveit et al., 2024). Participants had regular contact and feedback from the researcher (every 1–2 weeks), but more so during the familiarisation period (weeks 1–4). Participants completed a logbook and were given a fitness watch (Polar Unite, Finland) and chest heart rate monitor (Polar H9, Finland) to monitor real-time heart rate and record each session. Exercise intensity was guided using the percentage of peak heart rate ($\%HR_{peak}$) achieved during the pre-intervention cardiorespiratory fitness test.

Interval sessions involved alternating between two minutes of high-intensity exercise and active recovery. Participants were attempting to reach >80 $\%HR_{peak}$ by the end of each high-intensity interval. The majority opted to walk uphill, jog, or run. Participants started with five intervals per session, the workload progressively increased and finished with ten intervals. Circuit sessions involved six body-weight exercises (squats, high-knees, step-ups, press-ups, reverse lunges, and mountain climbers). Participants progressed from completing one to three sets of each exercise per session during the familiarisation and then completed

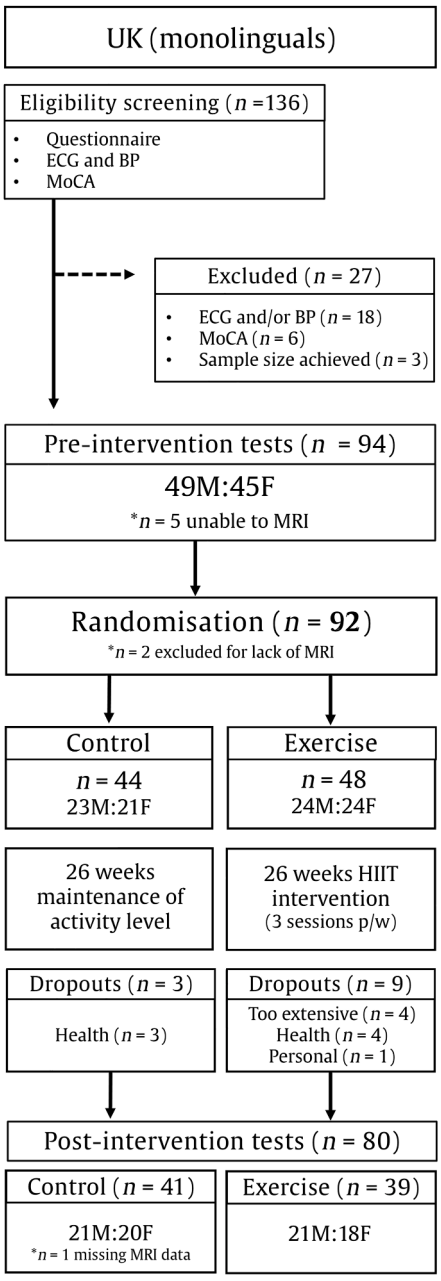

Fig. 1. CONSORT diagram of participant flow. BP: blood pressure, ECG: electrocardiogram, HIIT: high-intensity interval training, MoCA: Montreal Cognitive Assessment, MRI: magnetic resonance imaging.

3 × 45 second sets in weeks 5–26, aiming to perform as many repetitions as possible and reach >80 $\%HR_{peak}$ by the end of each set. Further exercise intervention details, including progressive overload (Tables S1 and S2) and example heart rate graphs (Figure S1), can be found in Section 2 of the Supplemental Material.

2.4. Intervention adherence

Detailed adherence methodology can be found in Section 2 of the Supplemental Material.

Physical activity levels in the control group were objectively measured during the first, middle, and final week of the intervention period using a waist-worn accelerometer (GT3X+, ActiGraph Inc., USA), categorised as minutes per day of sedentary behaviour, light physical activity (LPA), and moderate-to-vigorous intensity physical activity (MVPA) (Troiano et al., 2008).

Table 1
Participant characteristics.

	Control	Exercise
n (male:female)	33 (16:17)	32 (17:15)
Age (years)	65±5	66±5
Highest education level reached (%)		
Compulsory	27	25
Further	27	38
Undergraduate	27	9
Postgraduate	18	28
Resting SBP (mmHg)	141±14	139±12
Resting DBP (mmHg)	82±8	83±7
BMI (kg/m^2)	27.9 ± 4.1	26.2 ± 2.3
VO_{2peak} (mL/kg/min)	27.6 ± 3.5	27.8 ± 4.3

Values represent means ± standard deviation. BMI: body mass index, DBP: diastolic blood pressure, SBP: systolic blood pressure, VO_{2peak}: peak oxygen consumption.

In the exercise group, the logbook and heart rate recordings for each session enabled accurate determination of the number of sessions completed, session duration, and heart rate (mean, peak, and zones) for each participant. Adherence was calculated for a variety of metrics as the percentage completion relative to what was planned. The primary metric was adherence to cumulative metabolic equivalents minutes (MET-mins) during the intervention period (Nilsen et al., 2018). MET-mins for each session were calculated by multiplying session duration by the MET value corresponding to the mean $\%HR_{peak}$ of each session (Garber et al., 2011). Heart rate-specific MET values (Table S3) were calculated based on American College of Sports Medicine (ACSM) guidelines (Garber et al., 2011).

2.5. Outcome measures

2.5.1. Cardiorespiratory fitness

Participants completed an incremental exercise test on a treadmill (Pulsar 3p, H/P/Cosmos, Germany). Respiratory gases (VO_2: oxygen consumption, VCO_2: carbon dioxide production) were recorded continuously using a facemask (7450 V2, Hans Rudolph, USA) and metabolic cart (JAEGER Vyntus CPX, Vyaire, USA), as was heart rate and rhythm using a 12-lead ECG (Cardiosoft, Vyaire, USA). Rating of perceived exertion (RPE) (Borg, 1982) and finger-prick blood [lactate] (Biosen C-Line, EKF Diagnostics, United Kingdom) were measured between stages. Stages were 4 min with a 1 min rest period between each stage. Treadmill speed started and remained at 3.8 km/h until either all possible elevation stages were completed (4, 7, 10, 13, 16, 19, and 20 % gradient) or individual lactate threshold was reached (2.1 mmol/L increase over the mean of the two lowest values (Mamen et al., 2011)). If all elevation stages were completed, 4 min stages continued with speed increasing 0.5 km/h per stage until lactate threshold. After reaching lactate threshold, 1 min stages were completed where speed increased 0.5 km/h per stage (rest periods were removed). Figure S2 shows a treadmill test format example.

