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An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
of the requirements of the degree of
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Abstract

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Previous cross-sectional work has shown there to be a general pattern of decreased interhemispheric inhibition and increased bilateral activation during a unimanual motor task in sedentary older adults as compared to aerobically active adults. The current study aimed to examine the impact of a 12-week aerobic exercise intervention on relateralizing motor function to a single hemisphere in sedentary older adults. Twenty-four participants were randomized into an aerobic spin cycling exercise group or a non-aerobic balance training group. Participants completed a pre- and post-intervention battery of motor control tasks and a pre- and post-intervention cardiovascular fitness assessment (estimated VO_2max). Magnetic resonance images were acquired prior to and after the intervention and a block-design, right-hand motor task was used to evaluate interhemispheric cortical activation patterns. The aerobic exercise group showed significant improvements in their cardiovascular fitness as compared to the balance group. A significant decrease in bilateral primary motor cortex (M1) activity was not observed between the aerobic exercise group and the balance group. It was observed that those who completed the aerobic exercise intervention showed less left M1 and supplementary motor area (SMA) activity as compared to those who completed the non-aerobic balance intervention. Significant differences in motor performance were not observed between the groups although there was a trend for improved motor performance for those in the aerobic exercise condition as compared to those in the balance condition. In conclusion, the current study provides preliminary evidence indicating that a 12-week aerobic exercise intervention has the potential to alter cortical activation patterns. The present work also provides evidence suggesting that these changes in cortical activation patterns may be associated with clinically relevant improvements in motor functioning. Additional work is needed to precisely characterize the differential changes in cortical activation patterns between the right (ipsilateral) and left (contralateral) primary motor cortices after an acute aerobic exercise intervention and the rehabilitative significance associated with those changes.

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Tables and Figures

Introduction

According to the Population Reference Bureau (2015), the number of Americans ages 65 and older is projected to more than double from 46 million to approximately 98 million by the year 2060. This elderly (65-and-older) age group will comprise nearly 24 percent of the overall population by the year 2060. This exponential increase in the aging population has far-reaching implications for all sectors of our modern society, particularly the financial and health care sectors. Specifically, this population shift will impose a tremendous economic burden in the form of increased social security payments, increased medical care insurance costs, and increased long-term care costs related to services that address the needs of people who are frail or disabled (Knickman & Snell, 2002). According to the Centers for Medicare and Medicaid Services, the portion of the population living on fixed incomes with high health care expenses will increase as the proportion of elderly adults grows. As a result of this, the health care system and Medicare and Social Security will become increasingly financially strained. In the year 2017, personal health care spending for elderly adults between the ages of 65 and 84 was approximately 600 billion, with over half of the financial burden being placed on the Medicare system (National Health Expenditure Fact Sheet, 2017). Considering the alarming rate of growth for personal health care expenditures, it is becoming imperative to better understand and address both the proximal and distal determinants that drive this drastic increase. The massive population shift coupled with age-related deficits in cognitive and motor functioning are critical determinants that fuel this exponential growth in personal health care expenditures. For example, the aging of the baby boomer generation is expected to fuel a 75 percent increase in the number of Americans ages 65 and older requiring nursing home care, to approximately 2.3 million in 2030 from 1.3 million in 2010 (Population Reference Bureau, 2015).

Given our growing elderly population and the implications associated with that population shift, it is important to better comprehend the impact age has on both cognitive and motor functioning. This is particularly relevant in that cognition and motor functioning play a significant role in maintaining functional independence. The normal non-pathological aging process is associated with declines in a number of cognitive domains. Specifically, predictable and reproducible changes in cognition have been observed with regard to fluid intelligence, processing speed, attention, memory, language, visuospatial abilities, and executive functioning (Harada, Natelson-Love, Triebel, 2013; Murman, 2015). The cumulative impact of these age-related cognitive deficits directly limits the ability of older adults to quickly process or transform information in order to make decisions and this greatly impacts daily living.

Importantly for the context of this study, aging is linked to changes in motor control and performance. Age-related declines in fine motor control, coordination, gait, and balance result in the decreased ability of older adults to perform activities of daily living and maintain functional independence (Contreras-Vidal, Teulings, & Stelmach, 1998; Darling, Cooke, & Brown, 1989; Tang & Woollacott, 1996). For example, gait and balance problems are a major source of injury and morbidity in older adults and approximately 20-30% of older adults who fall suffer moderate to severe injuries that limit their mobility and reduce their quality of life (Alexander, Rivara, & Wolf, 1992). It has been previously shown that motor performance deficits in older adults are associated with dysfunctions of the central and peripheral nervous systems as well as the neuromuscular system (Seidler et al., 2009). A focal point of previous motor-based aging research has been on the impact of reduced gray matter volume. Of particular relevance is the susceptibility of the prefrontal cortex to exhibit age-related gray matter atrophy (Good et al., 2001; Jernigan et al., 2001; Raz et al., 1997; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003). Additionally, several studies have demonstrated that the parietal cortex shows greater age-related differences in gray matter volume than either the temporal or occipital cortices (Good et al. 2001; Resnick et al., 2003). These age-related decreases in gray matter volume in the prefrontal and parietal cortices may be associated with deficiencies in motor performance. Considering the susceptibility of the prefrontal and parietal cortices to undergo gray matter atrophy, numerous studies have also examined the age-related changes in gray matter volume in the primary motor and somatosensory cortices. With regard to these two cortical regions, there have been inconsistent findings. One study found that there was a minimal age effect on grey matter volume in both the motor and somatosensory cortices (Raz et al., 1997). This finding has been contradicted by numerous other studies that have shown significant age-related differences (Good et al., 2001; Salat et al., 2004; Hunter, Pereira, & Keenan, 2016; Harridge, & Lazarus, 2017). Using voxel-based morphometry, one study found there to be age-related differences in gray matter volume in both the pre- and post-central gyri (Good et al., 2001). A separate study found there to be a significant age effect in both the primary motor and somatosensory cortices with regard to cortical thickness, with the greatest effect being in the primary motor cortex (Salat et al., 2004). These studies have helped elucidate the potential susceptibility of these critical regions for motor control and performance to experience age-related atrophy.

