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Dose-dependent association of accelerometer-measured physical activity and sedentary time with brain perfusion in aging

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Abstract

INTRODUCTION—Age-related decreases in cerebral blood flow (CBF) may lead to cognitive decline, while physical activity (PA) can maintain CBF and cognition in aging. The intensity of PA needed to affect CBF in aging, and the independent effects of sedentary time on CBF are currently unknown. Moreover, research conducted in free-living environments with objective measures of PA (e.g., accelerometry) is lacking.

METHODS—This cross-sectional study used accelerometry to objectively measure sedentary time, all light PA [AllLightPA], moderate-to-vigorous PA [MVPA], and total activity counts [TAC] in 52 cognitively healthy older adults. Robust linear regressions investigated the association of CBF (using arterial spin labeling magnetic resonance imaging) in frontal and medial temporal regions, with each PA intensity and sedentary time.

RESULTS—Greater sedentary time was significantly associated with lower CBF in lateral and medial frontal regions after adjusting for MVPA, while higher AllLightPA (adjusted for MVPA), MVPA (adjusted for AllLightPA), and TAC were associated with greater CBF in lateral and medial frontal regions.

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DISCUSSION—Lighter activities, as well as MVPA, are beneficial to CBF in brain regions typically affected by the aging process and malleable to exercise interventions (i.e, the frontal lobes), whereas sedentary time is an independent risk factor for neurovascular dysregulation in normal aging.

Keywords

accelerometry; cerebral blood flow; physical activity; sedentary time; dose-response; cognition

1. Background

It is estimated that the number of adults older than 65 years will more than double In the United States between the years 2010 and 2050 [1]. Because of this unprecedented growth, research efforts have focused on the prevention of age-related decline to improve physical, cognitive, and mental health in aging. Reducing cardiovascular and neurovascular risk may help prevent physical and cognitive decline in aging [2,3]. Neurovascular function/activity can be assessed via cerebral blood flow (CBF), which provides the brain with a constant supply of needed oxygen and glucose for proper functioning. Although normal aging is related to global reductions in CBF [4] and localized reductions in frontal and middle-inferior temporal regions [5], greater dysregulation of CBF has been linked to cognitive decline and even dementia [3,5,6].

Fortunately, exercise and cardiovascular fitness have been associated with greater CBF [7,8], cerebral blood volume and perfusion of the hippocampus [9–11], increased CBF in the anterior cingulate cortex [12], slower age-related reductions in CBF [13,14], and improved cognitive functions [15–18]. The mechanisms underlying these changes include exercised-induced growth of new capillaries (angiogenesis) [19], up-regulation of endothelial nitric oxide synthase activity (which increases CBF by inducing vasodilation)[20], prevention of age-induced endothelial dysfunction [21,22], and increased cerebrovascular reserve [23]. Other mechanisms identified to play a role in the increased CBF response observed after exercise interventions include the up-regulation of vascular endothelial growth factor (VEGF) [24], brain-derived neurotrophic factor (BDNF)[25], and insulin-like growth factor (IGF-1), all important neurotrophic factors that seem to work together to support the chronic effects of exercise-induced neurogenesis and angiogenesis. Recent investigations suggest that higher intensity exercise may lead to comparable if not increased benefits in metabolic and cardiovascular health as compared to low-to-moderate training [26–30]. Yet, to our knowledge, research has not examined whether different intensities of physical activity (PA) outside of a laboratory setting could lead to similar brain benefits. Given that older adults struggle to meet PA guidelines, more research is needed to assess the intensity of activity needed to promote changes in CBF and cognition. This knowledge could help guide future lifestyle interventions to maintain CBF and prevent cognitive decline in older adults.

Sedentary behavior can be defined as “any waking behavior characterized by an energy expenditure of ≤1.5 metabolic equivalents (METs), while in a sitting, reclining, or lying posture” [31], such as watching TV or using a computer. Sedentary behavior has emerged as an independent predictor of negative health outcomes (i.e., mortality, cardiovascular disease,

metabolic disease) even after adjustment for PA [32,33]. Interestingly, sedentary behavior is distinct from time spent in moderate to vigorous PA (MVPA), since an individual can meet the current PA recommendations and be considered "active" (150 minutes per week of MVPA), while spending the rest of their daily time in sedentary behavior (i.e., sitting at work or watching TV) [34]. Thus, time spent in MVPA should be accounted for when studying the physiological correlates of sedentary time. Despite the importance of sedentary behavior to health, little is known about its relationship with CBF in aging. To our knowledge, only one study found that regular walking breaks prevent the decline in CBF associated with prolonged sitting in younger individuals [35].