Participants were asked to exercise to volitional exhaustion unless halted by the researcher due to ECG abnormalities. Cardiorespiratory fitness was determined using peak oxygen consumption (VO_{2peak}) (i.e., mean of the two highest 30 s intervals). Five control and ten exercise participants completed a sub-maximal test at pre-intervention and/or post-intervention. For these participants, predicted VO_{2peak} values were used at both timepoints even if only one test was sub-maximal (for consistency). Predictions used individual sub-maximal VO_2 and heart rate data acquired from three of the first possible six stages using a linear regression. See Section 3 of the Supplemental Material for full details and example (Figure S3) of the prediction method.

2.5.2. MRI acquisition and analysis

The MRI scan sessions included structural, functional, and arterial

spin labelling (ASL) scans, using a 3-T system (MAGNETOM Prisma, Siemens, Germany) with 32-channel receiver head coil. Here, the focus is the ASL data and related scans, analysis of other data acquired can be found elsewhere (Rahman et al., 2023). CBF and ATT data were collected using pseudo-continuous ASL sequence with 3D GRASE readout (17:22 mins) (Kilroy et al., 2014; Wang et al., 2013), see also Acknowledgements. Participants were advised to remain awake during the scan but could choose to keep their eyes open or closed, although this was not formally monitored or recorded.

ASL imaging parameters were: repetition time (TR) = 4100 ms, echo time (TE) = 30.56 ms, in-plane resolution = 3.5 mm^2, slice thickness = 3.5 mm, transversal slices = 32, field of view (FOV) = 224×224 mm, background suppression = yes, and post-labelling delays (PLD) = 200, 975, 1425, 1850, 2025, 2150, 2250, and 2300 ms. Four and twelve volumes of data were acquired for PLD of 200–2250 ms and 2300 ms, respectively. PLD times and number of volumes acquired were optimised according to recommendations (Woods et al., 2019). Slices were positioned axially from the motor cortex and angled anterior-posterior in line with the participant's anterior-posterior commissure (ACPC). A calibration M0 scan was acquired using these same parameters with the PLD set to 2000 ms with PCASL and background suppression disabled. The T1-weighted structural scan (4:54 mins) was acquired to facilitate data analysis including, normalisation to a standard template brain and differentiation of grey and white matter. Structural T1-weighted (MPRAGE) imaging parameters were: TI = 880 ms, TE = 2.03 ms, TR = 2000 ms, voxel size = 1 mm^3, sagittal slices = 208, FOV = 256×256×208 mm, and flip angle = 8°

ASL data were processed using the Oxford ASL toolbox (https://oxasl.readthedocs.io/en/latest/), which uses the FSL FABBER ASL package and Bayesian Inference to invert the kinetic model for ASL MRI (BASIL) to compute CBF and ATT maps (Chappell et al., 2009; Groves et al., 2009; Woolrich et al., 2006). Parameters input to the kinetic models to estimate CBF and ATT were: bolus duration = 1.5088 s, tissue T1=1.3 s, arterial blood T1 = 1.65 s, labelling efficiency = 0.85. All other input parameters were kept with default settings appropriate to PCASL acquisition. Partial volume error correction and adaptive spatial smoothing of the perfusion maps was performed using default settings in oxford_asl (Chappell et al., 2011; Groves et al., 2009).

Global and regional analysis was performed, assessed in native (individual participant) and MNI space, respectively. All CBF and ATT values refer to grey matter only. The number of voxels included in native space images at pre- and post-intervention were 12,322±933 and 12,449±1001 or 12,581±1228 and 12,486±1316 for control or exercise groups, respectively. Regions of interest were the cingulate gyrus and frontal, parietal, temporal, occipital, and motor cortices (Figure S4). Only participants with useable ASL data in both native and MNI space were included in analyses ($n = 65$). Native space difference maps at each PLD for each participant were visually inspected to ensure data quality. Particular attention was paid to ensure there were no: 1) excessive motion resulting in spurious edge effects in difference maps; 2) brain territories which did not appear to be perfused, due to suboptimal label positioning or unaccounted for vasculature; and 3) focal areas of high intensity in final CBF maps which would have suggested that the PLDs were insufficient. Seven participants were excluded for poor ASL data after visual inspection, difference maps from two exemplar excluded participants are shown in Figure S5. One further participant was excluded for poor MNI registration due to brain atrophy. Section 4 of the Supplemental Material contains additional information regarding data quality assessment and grey matter mask configuration.

2.5.3. Cognitive functions

Working memory: In a 2-back task, participants were presented a 3 × 3 grid. The stimulus was a single white square that continuously appears, disappears, and then reappears in one of the grid squares at random ($n = 60$ trials, 1 s each). Participants identified when the white square appeared in the same location as it did two trials prior. Trials were excluded from analysis if incorrect or if response time <200 ms or greater than two standard deviations above/below the mean per participant. The primary outcome measure was *d* prime (*d*'), a measure of discriminability, a greater *d*' indicates superior performance.

Attentional Network Task (ANT): The computerised ANT assessed orienting, alerting, and executive control. The stimulus is a row of five arrows, each pointing left or right. As fast and as accurately as possible, participants reported the direction of the centre arrow using the left and right arrow keys. A central fixation cross is displayed for 400 ms, then a fixation cross (500 ms) and cue (100 ms) are presented simultaneously, and then only the fixation cross is displayed for a further 400 ms. A stimulus is then shown for a maximum of 1700 ms. The centre arrow can be congruent or incongruent (i.e., pointing in the same or opposite direction as the flankers, respectively; $n = 96$ each), or neutral (i.e., central arrow flanked by target-irrelevant black blocks, $n = 96$). The stimulus can appear above or below the fixation cross, cued by a black square ($n = 216$) or not cued ($n = 72$). There are three cue conditions: a spatial cue, a centre cue, or a double cue ($n = 72$ each). The spatial cue indicates if the stimulus appears above or below the fixation cross, whereas the stimulus location remains ambiguous for the centre and the double cue. Twelve practice trials are followed by three blocks of 96 trials.

Trials were excluded from analysis if incorrect or if response time <200 ms or greater than two standard deviations above/below the mean per participant. Alerting scores were calculated as the no cue minus the double cue; Orienting scores by centre cue minus the spatial cue; Executive control scores were calculated by the incongruent target minus the congruent target (all for correct responses). High condition difference scores for alerting and orienting, and low condition difference scores for executive control, indicate better performance.