In addition to age-related changes in brain structures, there are also significant differences in brain neurochemistry between young and older adults. The dopaminergic and GABAergic systems have been specifically targeted as potential areas of interest. These two systems are considered to be highly relevant with respect to age-related motor dysfunctions. With regard to the dopaminergic system, it has been demonstrated that the aging brain exhibits a significant decline in dopamine transmission levels (Kaasinen & Rinne, 2002). This age-related decrease in dopamine transmission has been linked to decreases in the absolute concentration of the neurotransmitter dopamine (Garrett et al., 2015) and reductions in various dopamine receptors (Inoue et al., 2001; Kaasinen et al., 2000; Suhara et al., 1991) and dopamine transporters (Volkow et al., 1996). These decreases have a direct impact on locomotion, balance, and fine motor movements. Previous work utilizing proton emission tomography (PET) has shown an association between reduced levels of striatal dopamine transmission and impaired gait and balance (Cham, Perera, Studenski, & Bohnen, 2007; Cham, Studenski, Perera, & Bohnen, 2008). Primate research has also shown there to be a link between reduced dopamine transmission and deficits in fine motor control. Specifically, Emborg et al. (1998) demonstrated that aged Rhesus monkeys with reduced levels of nigral dopamine experienced difficulties with a fine motor control task. These studies provide robust evidence suggesting that there is a strong link between age-related decreases in dopaminergic activity and motor impairments.

Inhibitory cortical processes play a crucial role in modulating corticospinal excitability and age-related changes in these processes may result in a wide range of behavioral deficits. Specifically, it has been shown that the inability to effectively modulate corticospinal excitability mat result in deficits in motor performance in older adults (Sale & Semmler, 2005; Riecker et al., 2006; Fujiyama, Garry, Levin, Swinnen, & Summers, 2009; Fujiyama, Hinder, Schmidt, Garry, Summers, 2012; Cuypers et al., 2012). Considering the impact of cortical inhibitory processes on motor performance, it is important to examine the role of gamma-aminobutyric acid (GABA), the brain's main inhibitory neurotransmitter, on modulating corticospinal excitability. Previous work has demonstrated that the aging process may be responsible for a decrease in GABA tone in the neocortex (Gao et al., 2013; Mooney et al. 2017; Maes et al., 2018). Although this pattern of age-related decreases in GABA tone provides useful preliminary evidence, more research is still needed to better elucidate the impact of this decreased concentration of GABA on motor functioning.

Considering the growing evidence on both the structural and neurochemical differences between young and older adults and the role those differences have on motor functioning, numerous studies have sought to investigate if older adults exhibit differences in functional brain recruitment patterns during motor tasks. A major topic of interest has been on examining interhemispheric inhibition. This form of inhibition refers to the neurophysiological mechanism in which one hemisphere of the brain inhibits the opposite hemisphere. Importantly, interhemispheric inhibition is highly important for the execution of unimanual and coordinated bimanual movements (Ni et al., 2009; Giovannelli et al., 2009; Maes, Gooijers, Orban de Xivry, Swinnen, & Boisgontier, 2017; Pauwels, Maes, & Swinnen, 2018).

It has been previously shown that changes in interhemispheric inhibition can be assessed using functional magnetic resonance imaging (fMRI). fMRI is a non-invasive tool that has been extensively utilized to examine neural activity in the brain. The majority of studies that have employed fMRI measure the blood oxygenation level-dependent (BOLD) signal as a proxy for neural activity (Ogawa, Lee, Kay, & Tank, 1990; Ekstrom, 2009). The signal intensity of BOLD weighted MR images inversely depends on the local deoxyhemoglobin (deoxyHb) content. The deoxyHb content is subject to change based on variations in cerebral blood flow (CBF), cerebral blood volume (CBV), and the rate of oxygen consumption (CMRO2). The BOLD signal increases with increased CBF. In contrast, an increase in CBV or CMRO2 alone would cause a decrease in BOLD signal. A positive BOLD signal is associated with increased neuronal activity, which in turn induces an increase in the local CBF that exceeds the increase in CMRO2 (Fox and Raichle, 1986). The net result is a lowered deoxyHb content that causes an increase in BOLD signal (Ugurbil et al., 2000). In addition to characterizing and analyzing the positive BOLD signal, numerous studies have also examined the negative BOLD signal (Shmuel et al., 2002; Kastrup et al., 2008; Schäfer et al., 2012; Boorman et al., 2015). This signal has been reliably observed as a function of ipsilateral inhibition in the visual-, motor- and somatosensory cortices (Hlushchuk & Hari, 2006; Schäfer et al., 2012; Whittingstall, Wilson, Schmidt, & Stroink, 2008). Importantly, negative BOLD signals have been shown to be associated with reductions in CBF and neural activity (Devor et al., 2007; Boorman et al., 2010). Although these previous studies have shown a general trend of negative BOLD being associated with decreased neural activity or inhibition, what remains unknown is whether its mechanisms of neurovascular coupling are similar to the mechanisms observed for the positive BOLD response. Based on this current understanding of positive and negative BOLD signals, we have previously shown that both young and older adults and physically fit older adults and sedentary older adults exhibit distinctive cortical activation patterns. For example, utilizing cross-sectional data, we have shown that older sedentary adults tend to recruit both left and right hemispheres when performing a unimanual motor task, specifically within the primary motor cortex (McGregor et al., 2011, 2012, 2013). However, older adults who were more physically active showed patterns of activity that were more similar to younger adults when performing the motor task. That is, in the motor area controlling the moving hand, an increase in the BOLD response was found, indicating an increase in CBF and neural activity. However, in the opposite hemisphere, an inverse relationship was found. That is, a negative BOLD signal (indicating a decrease in blood flow relative to baseline) was apparent in the motor area ipsilateral to the moving hand.

In order to mitigate these age-related declines in motor functioning, previous studies have investigated the role of various behavioral and pharmacological interventions. Of particular interest, is the role of aerobic exercise on improving motor performance outcomes. Past research has shown there to be reliable age-related declines in tissue densities in the frontal, parietal, and temporal cortices. More importantly, it has been demonstrated that those age-related reductions were substantially reduced in older adults with higher cardiovascular fitness levels (Colcombe et al., 2003). Data from one longitudinal study, similarly showed that healthy sedentary older adults (N = 59) that enrolled in a six-month acerbic fitness intervention experienced significant increases in brain volume in both gray anterior (cingulate cortex, supplementary motor area, posterior middle frontal gyrus, and left superior temporal lobe) and white matter regions (anterior third of corpus callosum) as compared to older adults who were enrolled in a stretching (non-aerobic) control group (Colcombe et al., 2006). Although these studies provide promising evidence regarding the positive impact of cardiovascular fitness on improving the structural integrity of the brain in older adults, more work is needed to better understand to role of aerobic exercise and cardiovascular fitness on motor functioning in this population.