This cross-sectional study investigated the dose-dependent relationship of sedentary time and PA on frontal and medial temporal CBF and its associations with cognition in normal aging. We hypothesized that sedentary time would be negatively associated with CBF in frontal and medial temporal cortices, which are typically affected by the aging process and are responsive to exercise [36,37]. Similarly, we expected that MVPA would have a stronger positive association with CBF in these regions than less intense levels of PA, given previous evidence that moderate levels of activity may be necessary to influence brain health [12,38]. We also expected that cognitive functions would be positively associated with CBF in regions that are significantly correlated with PA, whereas these associations would be negative for sedentary time.

2. Methods

2.1. Participants

Fifty-two cognitively normal older adults between the ages of 65 and 85 were recruited from ongoing healthy aging studies at the San Diego VA Healthcare System and the University of California, San Diego. All participants were cognitively normal (did not exhibit scores within two or more cognitive domains < 1 SD of age-appropriate norms) based on formal neuropsychological testing. Cognitive testing was performed in close proximity (22 days on average, SD= 75 days) to the brain imaging scan and the accelerometer assessment (23 days on average, SD= 59 days).

Participants were excluded if they had mild cognitive impairment or dementia, contraindications to MRI, a history of severe head injury, uncontrolled hypertension, history of stroke or major vascular events, history of myocardial infarction, or had a Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition Axis I diagnosis of learning disability, attention deficit disorder, mood/psychotic disorder, or substance abuse. All participants provided written informed consent prior to enrollment. The protocol was approved by the VA San Diego Healthcare System and the UC San Diego Institutional Review Boards. Refer to Table 1 for participant demographic characteristics and cognitive performance scores.

2.2 Physical activity & sedentary time assessment

PA and sedentary time were objectively measured using tri-axial accelerometers (GT3X + and GT3X-BT, ActiGraph, LLC, Pensacola, FL) for 7 consecutive days, consistent with

recent studies [39,40]. Participants were instructed to wear the accelerometer on a belt on their hip, during waking hours, for a minimum of 12 hours per day and not to change their regular activities. To ensure compliance, all participants received two phone calls from study staff (on days 2 and 5 of the monitoring period). Participant data were considered valid only if they had a minimum of 600 minutes of accelerometer wear per day and a minimum of 3,000 total minutes of wear spread across at least 4 valid days.

Data were processed using the ActiLife version 6 software (Pensacola, FL). The unit of measurement for accelerometers is counts per minute (CPM), with higher counts indicating higher intensity of movement. Non-wear time was determined using a modified Choi algorithm [41] in which 90 consecutive minutes of 0 counts with a 2-minute spike tolerance was screened as non-wear. Data were aggregated to 60-second epochs so published cut points could be applied. Consistent with standard practice, sedentary time was defined as time spent at < 100 CPM, all light PA (AllLightPA) as 100 – 1951 CPM (excludes MVPA), and moderate to vigorous PA (MVPA) as ≥ 1952 CPM [42]. Minutes within each intensity level were averaged across days worn, reflecting the average time in minutes per day spent at each intensity level. We also calculated average daily total activity counts (TAC) based on total Axis 1 counts, which encompass frequency, intensity, and duration of activity, all of which confer health benefits [43] and are strongly associated with health biomarkers as compared to MVPA [44].

2.3 Neuropsychological assessment

Since executive and memory function scores are most responsive to exercise [45,46], we created executive and memory composite scores by converting raw scores into z-scores based on the entire sample, and then averaging across z-scores. Executive Composite: Delis-Kaplan Executive Function System (D-KEFS) Color Word Inhibition and Color-Word Inhibition/Switching, Trail Making Test Part B, number of correct categories on the Wisconsin Card Sorting Test, and total score on the Controlled Oral Word Association Letter Fluency Task (FAS). Tests in which higher scores reflect worse performance were reversed such that greater scores on the Executive Composite indicate better performance. Memory Composite: Wechsler Memory Scale-Revised (WMS-R) Logical Memory Immediate and Delayed Recall total scores, California Verbal Learning Test – II Total for Trials 1–5, Short and Long Delay Free Recall, and performance on a Famous Face Naming task developed by our research group. To determine normal cognitive status, normative scores derived from the respective testing manuals and available published norms (Heaton 2004 and Ivnik 1996) were used (Table 1).

2.4 Brain imaging acquisition parameters

Imaging data were acquired on one of two identical GE Discovery MR 750 3T whole body systems with a body transmit coil and an 8-channel receive-only head coil at the University of California, San Diego's Center for functional MRI. The structural brain sequence consisted of a high-resolution T1-weighted Fast Spoiled Gradient Recall (3DFSPGR) scan: 172 1 mm contiguous sagittal slices, field of view (FOV) = 25 cm, repetition time (TR) = 8 ms, echo time (TE) = 3.1 ms, flip angle = 12, inversion time (TI) = 600 ms, 256 × 192 matrix, Bandwidth = 31.25 kHz, frequency direction = S-I, NEX = 1, scan time = 8 min and