Processing speed: In a letter comparison task, participants were simultaneously presented with two strings of letters at the top and bottom of the screen, for a maximum of 2500 ms after presentation of a fixation cross (1000 ms). Strings were three or six characters long ($n = 48$ trials, 24 each). As fast and as accurately as possible, participants identified whether the strings were the same or different. Mean response time and accuracy were calculated for each participant using data from trials involving only six-character strings. Trials were excluded from analysis if incorrect or if response time <200 ms or greater than two standard deviations above/below the mean per participant.

2.6. Statistical analyses

The intention-to-treat principle was used: analysis was performed with all data, excluding dropouts, according to the original group allocation, despite adherence variations. All regressions used absolute changes, were completed separately for the control and exercise groups, and regional *P*-values were adjusted for multiple comparisons using the Bonferroni correction.

A mixed-design ANOVA compared within- and between-group differences in BMI and cardiorespiratory fitness (VO_{2peak}), including age and sex as covariates (SPSS Statistics v.29, IBM, USA). A separate mixed-design ANOVA compared differences in global and regional CBF_{GM} and ATT_{GM}, including age, sex, and pre-intervention BMI as covariates (SPSS Statistics v.29, IBM, USA). Variation in training-induced VO_{2peak} response was anticipated (Bouchard et al., 1999) and therefore sub-group analyses were planned by separating the exercise group into high and low VO_{2peak} response groups, stratified according to one standard deviation greater than the mean VO_{2peak} change of the control group.

Multiple linear regressions using RStudio (RStudio Team, 2021) assessed associations between changes in CBF_{GM} or ATT_{GM} and cardiorespiratory fitness. Dependant variables were ΔCBF_{GM} or ΔATT_{GM} with age, sex, ΔBMI, and ΔVO_{2peak} as independent variables. BMI has strong associations with both CBF_{GM} and ATT_{GM} (Feron et al., 2024) and thus was included as a covariate in these analyses because, despite randomisation, the exercise group had a significantly lower BMI at

pre-intervention (~−1.7 kg/m^2) and experienced significant BMI reductions at post-intervention (−0.4 ± 0.8 kg/m^2).

Two control and six exercise participants had incomplete cognitive data sets leaving 57 participants for analysis. A mixed-design ANOVA compared differences in processing speed (accuracy and response time), working memory (*d'*), and the three attentional domains (alerting, orienting, and executive control scores), including age, sex, and education as covariates (SPSS Statistics v.29, IBM, USA). Multiple linear regressions using RStudio (RStudio Team, 2021) assessed associations between changes in cognitive functions and VO_{2peak}, CBF_{GM} or ATT_{GM}. The dependent variable was either ΔVO_{2peak}, ΔCBF_{GM}, or ΔATT_{GM}, while independent variables were age, sex, education, and the change of the aforementioned six cognitive measures.

3. Results

3.1. Intervention adverse events, dropouts, and adherence

Overall, there were no serious adverse events resulting from the study and there were nine dropouts (one control and eight exercise participants), leaving $n = 65$ for primary analyses. Adherence to the exercise programme was high. Percentage adherence of the exercise group for cumulative MET-mins, sessions per week, and minutes >80 % HR_{peak} per session were 90±20 %, 87±15 %, and 92±56 %. In the control group, participants did not substantially change their normal physical activity levels. Further details can be found in the Section 5 of the Supplemental Material.

3.2. Changes in cardiorespiratory fitness and BMI

There was a significant group × time interaction for VO_{2peak} ($F_{1,61} = 17.4$, $P < 0.001$) and BMI ($F_{1,61} = 4.4$, $P = 0.041$). Specifically, VO_{2peak} increased from pre-to-post in the exercise group (descriptive: 2.2 ± 2.3 mL/kg/min or 8.3 ± 9.1 %, estimated: 2.2 [1.4, 3.0] mL/kg/min), whereas the control group did not change (Table 2). However, Fig. 2 highlights the inter-individual variability in VO_{2peak} responses to the exercise intervention. Regarding BMI, compared to the control group, BMI of the exercise group was significantly lower at both pre- and post-intervention, and the exercise group exhibited a significant reduction in BMI from pre-to-post (descriptive: −0.4 ± 0.8 kg/m^2, estimated: −0.4 [−0.6, −0.1] kg/m^2) whereas the control group did not change (Table 2).

3.3. Pre-to-post intervention changes in CBF_{GM} and ATT_{GM}

There were no significant group × time interactions for global or regional CBF_{GM} or ATT_{GM} (Table 2). Fig. 3 highlights the inter-individual variability in global CBF_{GM} and ATT_{GM} responses for both groups. Repeating analyses after excluding exercise participants with <80 % cumulative MET-mins adherence ($n = 7$) did not affect results. Descriptive means at pre-intervention, post-intervention, and for pre-to-post intervention change are shown in Table 2. See Figure S6 for pre- and post-intervention CBF maps. Comparisons of individual changes in VO_{2peak} (Fig. 2) and CBF_{GM} or ATT_{GM} (Fig. 3) were also explored and are shown in Figure S7.

The exercise group was stratified into high and low VO_{2peak} response groups (<2 or >2 mL/kg/min, respectively), based upon control group VO_{2peak} change (−0.2 ± 2.2 mL/kg/min). A two-tailed one-sample T-test showed the mean global CBF_{GM} change of the high VO_{2peak} response group ($n = 17$, 9M:8F, $\Delta VO_{2peak} = 4.0 \pm 1.4$ mL/kg/min) was significantly different from zero ($\Delta CBF_{GM} = -4.0 \pm 6.3$ [−7.3, −0.8] mL/100 g/min; $t_{16} = 2.6$, $P = 0.018$), whereas the low VO_{2peak} response group ($n = 15$, 8M:7F, $\Delta VO_{2peak} = 0.2 \pm 1.0$ mL/kg/min) was not ($\Delta CBF_{GM} = 1.7 \pm 10.7$ [−4.2, 7.7] mL/100 g/min; $t_{15} = 0.6$, $P = 0.545$) (Fig. 4A). Changes in ATT_{GM} were not significantly different from zero in either group (Fig. 4B). Figure S8 provides maps of pre-to-post intervention changes in CBF_{GM} for control and exercise groups that show widespread CBF_{GM} reductions for the exercise group, which are more pronounced in the high VO_{2peak} response group.