Given previous supporting evidence on the positive influence of cardiovascular fitness on age-related cognitive and motor deficits, our present work aimed to assess the impact of a 12-week aerobic exercise intervention on relateralizing motor function to a single hemisphere in sedentary older adults. Based on previous cross-sectional data that established a general pattern of decreased interhemispheric inhibition and increased bilateral activation during a unimanual motor task in sedentary older adults as compared to aerobically active adults, we hypothesized that older sedentary adults that completed a 12-week aerobic exercise intervention would demonstrate increased interhemispheric inhibition and relateralization of motor function as compared to those who completed a non-aerobic balance intervention (McGregor et al., 2011, 2013). Specifically, we expected to observe an increased positive BOLD signal (associated with a greater neural activity) in the contralateral hemisphere (left hemisphere) and an increased negative BOLD signal (associated with neural inhibition) in the ipsilateral hemisphere (right hemisphere). Based on these cortical activation patterns, we further hypothesized that those in the aerobic group would demonstrate improved motor control as compared to those in the non-aerobic group.

Methods

Participants

In this 12-week randomized controlled trial (RCT: NCT01787292), participants were randomized and divided into an aerobic spin cycling exercise group (Spin) or a non-aerobic balance training group (Balance) to equalize contact and monitoring. Each intervention lasted 12-weeks.

Study personnel explained the purpose of the intervention, the potential risks of the intervention, and completed the informed consent process with each participant following protocols approved by Emory University's Institutional Review Board (IRB00059193) in compliance with the Helsinki Declaration. All participants gave written informed consent filed with both the Atlanta VA Research and Development Office and Emory University’s IRB.

This study includes 24 participants that were recruited from a volunteer database, which included elderly individuals (60 years and older). To meet inclusion criteria participants had to (1) be between the ages of 60 and 85, (2) report being sedentary, defined as not engaging in structured physical activity and/or not accumulating 30 minutes or more of moderate to strenuous weekly physical activity, assessed with a modified Godin Leisure Time Exercise Questionnaire – LTEQ (Godin and Shephard, 1997), (3) have no history of depression or neurological disease (including Parkinson's disease, Alzheimer's disease, multiple sclerosis or stroke), (4) report being right-handed (using the Edinburgh handedness inventory; Oldfield, 1971), (5) report being a native English Speaker, and (6) obtain primary care physician's approval for study participation. Exclusion criteria included (1) failure to provide informed consent, (2) hospitalization within the past 6 months, (3) uncontrolled hypertension or diabetes (reported non-compliance with prescribed management program), (4) inability to walk 400m, and (5) significant cognitive executive impairment, defined as a score on the Montreal Cognitive Assessment (MoCA) of < 24. Due to the high incidence of hypertension medications in sedentary older adults (N = 12; 6 per group), we did not exclude individuals on these medications.

During intervention sessions, all participants wore a Polar FT7 chest strap heart rate monitor with paired monitor/wristwatch (Kempele, Finland). Heart rate was taken from each participant every 5 minutes during the sessions and logged on a data sheet. On infrequent occasions (<2% of HR acquisitions), the chest strap monitor would fail to synchronize with the watch during the intervention session. In such instances, we interpolated the heart rate data from adjacent recordings within each session provided that they were within reasonable ranges to each other (± ~5-10 bpm). If a heart rate monitor failed to synchronize at the onset of the intervention session (a problem with older adults with lower resting galvanic skin responses) we would use a battery-powered pulse oximeter or an Apple Watch (Cupertino, CA) to measure heart rate at the above-described intervals. For both interventions, we recorded attendance, attrition, and heart rate. All participants completed the 36 assigned sessions for each intervention though we had to accommodate for more absences for participants in the balance condition.

Aerobic "Spin" Intervention Protocol

Consistent with our previous study (Nocera et al., 2015, McGregor et al., 2018), the group exercise intervention began with 20 minutes of spin aerobic exercise three times a week for 12 weeks on stationary exercise cycles and was led by a qualified instructor. Importantly, the time of each session progressed based on the recommendation of the instructor by ~1-2 minutes as needed to a maximum time of 45 minutes per session. Heart rate reserve was assessed using the Karvonen method (220 bpm - age = maximum heart rate; heart rate reserve [HRR] = maximum heart rate - resting heart rate). Exercise intensity began at low levels (50% of HRR) and increased by 5% every week (as deemed appropriate by the instructor) to a target maximum of 75% HRR. Participants wishing to exceed this capacity could do so for limited exercise intervals if they so choose. Target exercise intensities were adapted for participants on diuretics, ACE-inhibitors, beta-blockers based on recent recommendations in the literature (Diaz-Buschmann et al., 2014; Taubert et al., 2015) to produce equivalent aerobic capacity improvement as non-medicated individuals. These included the "talk-test" and relative physical exertion estimation using the Borg 6–20 difficulty scale (6 = lowest effort; 20 = maximum effort).

The Spin intervention took place in a climate-controlled fitness facility. The instructor guided the participants through a light effort 5-minute warm up (not included in the data analysis), then a workout phase that included steady up-tempo cadences, sprints (increased rpm), and climbs (increased resistance). As such, the exercise routine employed an interval-based training approach. During the workout phase, the target HRR reserve was maintained by averaging increases and decreases in intensity/HR.

Balance/Light Strength Training Intervention Protocol

The main purpose of the balance and strength training group was to have participants engage in non-aerobic physical activities that may help reduce fall risk. Participants in the balance group were equalized to the Spin group with regards to contact and monitoring frequency. As such they reported to the same facility with the same interventionalists; however, instead of progressive aerobic exercise, they participated in group balance, stretching, and light muscle toning exercises. Beginning at the outset of the intervention, a baseline balance assessment was taken for each individual to titrate task difficulty depending on intake stability risk. This was formally measured using the short physical performance battery (SPPB), which is a measure consisting of a top score of 12 (scores lower than 10 indicate moderate fall risk). All participants in this study had a score of 11 or greater, indicating low fall risk from the SPPB. Participants began the intervention by practicing balance exercises on foam pads using a chair for support (if necessary). Balance exercises included single leg stand, dual-task (counting backward) and eyes closed conditions lasting approximately 10 minutes. Participants increased difficulty when they were able to perform the balance session without the use of the support chair. In place of foam pads, participants stood on less-stable air-filled pads as they advance through the 12-week intervention. Participants were also challenged to learn to step on moveable friction pads (six-inch diameter "dots") with variable positions on the floor. Instructors changed the positions of these pads as the session progressed to challenge participants to safely deviate center of mass location during foot placement in order to improve proprioception during gait. In addition, light strength training exercises included instructor-led bodyweight and resistance training using TheraBand (Akron, OH) stretch bands. These exercises focused on improving postural support with an emphasis on abdominal engagement and lateral hip abduction. Brief weekly meetings were held to discuss progress within the program and workload.