13 s. Since participant's data were selected from two separate ongoing studies, CBF was acquired with the Multiphase Pseudocontinuous Arterial Spin Labeling (MP-PCASL) sequence for 45/52 participants, and with a 2D PCASL sequence for 7/52 participants. Even though it has been reported that the MP-PCASL sequence retains much of the signal to noise ratio advantage of conventional PCASL methods[47], all statistical analyses included ASL sequence (MP-PCASL vs 2D PCASL) and MR scanner as co-variates to adjust for possible scan type and scanner effects. Moreover, we conducted a sensitivity analysis to further explore possible effects of scan sequence and results after removing the 7 participants with the 2D PCASL sequence (retaining MP-PCASL only) were similar to those reported with the entire sample, but clusters were only detected at a lower family-wise cluster correction threshold (voxel correction p=.01 and cluster adjustment for 5 contiguous voxels - 135 mm^3). MP-PCASL parameters: tagging duration = 2000 ms, TI = 3600 ms, TR = 4200 ms, TE =minimum, reps = 64, FOV = 22 × 22 cm, 20 5 mm axial slices with a single shot spiral acquisition, collecting 8 cycles where each cycle consists of 8 images acquired with unique phase offsets, acquisition time (TA) = 4:46 min. 2D PCASL parameters: TR = 4500 ms, TE = 3.2 ms, FOV = 24 cm, labeling duration = 1800ms, post-labeling delay = 2000 ms, with a single shot spiral acquisition and a total scan time of 4:18 min plus a 30 s calibration scan. For both MP-PCASL and 2D PCASL sequences: A calibration scan was obtained using a spiral readout with TR = 4 s and TE = 3.4 ms with 8 dummy radiofrequency (RF) pulses (amplitude set to zero) to generate a 32 s delay followed by a 90 degree RF pulse in the last repetition interval to generate proton density-weighted contrast (scan time: 36 s). This provided an estimate of the equilibrium magnetization of cerebral spinal fluid (CSF), which was used to convert the perfusion signal into calibrated CBF units (mL blood/100g tissue/min). Finally, a minimum contrast image was acquired to adjust for transmit and receive coil inhomogeneities. Two field map scans were also acquired and used for off-line field map correction for signal bunching and dropouts in the frontal/medial temporal lobes.

2.5 Brain imaging processing

CBF quantification was conducted using the Cerebral Blood Flow Biomedical Informatics Research Network (CBFBIRN)[48] database and analysis pipeline. This pipeline uses a combination of custom MATLAB[49] routines and various Analysis of Functional Neuroimages (AFNI)[50] and FMRIB Software Library (FSL)[51] functions. For the MP-PCASL data, the multi-phase ASL data were fit using the FSL Fabber software[52]. For the 2D PCASL data, MATLAB was used to form a mean ASL image from the average difference of the control and tag images. For CBF calibration, we utilized the CSF method [53] to estimate the equilibrium magnetization of arterial blood (M_{0a}), which is necessary for conversion of the ASL difference signal into physiological units (ml/100g/min). This method calculates M_{0a} using the ventricular CSF signal from a separately acquired proton density image. In addition, slice timing delays were accounted for, making the post-labeling delay slice specific. Skull stripping of the high-resolution T1-weighted image was performed using AFNI's 3dSkullStrip. Scans were manually edited to remove residual non-brain material when needed. Tissue segmentation was performed using FSL's Automated Segmentation Tool (FAST) algorithm to define CSF, gray matter (GM) and white matter (WM) regions. To correct CBF for partial volume effects and ensure that CBF values were not influenced by known decreased perfusion in the white matter or increased volume of CSF, we used the

method previously reported by Johnson and colleagues [54], which has been implemented in several perfusion studies of healthy aging [55,56]. These calculations assume that CSF has 0 CBF and that CBF in GM is 2.5 times greater than that in WM using the following formula: CBFcorrected = [CBFuncorrected/(GM + 0.4 * WM)]. A 4.0 mm full-width, half-maximum Gaussian filter was applied to the CBFcorrected data. The high-resolution T1-weighted image and partial volume segmentations were registered to ASL space. Voxels with negative intensities were replaced with zero. CBFcorrected data were registered to the MNI-152 atlas using FSL's FMRIB's Non-linear Image Registration Tool (FNIRT) and resampled to a 3 mm^3 resolution grid.

Two bilateral regions of interest (ROIS) previously associated with PA were selected [18]: 1) The frontal ROI was comprised of the 'frontal lobe' mask in the MNI Structural Atlas. 2) The hippocampal/parahippocampal ROI was comprised of the anterior and posterior parahippocampal divisions, as well as the right and left hippocampi from the Harvard-Oxford Cortical/Subcortical atlases respectively. See Figure 1 for a depiction of the ROI masks used in the analyses.