Table 2
Mean changes in cardiorespiratory fitness, CBF_{GM}, and ATT_{GM} to the control and exercise intervention.

	Control ($n = 33$)			Exercise ($n = 32$)		
	Pre	Post	Δ	Pre	Post	Δ
BMI (kg/m^2)	27.9 ± 4.1	27.9 ± 4.3	0.0 ± 0.7	26.2 ± 2.3*	25.8 ± 2.2*#	−0.4 ± 0.8
VO_{2peak} (mL/kg/min)	27.6 ± 3.5	27.4 ± 3.2	−0.2 ± 2.2	27.8 ± 4.3	30.0 ± 4.3*#	2.2 ± 2.3
CBF_{GM} (mL/100 g/min)						
Global	62.7 ± 13.2	63.6 ± 12.0	1.0 ± 8.6	62.2 ± 11.2	60.8 ± 9.8	−1.3 ± 9.0
Frontal	77.8 ± 17.6	79.3 ± 16.4	1.5 ± 12.4	78.5 ± 18.1	76.4 ± 13.6	−2.1 ± 15.9
Parietal	85.5 ± 19.3	86.1 ± 17.6	0.6 ± 13.6	84.3 ± 18.1	82.2 ± 14.0	−2.2 ± 13.1
Temporal	56.2 ± 13.3	57.4 ± 11.9	1.2 ± 7.4	55.5 ± 10.2	53.5 ± 9.3	−2.0 ± 7.9
Occipital	79.1 ± 20.3	80.1 ± 19.2	0.9 ± 15.1	76.1 ± 14.8	74.5 ± 13.9	−1.5 ± 10.2
Motor	95.0 ± 21.2	96.1 ± 19.5	1.1 ± 15.5	90.3 ± 19.0	88.8 ± 15.4	−1.5 ± 15.3
Cingulate	90.1 ± 21.1	90.4 ± 18.0	0.3 ± 12.8	87.9 ± 18.9	85.3 ± 15.0	−2.6 ± 14.8
ATT_{GM} (s)						
Global	1.41 ±0.19	1.40 ±0.17	−0.01 ±0.14	1.41 ±0.14	1.41 ±0.15	0.00 ±0.15
Frontal	1.38 ±0.15	1.38 ±0.15	0.00 ±0.13	1.37 ±0.13	1.38 ±0.15	0.02 ±0.13
Parietal	1.50 ±0.18	1.52 ±0.18	0.02 ±0.10	1.49 ±0.14	1.51 ±0.16	0.02 ±0.11
Temporal	1.26 ±0.14	1.26 ±0.13	0.00 ±0.11	1.26 ±0.11	1.26 ±0.12	0.00 ±0.12
Occipital	1.59 ±0.21	1.59 ±0.20	0.01 ±0.11	1.58 ±0.17	1.60 ±0.18	0.02 ±0.12
Motor	1.44 ±0.16	1.44 ±0.14	0.01 ±0.10	1.42 ±0.13	1.44 ±0.14	0.02 ±0.10
Cingulate	1.25 ±0.20	1.23 ±0.17	−0.03 ±0.18	1.24 ±0.16	1.24 ±0.15	−0.01 ±0.18

Values are descriptive means ± standard deviations. ATT_{GM}: grey matter arterial transit time, BMI: body mass index, CBF_{GM}: grey matter cerebral blood flow, VO_{2peak}: peak oxygen consumption, *: significant between-group difference at that timepoint ($P < 0.05$), #: significant within-group difference from pre-to-post ($P < 0.05$).

3.4. Associations between changes in CBF_{GM} or ATT_{GM} and cardiorespiratory fitness

Regression analysis over the whole exercise group ($n = 32$) revealed a non-significant negative trend between the absolute changes in global CBF_{GM} and cardiorespiratory fitness ($\beta = -0.33$ [−0.71, 0.06], $P = 0.093$) (Figure S9 and S10). A post-hoc analysis to identify if specific regions of the brain were driving this association identified that the association was strongest in the occipital region (Fig. 5 and Table S5). In the control group, absolute changes in global CBF_{GM} and cardiorespiratory fitness were not associated ($\beta = 0.28$ [−0.14, 0.71], $P = 0.187$; Figure S9). There were no significant associations between the absolute change in ATT_{GM} and cardiorespiratory fitness in the control (for all regions, $P > 0.12$) or exercise (for all regions, $P > 0.19$) group.

3.5. Changes in cognitive performance and associations with CBF_{GM} or ATT_{GM}

There were no significant group × time interactions for any of the

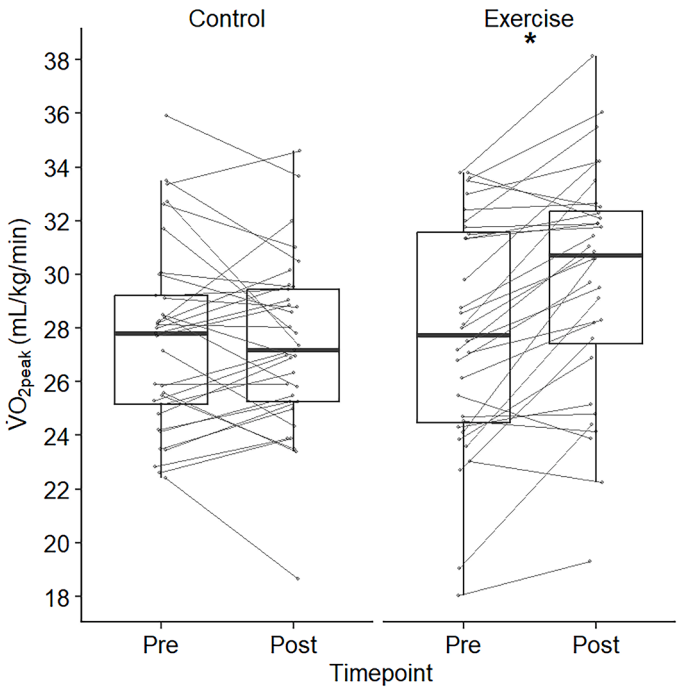

Fig. 2. Descriptive changes in cardiorespiratory fitness from pre-to-post intervention. Values are median (bold line) and interquartile range, with individual participant changes from pre-to-post intervention (grey lines). VO_{2peak}: peak oxygen consumption, *: significant difference from pre-to-post ($P < 0.05$).

cognitive measures, nor were changes in these measures associated with changes in cardiorespiratory fitness in either group. As with CBF_{GM} and ATT_{GM}, pre-to-post intervention changes in cognitive functions were assessed using one-sample T-tests for the high and low VO_{2peak} response groups separately, but these analyses did not find any meaningful differences (Table S6). Finally, there were no associations between changes in global CBF_{GM} or ATT_{GM} and any cognitive function measure in either group.