Similar to the aerobic 'spin' group session time frame, the balance and strength training group began with 20 minutes of contact time and progressed to a maximum of 45 minutes over the course of the 12-week intervention with a light 5-minute warm-up at the onset of each session. Additionally, heart rate was consistently monitored (using the Polar FT7 chest strap monitors) to assess general intensity during each session and to monitor whether participants were keeping their HR below aerobic levels (50% of HRR).

Assessments

Cardiovascular Fitness Assessment

To assess aerobic capacity, participants performed a YMCA submaximal fitness test on a Monark 828e (upright) or RC4 (recumbent) cycle ergometer (Vansbro, Sweden). This submaximal test was used to estimate the participant's maximal oxygen uptake (VO_2max) prior to and after interventions. The selected submaximal test is better tolerated than a maximum exertion treadmill test in the study's population (sedentary older adults). The YMCA-test uses an extrapolation method in which heart rate workload values are obtained at 2-4 points during stages of increasing resistance and extrapolated to predict workload at the estimated maximum heart rate (220 - age). VO_2max is then calculated from the predicted maximum workload. Prior to beginning the test, the procedures were explained and participants completed a 2-minute warm-up consisting of pedaling without a load so that they could adapt to the ergometer for the first minute and then pedaling with a 0.5 kg.m load during the second minute. The YMCA submaximal test has an R = 0.86 with VO2max and a SEE = 10% of the predicted VO2max (Beekley et al., 2004).

Motor Control Assessment

During behavioral assessment sessions, participants performed a battery of upper extremity motor tests. Participants completed motor assessments of the dominant hand including grip strength, the Halstead-Reitan Finger Tapping task (Reitan and Wolfson, 2003) simple reaction time, the Purdue Pegboard (peg and assembly) (Tiffin and Asher, 1948), and the Nine-Hole Pegboard task (Mathiowetz et al., 1985). Additionally, to test distal motor dexterity, participants engaged in a coin rotation task with two conditions. In the first condition (unimanual), the participant rotated a coin (U.S. quarter) 20 times as quickly as possible using the index finger, middle finger, and thumb with duration as the outcome measure. This test is used for assessment in routine neurological screening and has been shown to be diagnostic of distal motor function both in cases of suspected pathology and aging in the absence of pathology (Hanna-Pladdy et al., 2002; Hill et al., 2010). In the second condition (bimanual), the participant maintained an isometric pinch force of 20-30% of maximum voluntary force with a Jamar brand pinch grip dynamometer using a lateral grip during the rotations. Coin rotation tasks were performed with both the left and right hands. Both the hand used for coin rotation and trial condition (unimanual or bimanual task) were pseudo-randomized and counterbalanced across participants to account for potential order effects across eight runs (two left unimanual, two left bimanual, two right unimanual, two right bimanual). Accidental coin drops were noted but excluded from consideration and the trial was repeated should a drop occur. Participants were allowed 5 min of practice to acclimate to the rotation task in each task condition. Data acquisition began if the participant reported that they believed that additional practice time would not improve task performance. No participants requested additional time beyond the 5-minute practice period. The difference score between the bimanual and unimanual task conditions was calculated to assess the effect of bimanual activity on rotation performance.

Functional Imaging

Parameters

Magnetic resonance images were acquired on a 3-T Trio or Prisma Whole-Body Scanner (Siemens) using a 12-channel SENSE head coil. Head motion was minimized using foam padding and laser grid alignment. Prior to the acquisition of functional imaging sequences, structural images were acquired [160 mm x 1.0 mm thick sagittal slices, using a 3D T1-weighted sequence: time of echo (TE) = 8.057 ms; time of repetition (TR) = 3.685 ms; flip angle (FA) = 8]. Whole-brain high-resolution echo planer functional images (EPI) were acquired using 57 mm x 2 mm thick axial slices and the following parameters: TE = 30 ms; TR = 4000 ms; FA = 87; F0V =

192 mm x 192 mm x 114 mm; Matrix = 96 x 96; SENSE factor = 1.5. Two dummy EPI signals were acquired and discarded to allow for signal equilibrium.

Stimuli were presented on a first surface mirror presentation system situated at the rear bore aperture of the magnet. Stimuli were projected from a personal computer (PC) to a 30" high resolution (1600 x 1200 pixels) MR-compatible screen. A large mirror reflected the display into the bore of the magnet. A mirror situated on the head coil then reversed the mirror image for presentation to the participant.

fMRI task

A block-design, right-hand motor task was used to evaluate interhemispheric cortical activation patterns. Blocks consisted of seven images (28 seconds) for both rest and active conditions. Six cycles (alternating between seven rest images and seven active images) comprised each run (5 minutes 46 seconds). In the scanner, participants engaged in two runs of the motor task and all performance data (accuracy, reaction times) were saved for later analysis. Participants were trained on the task inside the scanner prior to data acquisition. Between runs, participants verified their understanding of the task via verbal report.

The motor task was a block presentation of a repeated button squeeze using an index finger to thumb opposition (“button tapping”). This task has been shown to exhibit a negative BOLD response in the ipsilateral primary motor cortex (M1) in younger adults (Allison et al.,2000; Riecker et al.,2006; McGregor et al.,2011). Performance of similar tasks in sedentary older adults, however, has shown positive BOLD responses in ipsilateral M1 (McGregor et al., 2009, 2011). Stimuli were presented using E-Prime software (PST Software, Pittsburgh, PA, USA). Button responses were made on an RP04U button response unit (BRU) manufactured by MagConcept (Sunnyvale, CA, USA) connected to the presentation computer. Researchers positioned the participants’ fingers in the correct posture on the BRU prior to acquisition and instructed on target force output. The participants were asked to use the index finger-thumb squeeze to depress a button for each trial press with only as much force as required to generate a tactile “click” on the responsive device (equivalent to roughly 3N). The participants’ left (non-active) hand was placed in a prone, resting position along the side of the body. Participants were visually monitored for movements of this hand during active task blocks. Consistent overt mirrored movement was used as a criterion for exclusion.