2.6 Statistical analyses

2.6.1 Associations between cognitive functions and accelerometer measures—

Bivariate Pearson correlations examined the direct association of accelerometer measures (sedentary time, AllLightPA, MVPA, and TAC) with cognitive performance scores (executive and memory composite scores).

2.6.2 Region of interest (ROI) analyses of CBF with accelerometer measures

—Four voxel-wise robust linear regression models were conducted in R (https://www.r-project.org/) for each ROI with voxel-wise CBF as the dependent variable and either sedentary time, AllLightPA, MVPA, or TAC as independent variables. All analyses adjusted for age, sex, scanner (one of two identical scanners at UC San Diego), and scan type (MP-PCASL versus 2D PCASL Geriatrics pulse sequence). Additionally, the models investigating the effects of sedentary time and AllLightPA on CBF were adjusted for MVPA to investigate the independent effects of these variables on CBF. Similarly, MVPA analyses were additionally adjusted for AllLightPA. Sedentary time analyses were additionally adjusted for accelerometer wear time given the strong associations reported in the literature between these variables[57,58].

To guard against false positives, we used a search region approach by applying cluster-size correction derived from Monte-Carlo simulations via AFNI's 3dClustSim to determine significance for each of the ROIs. For the frontal ROI, a minimum cluster volume of 13 contiguous voxels (351 mm^3) was required to correct for multiple comparisons at $p<.01$ corresponding to a voxel-level threshold of $p<.01$, and a cluster size of 12 contiguous voxels (324 mm^3) ensured an overall correction of $p<.01$ (family-wise) corresponding to a voxel-level threshold of $p<.01$ for the hippocampal/parahippocampal gyrus ROI. To characterize the direction of the significant associations between CBF and accelerometer measures, we extracted the mean CBF from each significant cluster within each ROI and plotted them against the accelerometer measures.

2.6.3 Associations between cognitive functions and CBF in significant clusters—

Bivariate Pearson correlations examined the associations between cognitive functions (executive and memory composite scores) and CBF extracted from clusters with significant accelerometer-based associations.

2.6.4 Exploratory whole-brain voxel-wise analyses of CBF with accelerometer measures—

Exploratory whole-brain voxel-wise analyses using the same models described above were also performed. A minimum cluster volume of 15 contiguous voxels (405 mm3) ensured an overall correction of $p<.01$ (family-wise) corresponding to a voxel-level threshold of $p<.01$.

3. Results

3.1 Accelerometer assessment

Participants were highly compliant with accelerometer wear during the assessment period. Table 2 displays accelerometer metrics and the amount of time participants spent on average within each activity intensity category.

3.2. Associations between cognitive functions and accelerometer measures

There were no significant direct correlations between accelerometer-measured sedentary time, AllLightPA, MVPA, and TAC with either executive or memory composite scores (all *ps*>.05).

3.3 Region of interest (ROI) analyses of CBF with accelerometer measures

3.3.1 Sedentary time and CBF—

Average daily sedentary time was negatively associated with CBF only in the frontal ROI after adjusting for the effects of age, sex, scanner, scan type, MVPA, and accelerometer wear time ($p<.01$ voxel, $p<.01$ cluster corrected). Significant clusters in the frontal ROI were in 1) right anterior middle frontal gyrus; 2) right paracentral lobule; and 3) right posterior middle frontal gyrus (Table 3 and Figures 2&3A).

3.3.2 All light physical activity (AllLightPA) and CBF—

Average daily AllLightPA was positively associated with CBF in the frontal ROI only, specifically in the right inferior and middle frontal gyrus, after adjusting for age, sex, scanner, scan type, and MVPA ($p<.01$ voxel, $p<.01$ cluster corrected) (Table 3 and Figures 2&3B).

3.3.3 Moderate to vigorous physical activity (MVPA) and CBF—

Average time spent in MVPA was positively associated with CBF in the frontal ROI only, specifically in the left inferior frontal gyrus, after adjusting for age, sex, scanner, scan type, and AllLightPA ($p<.01$ voxel, $p<.01$ cluster corrected) (Table 3 and Figures 2&3C).

3.3.4 Total activity counts (TAC) and CBF—

Average daily TACs were positively associated with CBF only in the frontal ROI after adjusting for age, sex, scanner, and scan type ($p<.01$ voxel, $p<.01$ cluster corrected). Significant clusters in the frontal ROI were: 1)

left supplementary motor area/superior medial gyrus; 2) left inferior frontal gyrus; 3) left precentral gyrus; and 4) left/right superior medial gyrus (Table 3 and Figures 2&3D).

3.3.5 Associations between cognitive functions and CBF in significant clusters—

There was a significant correlation between CBF associated with TACs in the left supplementary motor area/superior medial gyrus with memory ($r = .31$, $p < .05$) and executive functions ($r = .28$, $p < .05$). CBF in all other significant clusters was not associated with cognitive scores.