4. Discussion

The present 26 week home-based exercise intervention increased cardiorespiratory fitness and reduced BMI in healthy older adults. There were no between-group differences in pre-to-post intervention changes in CBF_{GM} or ATT_{GM}; however, exercise participants with the greatest gains in cardiorespiratory fitness experienced reductions in global CBF_{GM}. Neither group experienced changes in cognitive functions, nor were changes in cognitive functions associated with changes in VO_{2peak}, CBF_{GM}, or ATT_{GM} in either group. Collectively, these data indicate that exercise training induces widespread CBF_{GM} reductions in older adults when cardiorespiratory fitness gains are greater than 2 mL/kg/min, but these changes in cardiorespiratory fitness or CBF_{GM} were not associated with changes in cognitive functions.

4.1. Global CBF_{GM} was reduced in participants with a high cardiorespiratory fitness response

The cardiorespiratory fitness-dependant reductions in global CBF_{GM} observed in the present study indicate that for each 1 mL/kg/min increase in VO_{2peak}, global CBF_{GM} fell by −1.3 [−2.8, 0.23] mL/100 g/min ($P = 0.093$). Of note, given that global CBF_{GM} is reported to decrease by 3.1 ± 1.1 mL/100 g/min per decade of life (Damestani et al., 2023), the reductions observed in the high VO_{2peak} response group would equate to ~13 years of age-related changes. Thus, these shorter-term changes seem likely to reflect changes in brain vascular physiology that are different to those mediated via ageing.

All previous research has reported no changes to global CBF_{GM} following an 8 week (Kleinloog et al., 2019), 12 week (Alfini et al., 2019; Chapman et al., 2013; Maass et al., 2015), or 6 month (Flodin et al., 2017) exercise intervention in healthy older adults. Notably, these studies generally used shorter intervention periods and had smaller sample sizes than the present study, potentially limiting the time for CBF_{GM} changes to occur and the ability to analyse cardiorespiratory fitness-based sub-groups. Differences in CBF_{GM} of focal regions have been observed previously, with both increases (Alfini et al., 2019; Chapman et al., 2013; Kleinloog et al., 2019) and decreases (Kleinloog et al., 2019; Maass et al., 2015) reported. Only two previous studies have investigated relationships between changes in cardiorespiratory fitness and global CBF_{GM}, reporting either no association within control or exercise groups (Flodin et al., 2017), or a positive association within the exercise group (Maass et al., 2015). Interestingly, in opposition to present findings, a one-year exercise intervention increased global volumetric CBF (i.e., blood flow through large cerebral arteries normalised for total brain volume), and these increases were positively associated

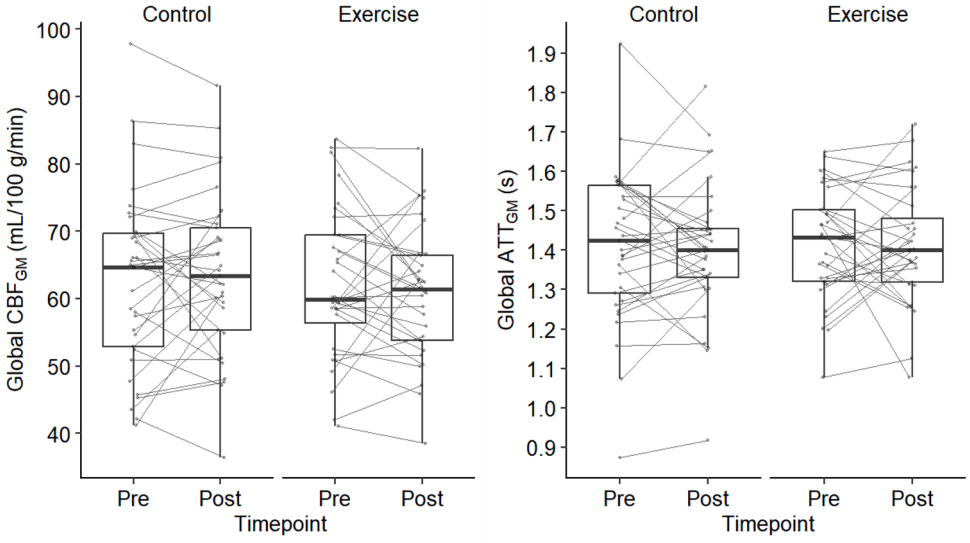

Fig. 3. Descriptive changes in global CBF_{GM} (left) and ATT_{GM} (right) from pre-to-post intervention. Values are median (bold line) and interquartile range, with individual participant changes from pre-to-post intervention (grey lines). CBF_{GM}: grey matter cerebral blood flow, ATT_{GM}: grey matter arterial transit time.