During the functional run, participants fixated gaze on a central fixation cross of a computer screen throughout each of the two runs. Blocks were cued by the change of fixation cross varying between the word “Squeeze” (active condition) or the word “Rest” (rest condition). During the active condition, participants were instructed to time button presses with the flashing visual stimulus (1 Hz). Trials were briefly practiced in the scanner prior to image acquisition. Researchers in the scanner operation room monitored the participants’ performance during the task.

fMRI Preprocessing

DICOM to NIfTI Conversion: We used MRIcron to convert images from the DICOM scanner format to the NIfTI format. Files were gzipped to save disk space.

Run 1/Run 2: We performed data preprocessing within each of the two runs acquired per scan to account for potential signal differences across the acquisition. After preprocessing, EPI data were concatenated into a single run.

Slice Timing Correction: We performed this step to correct for delays in slice acquisition throughout the acquisition of an image volume. Slice timing information was stored in the NiFTI file header and was corrected using FSL software.

Bias Field Removal: Due to the distortions in the desired anatomical image which is caused by a multiplicative bias field (related to engineering issues such as imperfections in the radio frequency coils used to record the MR signal) corrupted images were acquired. This step was performed to estimate the uncorrupted image from the corrupted image. This procedure was completed using FSL and FreeSurfer.

Data Deobliquing: Oblique datasets were sometimes acquired for the EPI time series dataset, despite a preference for acquisition using the cardinal planes. To correct for this and to standardized across the dataset, data deobliquing was done to transform the oblique EPI dataset to a cardinal (orthogonal) orientation. We used AFNI, FSL, and FreeSurfer to deoblique the EPI sets.

Axial RPI (axRPI) Conversion: Images were standardized to this format to allow for consistency across the dataset. We converted data from the RAI NIfTI transform into the FSL friendly RPI format.

Volume Registration: Motion correction was completed to try to decrease image-by-image variability due to head movement or changes in MR susceptibility. We selected a reference volume (in this case one that was in the center of the function run - image 35) and performed a rigid body translation of voxels to one another. This is a 6-parameter registration that attempts to reduce systematic spatial variance that might be due to head movements. This can be done because we check for differences at a voxel by voxel level in changes in x, y, z directions and using yaw, pitch, and roll (those are the 6 parameters). Systematic variance was reduced by applying a warping matrix. The values from the warping matrix were saved and then applied during the statistical analysis as a regressor of non-interest, which affords us to decrease the amount of noise in our data. We used AFNI's 3dVolreg to complete this procedure.

Independent Component Analysis (ICA): We performed an independent component analysis approach using FSL's MELODIC software. Independent component analysis was used here to denoise the data. The first step in the process consisted of running a principal component analysis (PCA). A principal component analysis evaluates linear combinations of the covariance matrix of the data in both spatial and temporal domains. These data were then rotated using an orthogonal transform (varimax) and evaluated for similarity using principal eigenvalues of the rotated matrix. At this point, the linear combinations were evaluated for differences amongst the selected components. This is the independent component analysis, which creates a summary of the temporal time course and power spectra of the associated spatial combinations. Using both the spatial and temporal data, we hand-classified components as either valid signal (BOLD) or noise components (respiration, cardiac, head movement, susceptibility, MR artifacts). To denoise the data, we pseudo-randomly selected 6 pre and 6 post datasets from the study (we always include the dataset visually inspected to report the least signal) and performed the hand classification process on these data as described above.

FMRIB's ICA-based X-noiseifier (FIX) Denoising: Once the classification dataset was aggregated, classifiers were trained to be able to automatically classify and remove structured noise-components (e.g., motion-effects, scanner artifacts, non-neuronal physiological noise, etc.). The version employed in the current work was FSL FIX 1.066.

Spatial Normalization: The aim of this processing step was to establish a one-to-one correspondence between the brains of different individuals. This process required the use of a reference image (Montreal Neurological Institute brain template - MNI152) in order to achieve spatial congruence across all subjects. This method specifically corrects for global shape differences while preserving regional asymmetries. We first removed spatial information from the ventricles and non-brain regions using an OPTIBET shell script. The images were then segmented to account for cerebrospinal fluid variance. After segmentation, the CSF related variance was removed (essentially punching out the ventricles).

Smoothing: This process consisted of applying a small blurring kernel (FWHM = 4mm) across each image to average the intensities from neighboring voxels together. The effect of this processing step is to slightly blur the image and make it smoother and this results in the lowering of the overall spatial frequency and an improvement in the signal-to-noise ratio. We employed the program 3dBlurInMask to complete this procedure.

Scaling (Z-transform): This preprocessing step was done to account for the fact that the level of signal may vary between voxels. This step is particularly important for multi-subject analyses since the signal level may be substantially different at corresponding voxels across subjects.

The scaling approach used in this study was a z-transformation. In this approach, the signal in a voxel is mean-centered (subtraction of mean) and related to the standard deviation of the signal fluctuations. With this transformation, signal fluctuations from time point to time point are expressed as units of standard deviation. These data are to be compared to results from a previously completed resting state study, which used a z-transform.

Concatenation: Once the z-transformation was completed, the time-series from each participant (run 1 and run 2) was concatenated in order to simplify the statistical analysis of the fMRI data. Linear trends were removed to account for gradient heating using the -rlt++ flag in 3dTcat in AFNI.

Data Analysis

Behavioral Data

Statistical analyses were conducted using Microsoft Excel, IBM SPSS (Chicago, IL), and JMP 12 (SAS Institute, Cary, NC). Potential group differences at baseline on demographic and behavioral parameters were evaluated using a between-subjects t-test. To evaluate pre-post differences between groups, change scores for behavioral data were computed using the convention: change = pre − post. Intervention effects were examined by independent sample t-test on change scores to determine between-group differences for the variables of interest: upper extremity motor battery and cardiovascular fitness assessment.

Imaging Data

A linear regression was performed using AFNI 3dDeconvolve. The task regressor was generated using AFNI's waver function convolving a GAM (gamma) variate against the stimulus timing for the BLOCK design. Motion parameters were regressed in the Deconvolution as a factor of non-interest. These included movements estimated from the 3dVolreg procedure to account for head motion in the x, y, and z planes as well as correcting for yaw, pitch, and roll. The regression coefficient (beta weight) was output for each subject and session and input into a three-dimensional multivariate modeling technique to account for post-pre changes in a random effects design. To evaluate group differences as a result of the interventions, a split-plot (2 between × 2 within) ANOVA was performed as implemented in AFNI's 3dMVM with intervention (Spin and Balance) group as the between factor and session (pre/post) as the within-subjects factor (Chen, Adleman, Saad, Leibenluft, & Cox, 2014). Subjects were held as a random factor. This approach enters random effects variance (pre-post within subject) as a covariate into the overall model. As such, it attempts to account for random effects variability by essentially holding this variance as a multi-variate regressor of non-interest.