3.4 Exploratory whole brain voxel-wise analysis of CBF with all accelerometer measures

In addition to clusters identified in the ROI analyses, areas of significant associations between 1) CBF and sedentary time were found in left supramarginal gyrus and right fusiform gyrus, 2) CBF and AllLightPA were found in the left anterior cingulate, and 3) CBF and TAC were found in the right lingual gyrus, right middle occipital gyrus and left insula (Supplementary Table 1). The direction of associations was consistent with that observed in the search region (ROI) analysis (negative for sedentary time and positive for all others).

4. Discussion

This is the first study to investigate the dose-dependent effect of everyday life, objectively measured PA and sedentary time on regional CBF in normal aging. We found consistent negative associations between sedentary time and CBF in medial and lateral frontal regions, whereby higher sedentary time was related to lower CBF. In addition, we found a consistent pattern in which more time spent at all levels of PA was associated with greater CBF in lateral and medial frontal regions, suggesting that PA and sedentary time confer independent positive and negative effects on CBF. Moreover, all intensities of PA had a positive effect on inferior frontal gyrus CBF. This is not surprising given the increasing evidence for the role of the inferior frontal gyrus in cognitive control [59] and in protecting memory performance against Alzheimer's disease pathology in old age [60]. Our results indicate that CBF in the inferior frontal gyrus may be particularly sensitive to light and moderate intensity PA.

Unlike previous studies reporting consistent effects of PA in the hippocampus [37,61], we did not find such associations. Research shows that CBF increased in the hippocampus of older adults assigned to an exercise intervention for four months; however, our study is a cross-sectional analysis of sedentary time/PA in free-living environments rather than an intervention trial. Nonetheless, our findings suggest that in cognitively healthy older adults, frontal lobe CBF is selectively sensitive to free-living PA and sedentary time, while the hippocampus may be more malleable and responsive to exercise interventions.

Our results add to the limited extant literature indicating that sedentary behavior is associated with poor brain health outcomes. Recently, sedentary time has been associated with decreases in gray and white matter volumes [62], lower integrity of white matter in the parahippocampal gyrus [63], greater amyloid β burden (a hallmark of Alzheimer's disease) in older adults [64], lower brain-derived neurotrophic factor (BDNF) bioavailability [65], reduced

medial temporal lobe thickness [66], and has been identified as a behavioral risk factor for CBF dysregulation in those at genetic risk for developing Alzheimer's disease [67].

Taken together, these findings suggest that future behavioral interventions to maintain brain health should focus not only on increasing all levels of PA, but also on reducing sedentary time. Since the way in which sedentary time is spent may differentially affect cognition [68,69], more research is needed to investigate what kinds of sedentary activities may be detrimental to cognition and which ones could boost performance. For example, TV watching time is related to poor executive functions, while increasing computer use is associated with better verbal memory and executive functioning in older adults [70].

Of note from our current findings, AllLightPA and MVPA were associated with CBF in only one frontal brain region each (right inferior/middle frontal gyrus and left inferior frontal gyrus, respectively), while TACs, which have emerged as a valid measure of total volume of PA (including frequency, intensity and duration of activity), were positively associated with CBF in four frontal brain regions (left supplementary motor area, left inferior frontal gyrus, left precentral gyrus, and left/right superior medial gyrus). This suggests that TACs may be an accelerometer-derived measure that is more sensitive to CBF than arbitrary accelerometer cutoff points. Indeed, TACs have stronger associations with health outcomes, such as insulin resistance and cardiometabolic biomarkers than MVPA [43,44] and it was the only measure for which associated CBF was related to cognition (there were significant correlations between CBF associated with TAC in the left supplementary motor area/superior medial gyrus with memory and executive function performance scores).

This study is not without limitations: 1) The cross-sectional design does not allow us to make causal interpretations. 2) We identified few relationships between cognition and CBF associated with PA, and none with sedentary behavior. This is not surprising given the lack of correspondence between brain MRI findings and cognitive gains [18] and the fact that CBF changes have been observed prior to changes in cognitive functions in exercise interventions [12]. Future intervention work is needed to further test the relationship between physical activity related changes in CBF and cognition to reveal possible mechanisms of cognitive decline. 3) We did not find direct associations of accelerometer measures with cognitive functions. Although some studies have found direct associations of objectively-measured PA with cognitive functions[71,72], these are scarce and include much larger samples compared to our study. 4) Participants were not specifically instructed to refrain from exercise bouts prior to their cognitive testing and MRI sessions. Since exercise has been shown to have acute effects on cognition and CBF [73–75], this may have had an impact on cognitive testing performance and CBF measurement for some participants and not others. That said, a recent study found that global CBF decreased 10-min post exercise and returned to baseline levels at 40-min post exercise[76]. As such, the impact of exercise bouts prior to MRI scanning in this study is likely minimal (since participants met with study staff for at least 30 minutes prior to brain imaging). 5) We did not collect body mass index (BMI) data in the current study and were thus unable to adjust our statistical analyses for the possible influence of BMI in the relationship between PA, CBF, and cognition. Despite these limitations, strengths of this study include the use of a well-characterized sample of cognitively normal older adults, the use of ASL MRI to measure CBF (which is a non-invasive and reliable method to

assess neurovascular function in humans), and the use of accelerometry to objectively measure PA and sedentary time as they occur in free-living environments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The authors report no conflicts of interest.