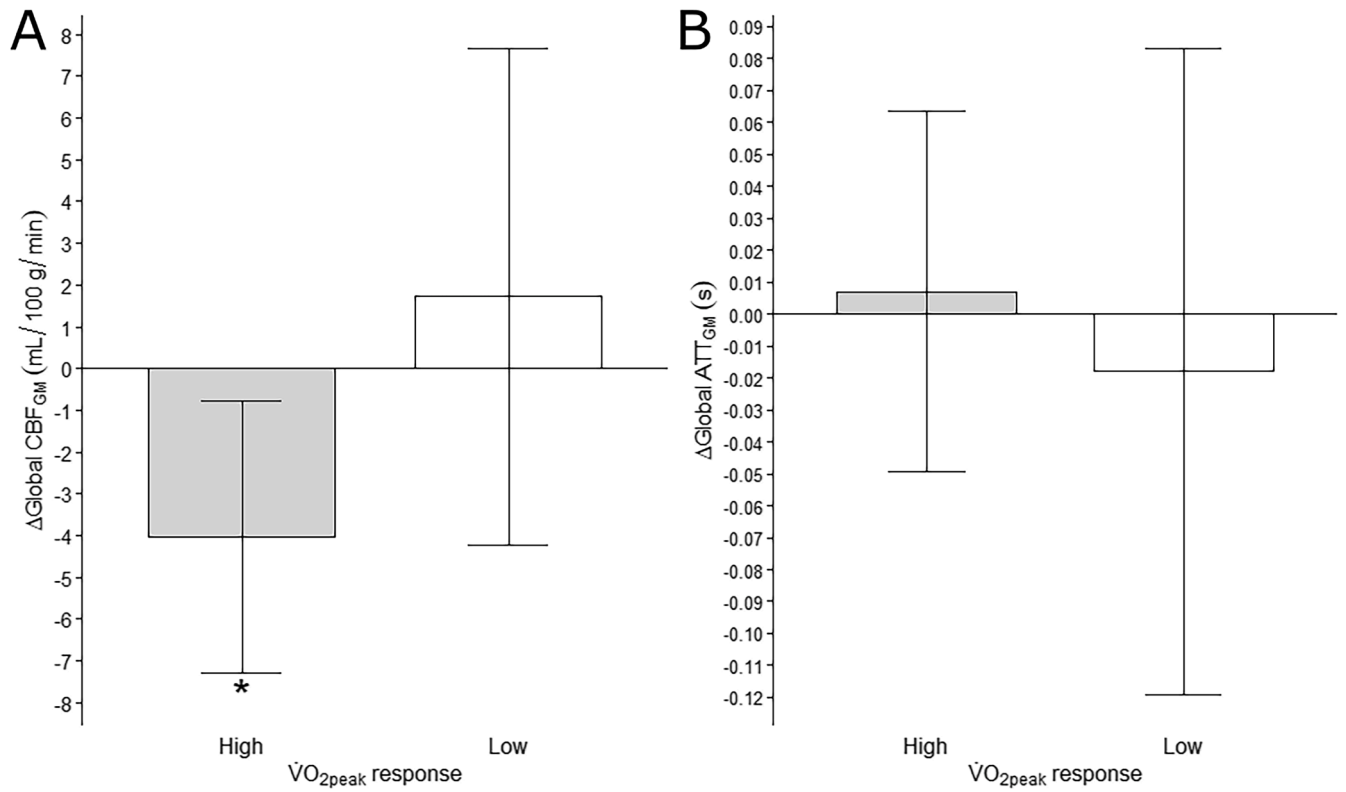

Fig. 4. Pre-to-post intervention change in global CBF_{GM} (panel A) and global ATT_{GM} (panel B) with 95 % confidence intervals from exercise group participants with either a high or low VO_{2peak} response to exercise training (i.e., >2 or <2 mL/kg/min increase, respectively). In the high group, but not the low, CBF_{GM} was significantly different from zero (−4.0 [−7.3, −0.8] mL/100 g/min). CBF_{GM}: grey matter cerebral blood flow, ATT_{GM}: grey matter arterial transit time, VO_{2peak}: peak oxygen consumption, *: significant difference from zero ($P = 0.018$).

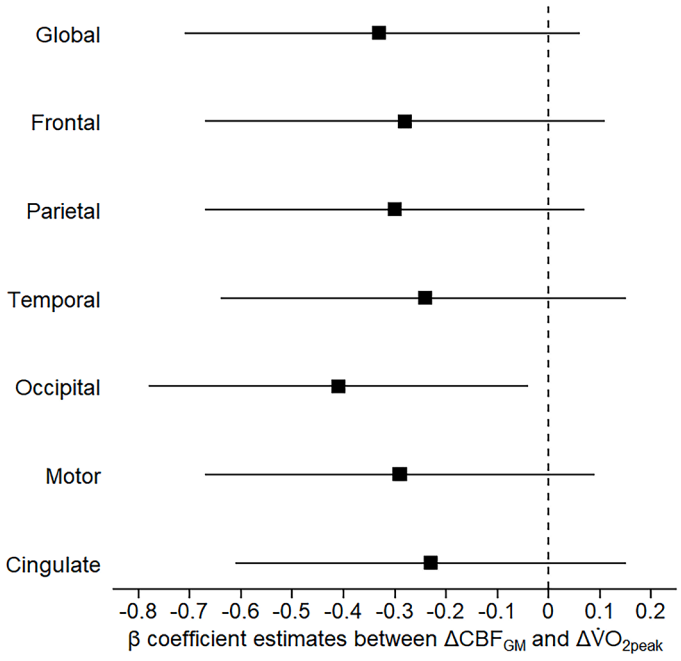

Fig. 5. Partial regression associations with 95 % confidence intervals between pre-to-post intervention changes in global or regional CBF_{GM} and cardiorespiratory fitness within the exercise group ($n = 32$), adjusted for age, sex, and ΔBMI. β: standardised beta coefficient, BMI: body mass index, CBF_{GM}: grey matter cerebral blood flow, VO_{2peak}: peak oxygen consumption.

with cardiorespiratory fitness changes within the exercise group (Tomoto et al., 2023). The present data also oppose single-delay ASL findings that masters athletes experience reduced age-related global CBF_{GM} declines (Sugawara et al., 2020) or have elevated regional CBF_{GM} compared to sedentary peers (Tarumi et al., 2013). However, it is possible that reduced CBF_{GM} is a short-term response which changes when training is maintained for longer periods (i.e. several years).

Regarding adherence, compared to the low response group, the high VO_{2peak} response group had higher percentage adherence for cumulative MET-mins, total session number, and minutes >80 $\%HR_{peak}$ per session by ~9 %, ~7 %, and ~30 %, respectively, though these differences were not statistically significant (T-tests, see Table S7). Notably, the largest adherence difference was to exercise intensity, rather than volume, whereby the high response group spent an additional 3.0 [−1.1, 7.2] mins/session >80 $\%HR_{peak}$. Indeed, the present study is the first to investigate CBF_{GM} responses to high-intensity interval training in healthy older adults, rather than a more traditional aerobic exercise intervention. Therefore, specifically high-intensity exercise training may induce more substantial cerebral adaptations, possibly related to repeated lactate exposure which is shown to mediate training-induced cerebral angiogenesis in rodents (Morland et al., 2017), which warrants further investigation.