We used AFNI's 3dClustSim (compiled September 2015) program to correct for multiple comparisons with a voxel-wise threshold level $p < .01$ holding alpha at .01 for a minimum cluster size of 100 voxels at 2 × 2 × 2 mm3 (MNI space). We selected this conservative threshold in light of recent work discussing random field theory in cluster correction (Eklund, Nichols, & Knutsson, 2016).

Results

Behavioral Data

No significant differences were observed across participants (N = 24) in any of the baseline demographic and exercise metrics that were assessed (**see Table 1**).

No significant differences were observed across participants (N = 24) in any of the baseline motor comparisons that were assessed (**see Table 3**).

There was a significant difference between the change scores for the cardiovascular fitness assessment (estimated VO*2*max) of the Spin group (**μ = -6.3**) and the Balance group (**μ = 0.9**); (**t(24) = 2.64, p ≤ 0.05**) (**see Table 2**).

Across a battery of motor indices, individuals completing the Spin Intervention showed a pattern of improvement on measures of dominant upper extremity, as compared to no change or worsening in the Balance condition. These data are shown in **Table 4** and were derived from the reduced model comparison as computed by JMP12. Notably, significant differences were observed between the Spin group (**μ = -0.24**) and the Balance group (**μ = -3.45**) in the bimanual coin rotation task (**t(24) = 2.42, p ≤ 0.05**).

Imaging Data: Post-group Comparisons

Bilateral M1 recruitment was shown at baseline across participants (**see Figure 1**). Baseline group differences in BOLD activity for the Aerobic Spin and Baseline conditions are presented in **Figure 2**. No significant differences were observed in cortical activation patterns when comparing between the two conditions. (**see Figure 3**). Post group differences in BOLD activity for the Aerobic Spin and Baseline conditions are presented in **Figure 4** (Balance condition exhibited increased left MI and SMA activity as compared to the Aerobic Spin condition). Negligible group differences were evident at the selected threshold in this comparison utilizing a whole-brain analysis. Groups differences in BOLD activity in the post-session are presented in **Table 5.** Brain regions (left M1 and SMA) showed lower levels of BOLD activity in the Aerobic Spin group as compared to the Balance group (**see Figure 5**).

Discussion

The aim of the current study was to examine changes in interhemispheric inhibition in a previously sedentary cohort of older adults following a 12-week aerobic exercise intervention as compared to a non-aerobic balance intervention. Specifically, this study was focused on examining the effectiveness of an acute 12-week aerobic exercise intervention on relateralizing motor function to a single hemisphere and improving motor control. The current findings of this study do not fully support our hypothesis, in that, a significant decrease in bilateral primary motor cortex (M1) activity was not observed between the aerobic exercise group and the non-aerobic balance group and significant differences in motor behavior were not observed between the groups. Although our primary hypothesis was not fully supported, our findings do provide evidence regarding the role of dedifferentiation and compensation as they relate to changes in cortical activation patterns and motor performance. The dedifferentiation hypothesis refers to the fact that brain structure-function relationships become less distinctive with age and thus increased brain activity has either no or negative behavioral consequences (Langan et al., 2010). In contrast, the compensatory model argues that additional brain recruitment is associated with improvements in task performance (Heuninckx, Wenderoth, & Swinnen, 2008). Interestingly, it has been shown that dedifferentiation- and compensation-like brain activation patterns can be observed in the same participants for the same task (Carp, Gmeindl, & Reuter-Lorenz, 2010), indicating that both these models are useful for better understanding the complex patterns associated with age-related changes in cortical activation and recruitment. In the present study, we observed that those who completed the aerobic exercise intervention showed less left M1 and supplementary motor area (SMA) activity as compared to those who completed the non-aerobic balance intervention. We can interpret these findings to mean that those who were more aerobically fit tended to recruit less cortical areas to perform the same motor task as compared to those who were less aerobically fit. Furthermore, we can interpret this trend to mean that those in the aerobic condition relied less on compensatory mechanisms, in that they did not actively recruit additional cortical areas during the unimanual right-handed motor task as compared to those in the balance condition. It is important to note that these interpretations are based on the understanding that the changes in cortical activity measured using fMRI are predominately neural in nature. Considering that our intervention targeted the cardiovascular system, we would expect differential vascular effects between the intervention groups and these effects might influence the changes in cortical activity measured between the two conditions. This directly limits the interpretations of the data in this study, in that it is not feasible to differentiate neural signal between changes in cerebral blood flow utilizing the methodological tools employed in the current study. In order to address this limitation going forward, we plan to incorporate resting state fMRI data in order to investigate if changes in resting state networks can predict changes in task-based activity. Using this approach will give us a more concrete understating of the changes in cortical activation patterns between the two conditions.

Importantly, this study replicates previous findings that older sedentary adults exhibit bilateral M1 activation (increases in positive BOLD in both the contralateral and ipsilateral hemispheres) during a unimanual motor task (McGregor, Craggs, Benjamin, Crosson, & White, 2009; McGregor et al., 2011; McGregor et al., 2012; McGregor et al., 2013). This increased bilateral activation may be associated with deficits in motor performance (Langan et al., 2010; Fling & Seidler, 2011; McGregor et al., 2011, 2012). Beyond this association between bilateral activation and motor deficits, previous work has demonstrated an interaction between higher levels of aerobic fitness and increased motor performance (McGregor et al., 2011, 2012, 2013; Hübner, & Voelcker-Rehage, 2017). Although the current study does not provide robust behavioral evidence regarding the efficacy of an aerobic exercise intervention to significantly improve motor outcomes, it does show there to be a general trend of improved motor performance for those in the aerobic condition as compared to those in the balance condition. Specifically, we observed improvements in both the Purdue Pegboard and 9-Hole Peg assessments for those in the aerobic group compared to those in the balance group. Although these differences were not statistically significant it can be argued that the behavioral changes observed in this study as a result of the aerobic exercise intervention have some rehabilitative or clinical significance in that a positive trend was still observed. It is important to consider the fact that the interpretation of clinical research outcomes should not be based solely on the presence or absence of statistically significant differences particularly in cases where the study has considerable limitations associated with it (e.g., small sample size) (Page, 2014).