Abbreviations

AllLightPA	All Light Physical Activity
ASL	Arterial Spin Labeling
CBF	Cerebral Blood Flow
CPM	Counts per Minute
MRI	Magnetic Resonance Imaging
MVPA	Moderate to Vigorous Physical Activity
PA	Physical Activity
ROI	Region of Interest
TAC	Total Activity Counts

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Highlights

- Blood flow to the brain is essential for cognition and it decreases with age
- The intensity of physical activity needed to improve brain blood flow is unknown
- Sedentary time is bad for health, but we don’t know if it affects brain blood flow
- All intensities of physical activity can positively impact brain blood flow
- Sedentary time is detrimental for brain blood flow, independent of physical activity

Figure 1: Regions of Interest (ROIs) selected for search region regression models

Figure 1 Notes: Frontal (yellow) and Hippocampal/Parahippocampal (red) Regions of Interest (ROIs) used in the search region analyses. The Frontal ROI was derived from the MNI Atlas available in FSL. The Hippocampal/Parahippocampal ROI was derived from the Harvard-Oxford Subcortical and Cortical Atlases respectively.

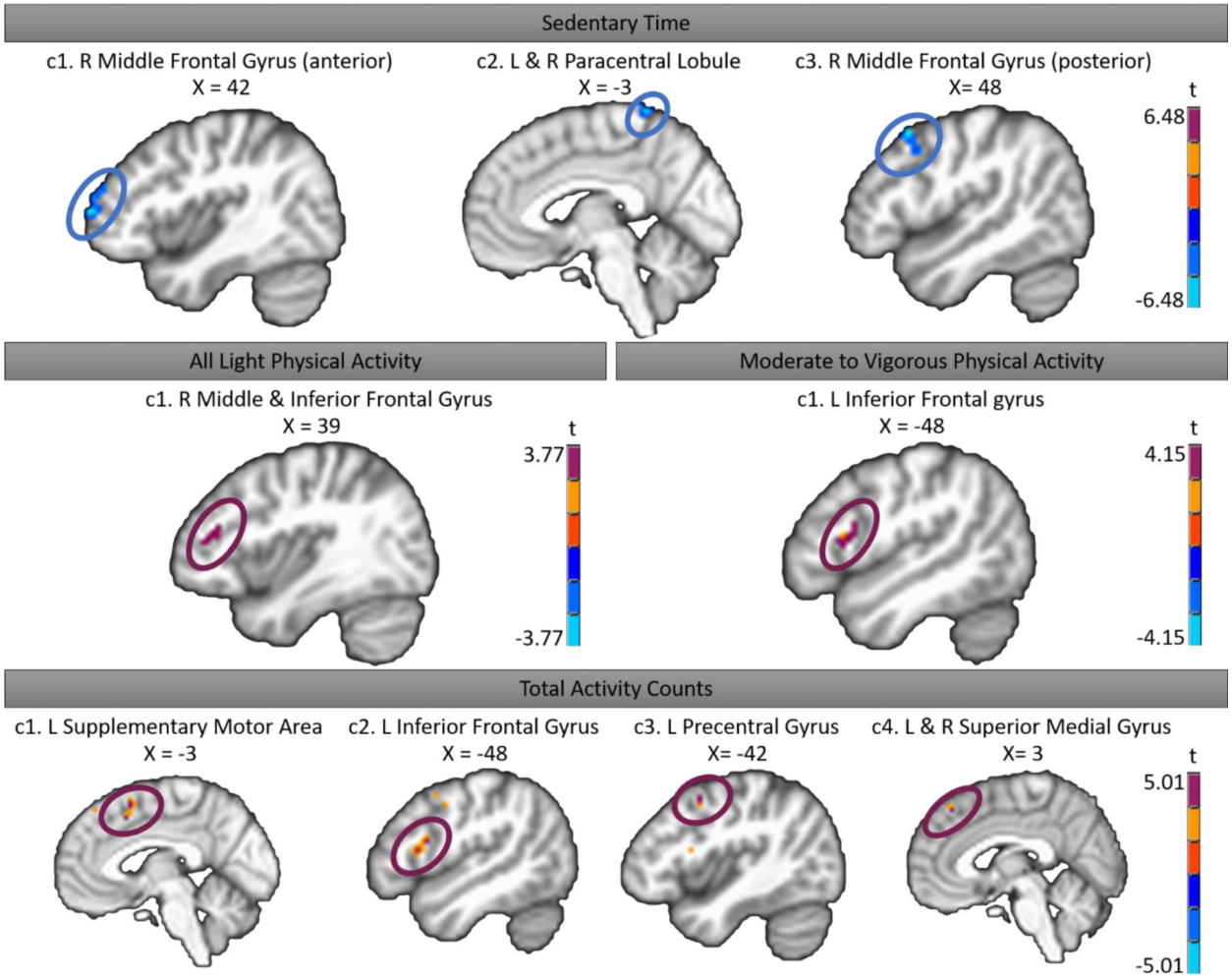

Figure 2: ROI analyses: areas within the frontal ROI with significant associations of CBF and accelerometer measures.