4.2. *Mechanisms for exercise training-induced CBF_{GM} reductions*

Whilst the absolute reductions in CBF_{GM} observed are relatively small (−4.0 [−7.3, −0.8] mL/100 g/min) and oppose previous studies, they do align with literature investigating exercise training-induced peripheral blood flow changes. A putative explanation for this observation is that training-induced resting CBF_{GM} reductions could be a result of adaptations that improve cerebral oxygen extraction and/or utilisation, which occur during exercise training. This concept is true for

skeletal muscle, whereby exercise training can reduce blood flow during sub-maximal exercise (Proctor et al., 2001; Varnauskas et al., 1970) driven by improvements in oxygen extraction and metabolic efficiency (Bransford and Howley, 1977; Skattebo et al., 2020). Interestingly, a pilot study in young adult athletes reports a positive correlation between cardiorespiratory fitness and resting cerebral oxygen extraction of the right striatum (Bao et al., 2019) and 3 months exercise training reduced global cerebral metabolic rate of oxygen during sub-maximal exercise in overweight adults (Seifert et al., 2009).

Several possible exercise-induced adaptations could be contributing to CBF_{GM} reductions. For example, exercise training increases red blood cell count and [haemoglobin] in middle-aged adults (Sellami et al., 2021), subsequently increasing the oxygen carrying capacity of the blood (Mairbäurl, 2013). Furthermore, structural cerebrovascular changes are also evident, including a larger number of small cerebral vessels in masters athletes (Bullitt et al., 2009) and cerebral capillarisation in exercising rodents (Morland et al., 2017; Stevenson et al., 2020). Increased capillary density reduces diffusion distance, a key determinant of oxygen extraction (Dunn et al., 2016). Additionally, exercise training improves cerebral artery elasticity in middle-aged and older adults (Tarumi et al., 2013; Tomoto et al., 2023). Changes in cerebral arterial vessel diameters are essential for CBF regulation (Claassen et al., 2021) and thus increased vessel elasticity may improve CBF regulation efficiency. Regarding cerebral oxygen utilisation, exercise training in rodents increases cerebral mitochondrial number and function (Braga et al., 2021; Dominiak et al., 2022; Steiner et al., 2011). Similarly, in older adults, cardiorespiratory fitness is positively associated with *N*-acetyl-aspartate (NAA), a marker of neuronal integrity and metabolism (Erickson et al., 2012; Gonzales et al., 2013). Training-induced improvements to cerebral metabolic efficiency could also reduce blood flow requirements. Future research is required to determine whether cerebral oxygen extraction and/or utilisation changes in response to exercise training and if these are linked to changes in CBF, such as those observed here. Such changes could help explain the poorly understood mechanisms regarding exercise training-induced cognitive benefits.

4.3. Exercise training did not induce changes in ATT_{GM}

The present study is the first to investigate changes in ATT_{GM} following exercise training, reporting no changes in healthy older adults. Training-induced lengthening of ATT_{GM} was hypothesised based on cross-sectional data from the present cohort showing cardiorespiratory fitness was associated with longer ATT_{GM} in parietal and occipital regions (Feron et al., 2024). However, in line with the present data, cerebral blood velocity, which is inversely correlated with ATT_{GM} (Burley et al., 2021), was unaffected by a one-year exercise intervention in older adults (Tomoto et al., 2023), supporting the present findings.

Given that ATT_{GM} reflects the speed at which blood travels from large cerebral arteries to the grey matter tissue, the primary determinants are blood velocity and the vascular path length. Masters athletes have more small cerebral vessels and reduced cerebral vessel tortuosity (Bullitt et al., 2009). Theoretically, long-term training-induced small vessel angiogenesis could reduce overall blood velocity by increasing total vessel cross-sectional area, lengthening ATT_{GM}. Conversely, tortuosity reductions could shorten vascular path length, shortening ATT_{GM}. Regarding large artery cerebral blood velocity, both non-significant elevations (Bliss et al., 2023; Sugawara et al., 2020) and reductions (Zhu et al., 2013) in masters athletes have been reported. The present intervention may not have been intense or long enough to induce these types of structural adaptations that could affect blood velocity, vessel diameter, and vascular path length.

Another factor to consider is BMI, which has strong and widespread associations with both CBF_{GM} and ATT_{GM} (Feron et al., 2024). Although the present study reports CBF_{GM} changes in the absence of substantial changes in BMI or body mass (-1.1 ± 2.4 kg), this could be more relevant for ATT_{GM}. A one-year diet or diet and exercise intervention inducing ~10 kg losses lead to widespread CBF_{GM} increases in overweight or obese middle-aged adults (Stillman et al., 2021). Longer-term exercise interventions or interventions specifically targeting body mass in overweight older adults may have more pronounced effects on ATT_{GM}.

4.4. Changes to CBF_{GM} or ATT_{GM} were not associated with changes to cognitive functions

The present 26 week intervention did not induce changes to processing speed, working memory, or attention. Previous findings regarding training-induced cognitive improvements in older adults are inconsistent, with meta-analyses reporting a lack of (Kelly et al., 2014; Young et al., 2015) or beneficial effects (Barha et al., 2017; Colcombe and Kramer, 2003; Northey et al., 2018). Studies specifically involving six month interventions have reported cognitive improvements (Jonasson et al., 2017; Vidoni et al., 2015), although not by all (Brown et al., 2021). Interestingly, these reported cognitive benefits were seen in participants with lower baseline cardiorespiratory fitness than the present sample and thus experienced greater training-induced improvements (~9–28 % vs. 8.3 ± 9.1 %). Indeed, cardiorespiratory fitness gains, rather than the volume or intensity of exercise, is suggested to be most predictive of cognitive benefits (Voss and Jain, 2022). This has been shown in studies both with (Kovacevic et al., 2020; Vidoni et al., 2015) and without (Brown et al., 2021; Maass et al., 2015; Voss et al., 2012) group-level cognitive differences. However, associations with cardiorespiratory fitness changes were also absent in the present study. The present findings may be explained by the sample having not experienced significant age-related cognitive decline due to their health and education status (28 % of the exercise group achieved postgraduate education). Additionally, higher intensity exercise interventions (i.e., sprint intervals) may elicit stronger cognitive benefits because of greater exercise-induced lactate exposure, linked with learning and memory in rodents (El Hayek et al., 2019).