The characterization of the physiological and neurochemical mechanisms that cause these age-related changes in cortical activation patterns and ultimately behavior have yet to be fully assessed and understood. Although this is beyond the scope of the present study, it is critical to better understand the potential mechanisms that drive these age-related changes. Currently, there are various hypotheses regarding potential physiological and neurochemical mechanisms including changes in brain-derived neurotrophic factor (BDNF) and other growth factors (Voss et al., 2012; Erickson et al., 2011), changes in inhibitory cortical systems (with a focus on the GABAergic neurotransmitter system) (Northoff et al., 2007; McGregor et al., 2013), and changes in vascular perfusion (Thomas et al., 2013). Although all three of these hypotheses hold some validity, there is now growing evidence demonstrating the central role of inhibitory processes. Specifically, numerous studies have shown that older adults exhibit a significant loss of cortical inhibition when compared to younger adults (Heise et al., 2013; Fujiyama et al., 2012; Fling & Seidler, 2012). These findings on the age-related changes in inhibitory cortical processes have been heavily informed by studies employing the use of transcranial magnetic stimulation (TMS). Due to the fact that there has been such a high reliance on this specific modality for examining inhibitory patterns, future studies should focus on utilizing a more diverse set of neuroimaging and neurophysiological techniques (e.g., functional magnetic resonance imaging; functional magnetic resonance spectroscopy) to better characterize the physiological mechanisms that promote these age-related changes in cortical inhibition.

The current study has notable limitations that should be addressed. One apparent limitation of the study is that the sample size is considerably low. Low sample sizes result in reductions to the statistical power of a study and decreases in the reproducibility of a study’s results (Button et al., 2013; Faber & Fonseca, 2014). In the context of the present study, the sample size (N = 24) resulted in a decreased ability to detect differences in cortical activation patterns between the aerobic exercise group and the balance group. Another limitation associated with the current study is the length of the aerobic exercise intervention. Considering this study recruited sedentary older adults, it is possible that a 12-week intervention would not be sufficient to increase aerobic fitness to a level that would significantly impact brain physiology and motor performance. Previous studies that have employed an aerobic exercise intervention have utilized a six-month framework and have shown promising results related to improvements in a wide range of cognitive functions (Colcombe et al., 2006; Jonasson et al., 2017). Another considerable limitation concerns the fact that the present study cannot accurately characterize the nature of how the BOLD signal changes. Due to the nature of the intervention employed in this study, it is considerably difficult to differentiate the vascular effects that result from the aerobic exercise as compared to neural changes. While it is not feasible to dissociate between vascular and neural changes using fMRI, it is reasonable to assume that improvements in vascular flow dynamics as a result of increased aerobic activity directly impacts changes in neural activity. Future work is needed with alternative methodological tools to identify the focal mechanism of change presented here. Finally, as a methodological note, the scope of the statistical analysis in the current study does not provide a robust understanding of the interactions occurring between changes in aerobic fitness, cortical activation patterns, and motor behavior. The current study employed a whole brain analysis that would detect generalized changes in neural activity across all cortical areas. Although this is an appropriate and necessary first-level analysis, it would have been highly useful to conduct a region of interest (ROI) analysis in that in this study we would expect to observe differential neural activity in a specific region (e.g., MI) between the two intervention conditions (Poldrack, 2007). Additionally, the current study would have benefited from utilizing more advanced models of randoms effects variance to investigate individual variability (a key focus for precision rehabilitation research). For example, future analyses could better account for random effects differences with the employment of a random effects maximum likelihood (REML) analysis whose output would then be entered into a mixed effects meta-analysis (3dMEMA). Lastly, the current study would have also benefited from the inclusion of regression analyses to test for significant correlations between change scores in the motor assessments and changes in the estimated VO_2max in prediction of BOLD activity in the post-session. These correlations would have provided highly relevant information regarding the previously described interactions in aerobic fitness, cortical activation patterns, and motor behavior.

In conclusion, the current study demonstrated that a 12-week aerobic exercise intervention has the potential to alter cortical activation patterns as demonstrated by the fact that those in the aerobic intervention exhibited reduced left M1 and SMA activity as compared to those who completed the non-aerobic balance intervention. The present work also provides preliminary evidence suggesting that these changes in cortical activation patterns may be associated with clinically significant improvements in motor functioning. This may have a direct rehabilitative implication, in that these improvements in motor functioning may translate to the maintenance of or improvements in functional independence for older adults. Additional work is needed to precisely characterize the differential changes in cortical activation patterns between the right (ipsilateral) and left (contralateral) primary motor cortices after an acute aerobic exercise intervention and the rehabilitative significance associated with those changes.

Table 1 | Baseline demographic and exercise metrics: Body mass index (BMI), level of oxygen consumption during exercise (estimated VO_2), and Montreal Cognitive Assessment (MoCA).

Metric	**Aerobic Exercise (N = 12, 7 females)**	**Balance (N = 12, 7 females)**
Age (years)	69 (7.2)	68 (7.7)
Education (years)	14 (2.8)	13.8 (2.6)
BMI	29.5 (4.5)	29.2 (4.7)
Handedness	.97 (.05)	.98 (.03)
VO_2 (ml/min/kg)	17.6 (6.4)	18.2 (7.5)
MoCA	26.8 (1.6)	26 (2.9)

No significant differences. The parenthetical numbers represent standard deviation.

Table 2 | Change metrics in behavioral performance comparing intervention groups (std. dev.): Level of oxygen consumption during exercise (estimated VO_2).

Metric	**Aerobic Exercise (N = 12, 7 females)**	**Balance (N = 12, 7 females)**
VO_2 (ml/min/kg)	**-6.3 (5.6)**	**0.9 (7.6)**

BOLD denotes statistical significance below $p \leq 0.05$. The parenthetical numbers represent standard deviation.

Table 3 | Baseline motor comparisons between intervention groups: Halstead Reitan Tapping, Purdue Peg, Purdue assembly, 9-Hole Peg, Hand grip, Pinch grip, Coin-rotation, Scanner – Reaction time.