Figure 2 Notes: Locations within the frontal cortex region of interest (ROI) where there were significant associations of cerebral blood flow (CBF) with accelerometer measures. Cluster numbers (c1, c2, c3, etc) in this figure correspond to those in Table 3. Refer to Table 3 for cluster locations and coordinates. Negative X coordinates correspond to the left hemisphere, while positive X coordinates correspond to the right hemisphere in MNI space (3 × 3 × 3 mm).

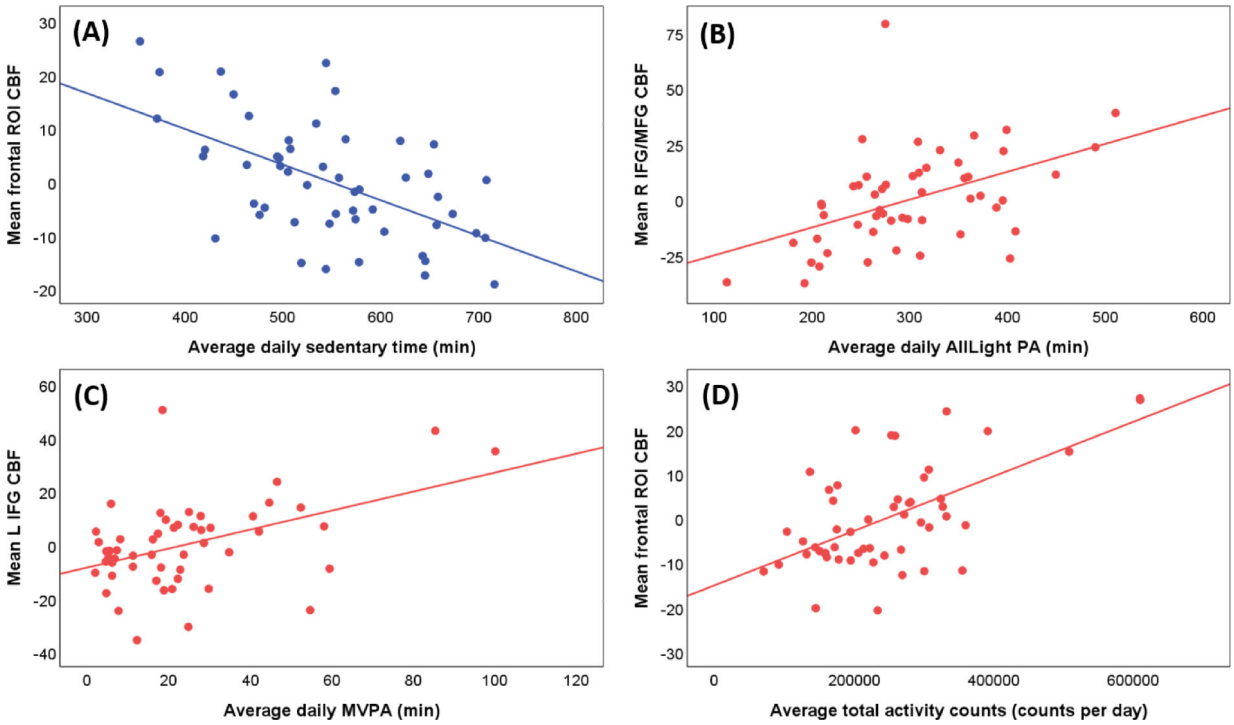

Figure 3. Scatterplots of accelerometer measures with CBF extracted from significant clusters in the frontal lobe ROI.

Figure 3 Notes: Scatterplots depict the direction of associations between the unstandardized residuals of cerebral blood flow (CBF) on the Y-axis (adjusted for covariates) and the different accelerometer measures on the X-axis. CBF is measured in mL/100g of tissue/ minute, but these plots represent the unstandardized residuals (explaining why values in the Y axis range from positive to negative). For total activity counts (TAC) and sedentary time, the mean CBF was averaged across all significant clusters for display purposes (the direction of associations was consistent within each individual cluster). AllLight PA= All light physical activity; MVPA= Moderate to vigorous physical activity; R= Right; L=Left; IFG=Inferior frontal gyrus; MFG=Middle frontal gyrus; CBF=Cerebral blood flow; ROI=Region of interest.