Given the lack of group-level changes in CBF_{GM}, ATT_{GM}, and cognitive functions, it is unsurprising that there were also no significant associations observed between changes in global CBF_{GM} or ATT_{GM} and any of the cognitive measures in either group. Previous research indicates that lower CBF_{GM} predicts cognitive decline over the longer term (i.e., years) in older adults (De Vis et al., 2018; Ebenau et al., 2023; van Dinther et al., 2023). As discussed, the exercise training-induced CBF_{GM} reductions observed may indicate improved cerebral oxygen extraction and/or utilisation. If so, these changes may not have been present long enough to induce detectable cognitive improvements, explaining the lack of associations. Alternatively, CBF_{GM} reductions are potentially only a short-term training response that changes over time, and these longer-term, training-induced changes to cerebral haemodynamics may be more predictive of cognitive functions. Additionally, other exercise-induced cerebral improvements may play a larger role in cognitive health, such as grey matter volume (Erickson et al., 2014), cerebral angiogenesis (Bullitt et al., 2009; Morland et al., 2017), or neuronal viability (Erickson et al., 2012).

4.5. Future directions and technical considerations

The present study's unexpected findings that exercise training induces CBF_{GM} reductions unveil new research questions. Primarily, 1) whether reductions are associated with changes in cerebral oxygen extraction and/or utilisation, and 2) whether reductions are a short-term response or persistent over longer-term exercise training (i.e., years). Furthermore, future research is warranted investigating whether ATT_{GM} changes in response to longer-term exercise training or weight-loss interventions.

Generally, greater CBF_{GM} is assumed to indicate better brain health, but the present findings and evidence of compensatory hyperperfusion

in cognitive impairment (Swinford et al., 2023) challenge this assumption. This should be considered when planning future research to further improve understanding. Given that the present study is the first to report training-induced global CBF_{GM} changes in healthy older adults (with a high VO_{2peak} response) and the only to use a high-intensity interval training programme, future research investigating similar brain health measures should prescribe, at least some, high-intensity exercise because of the potential substantial impacts of lactate exposure on brain health (El Hayek et al., 2019; Kujach et al., 2020; Morland et al., 2017).

Comparisons between the present study and previous findings, using single-delay ASL (Alfini et al., 2019; Chapman et al., 2013; Flodin et al., 2017; Kleinloog et al., 2019), are limited by measurement technique. Unlike the present study, CBF_{GM} was previously not adjusted for regional and individual ATT_{GM} differences, compromising estimation accuracy. Assuming ATT_{GM} is unchanged following the intervention for all participants, single-delay ASL may have caused a consistent, systematic underestimation of CBF_{GM}. However, age, BMI, blood pressure, and cardiorespiratory fitness are all expected to affect ATT_{GM} (Damestani et al., 2023; Feron et al., 2024; Yetim et al., 2023) and therefore using a single PLD with an assumed constant ATT may have missed important effects and lead to a non-systematic underestimation of CBF (Dai et al., 2017). Consequently, we believe that multiple-delay ASL is vital for this type of investigation to ensure accurate characterisation of CBF_{GM}. We used a range of PLDs based on the optimal for ATT <2000 ms (Woods et al., 2019). This appears sufficient for our relatively healthy older population as shown by the observed ATTs (Fig. 3). However, the longest PLD used (2300 ms) may not be sufficient to capture more prolonged ATT in adult samples that are older or less healthy than our cohort.

Future research assessing cerebral haemodynamic changes should consider controlling for diet and partial pressure of end-tidal CO_2 ($PetCO_2$), which was not done in the present study. For example, caffeine and polyphenol intake can acutely alter global CBF_{GM} by 20–60 % (Francis et al., 2006; Lamport et al., 2015; Vidyasagar et al., 2013). Moreover, $PetCO_2$ is a proxy for arterial partial pressure of CO_2 ($PaCO_2$), the most powerful regulator of CBF (Willie et al., 2014), which could be manipulated by anxiety-induced ventilatory changes during an MRI scan.

Finally, whole-group baseline accelerometery data indicated 86 % of participants actually met the activity guidelines they self-reported not to, although participants possibly modified their normal behaviours (Clemes et al., 2008). Therefore, the generalisability of findings may be limited, and future research should assess if training-induced CBF_{GM} or ATT_{GM} changes differ between habitual high and low activity groups.

4.6. Conclusion

In summary, a 26 week home-based high-intensity interval exercise intervention was well adhered to and improved cardiorespiratory fitness in healthy older adults. Furthermore, global CBF_{GM} reductions were present in exercise participants with the greatest gains in cardiorespiratory fitness, but there were no changes in ATT_{GM}. A lower resting CBF_{GM} could indicate lower cerebral tissue blood flow requirements, resulting from exercise-induced adaptions that enhance oxygen extraction and/or utilisation. Regarding cognitive function, the exercise intervention had no group-level effects on processing speed, working memory, or attention, nor were changes in cognitive functions associated with changes in cardiorespiratory fitness, CBF_{GM}, or ATT_{GM} in either group. Future research should investigate how cerebral oxygen extraction responds to exercise training and whether longer-term exercise training (i.e., years) changes the CBF_{GM} response and whether potential accompanying longer-term structural cerebral adaptations influence ATT_{GM}.

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Ethical approval and participant consent

The study was approved by the STEM Ethical Review Committee at the University of Birmingham (ERN_20–1107). All participants gave informed consent and were free to withdraw from the study at any time.

CRediT authorship contribution statement

Jack Feron: Writing – review & editing, Writing – original draft, Visualization, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Foyzul Rahman:** Writing – review & editing, Project administration, Investigation, Data curation. **Sindre H Fosstveit:** Writing – review & editing, Methodology, Investigation. **Kelsey E Joyce:** Writing – review & editing, Investigation, Data curation. **Ahmed Gilani:** Investigation. **Hilde Lohne-Seiler:** Writing – review & editing, Investigation. **Sveinung Berntsen:** Writing – review & editing, Investigation, Funding acquisition. **Karen J Mullinger:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Katrien Segaert:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Funding acquisition, Conceptualization. **Samuel J E Lucas:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Katrien Segaert reports financial support was provided by the Research Council of Norway. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data sharing and availability

The data for the present study were collected as part of a larger study, The FAB Project (preregistration: https://osf.io/6fqg7, materials and data: https://osf.io/d7aw2/).

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2024.120919.

Data availability

The manuscript and data availability statements contain a link to an online repository containing relevant data

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