Table 1.

Participant demographic characteristics and cognitive performance scores (N=52)

	Mean	Standard Deviation
Age	72.3	5.0
Years of Education	16.4	2.2
Sex (% women)	30 women (57.7%)	
Ethnicity	Caucasian (49), Latino (2), African-American (1)	
FSRP % Stroke Risk	9.2	6.6
Average Blood Pressure (systolic)	129.6	16.2
Average Blood Pressure (diastolic)	76.0	9.3
Geriatric Depression Scale Score	2.3	2.8
Dementia Rating Scale Total Score	141.1 (T = 55.4)	2.3
Executive Functions Composite Score		
Trail Making Test Part B*	69.24 (T = 56.6)	21.4
D-KEFS Color-Word Inhibition	61.84 (ss = 11.7)	11.4
D-KEFS Color-Word Inhibition/Switching	65.94 (ss = 11.9)	15.9
COWAT Letter Fluency Total (FAS)	46.31 (T = 54)	13.2
WCST-48 (number of correct categories)	5.6 (T = 53.5)	0.7
Memory Composite Score		
WMS-R Logical Memory I	30.71 (ss = 13.6)	5.8
WMS-R Logical Memory II	28.19 (ss = 14.2)	6.7
CVLT-II List A 1–5 Total	49.73 (T = 57.1)	11.3
CVLT-II Short Delay Free Recall	10.36 (z = 0.7)	3.1
CVLT-II Long Delay Free Recall	10.92 (z = 0.5)	3.0
Famous Faces Naming Task Total	48.9/60	8.9

Table 1 Notes: Raw scores are presented unless stated otherwise. FSRP = Framingham Stroke Risk Profile; D-KEFS = Delis-Kaplan Executive Functions System; COWAT = Controlled Oral Word Association Test; WCST = Wisconsin Card Sorting Test; WMS-R = Wechsler Memory Scale – Revised; CVLT-II = California Verbal Learning Test – II; T = T-score; ss = scaled score; z = z-score.

Table 2.

Accelerometer metrics

	Mean	Standard Deviation	Min	Max
Days of Wear	6.96	0.79	4	8
Daily Minutes of Wear	872.49	69.85	741.33	1028.86
Average Sedentary Minutes/Day (CPM 0–99)	547.99	91.31	354.13	716.43
Average All Light PA Minutes/Day (CPM 100–1951)	300.52	80.59	112.88	510.71
Average Moderate to Vigorous PA Minutes/Day (CPM ≥1952)	23.99	20.62	2.00	100.14
Average Total Activity Counts/Day (Axis 1 Counts)	247208.97	111805.65	70696.63	610304.29

Table 2 Notes: CPM= Accelerometer counts per minute; Min= Minimum; Max= Maximum.

Table 3.

ROI analyses: significant cluster locations and coefficients for each activity intensity predicting frontal ROI CBF

	Volume (mm^3)	Max t	X	Y	Z	B	SE	β
Sedentary time *								
c1. R middle frontal gyrus (anterior)	594	−6.48	42	60	9	−.10	.02	−.58
c2. L & R paracentral lobule	594	−4.89	−3	−45	72	−.08	.03	−.47
c3. R middle frontal gyrus (posterior)	540	−4.44	48	18	51	−.11	.02	−.63
All light physical activity **								
c1. R middle and inferior frontal gyrus	648	3.78	39	39	15	.15	.04	.50
Moderate to vigorous physical activity ***								
c1. L inferior frontal gyrus	432	4.16	−48	18	12	.43	.11	.45
Total activity counts ****								
c1. L supplementary motor area/superior medial gyrus	648	4.27	−3	12	54	7.969E-5	.00	.50
c2. L inferior frontal gyrus	486	5.09	−48	18	12	7.761E-5	.00	.45
c3. L precentral gyrus	459	3.78	−42	6	48	8.278E-5	.00	.47
c4. L & R superior medial gyrus	351	3.74	3	36	48	5.698E-5	.00	.38

Table 3 Notes: L= Left; R= Right; Max t= Maximum t value within each significant cluster; X, Y, Z are the Peak XYZ cluster coordinates in MNI space (3 × 3 × 3 mm); B= coefficient b (unstandardized); SE= standard error of B; β= standardized coefficient; c1= cluster 1; c2= cluster 2, etc.

* Adjusted for age, sex, scanner, scan type, MVPA, and accelerometer wear time.

** Adjusted for age, sex, scanner, scan type, and MVPA.

*** Adjusted for age, sex, scanner, scan type, and AllLight PA.

**** Adjusted for age, sex, scanner, and scan type. All clusters were significant (p<.01 voxel, p<.01 cluster-corrected).