Metric	**Spin**	**Balance**
Halstead Reitan Tapping	42.90 (8.2)	43.86 (8.7)
Purdue Peg	10.47 (4.5)	11.4 (5.7)
Purdue assembly	10.28 (3.9)	9.93 (5.5)
9-Hole Peg	21.79 (7.3)	20.72 (6.7)
Hand grip left	63.1 (18.9)	63.47 (22.25)
Hand grip right	68.42 (20.9)	66.95 (21.5)
Pinch grip left	13.15 (3.5)	13.8 (2.2)
Pinch grip right	14.25 (3.9)	12.67 (3.2)
Coin-rotation L (uni)	14.74 (5.3)	15.34 (7.8)
Corn-rotation R (uni)	14.1 (4.7)	14.99 (3.6)
Coin-rotation L (bi)	13.44 (2.9)	12.60 (5.3)
Coin-rotation R (bi)	12.48 (8.4)	12.95 (5.4)
Coin-rotation diff L	1.3 (3.7)	2.74 (4.9)
Coin-rotation diff R	1.62 (6.3)	2.03 (3.24)
Scanner – Reaction time	282.05 (27.1)	289.2 (35.2)

No significant differences. The parenthetical numbers represent standard deviation.

Table 4 | Change metrics in behavioral performance comparing intervention groups (std. dev.): Purdue Peg —Higher score is better; 9-Hole pegboard and Unimanual coin rotation—lower is better.

Metric	Spin	Balance	p-value
Scanner Accuracy - Tapping	0.95% (1.9)	-1.5% (5.2)	0.18
Scanner – Reaction time	-30 (65.4)	14 (50.9)	0.08
Halstead Reitan Tapping	3.2 (4.6)	0.7 (5.3)	0.23
9-Hole Peg	-2.4 (2.02)	0.99 (5.7)	0.06
Purdue Peg	1.2 (1.8)	-0.3 (1.9)	0.06
Purdue assembly	0.42 (1.5)	0.16 (1.40)	0.66
Coin rotation			
Right unimanual	-0.91 (4.42)	-2.41 (5.01)	0.44
Bimanual difference score	**-0.24 (2.75)**	**-3.45 (2.54)**	**0.01**

Bimanual difference is the difference between unimanual and bimanual coin rotation tasks. Data is from reduced model as implemented in JMP12. BOLD denotes statistical significance below $p \leq 0.05$.

Figure 1 | Bilateral M1 recruitment was shown at baseline across participants. Data was corrected utilizing a voxel-wise cluster size of 100 voxels (t = 3.50; p < .001 holding alpha at .001).

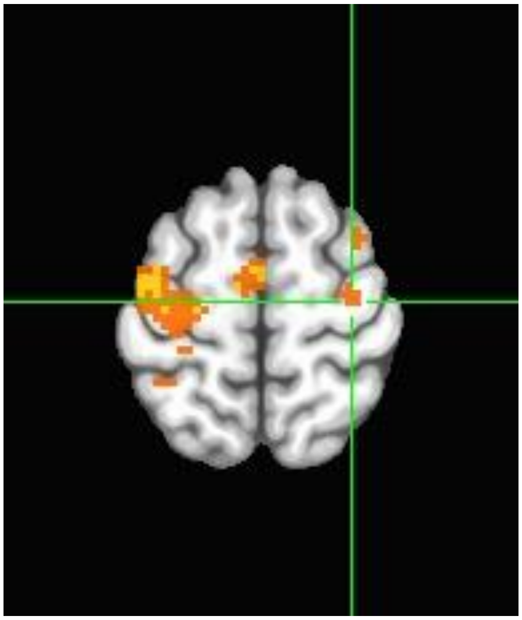
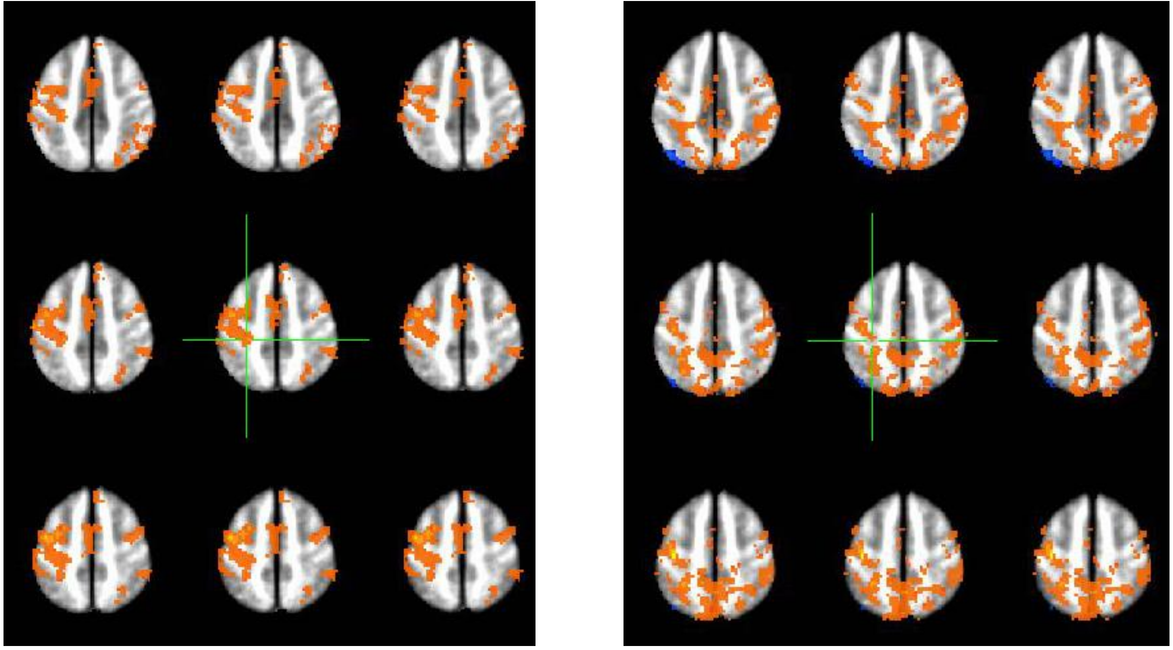


Figure 2 | Baseline group differences in BOLD activity for the Aerobic Spin and Balance conditions (hues: orange indicates positive t -statistic; blue indicates negative t -statistic). Data was corrected utilizing a voxel-wise cluster size of 100 voxels (t = 3.68; p < .01 holding alpha at .01).



(a) Aerobic Spin Condition

(b) Balance Condition

Figure 3 | Analysis of pre-session imaging data between Aerobic Spin and Balance conditions. Data was corrected utilizing a voxel-wise cluster size of 100 voxels (t = 3.68; p < .01 holding alpha at .01). No significant differences were observed in cortical activation patterns between the two conditions at baseline.

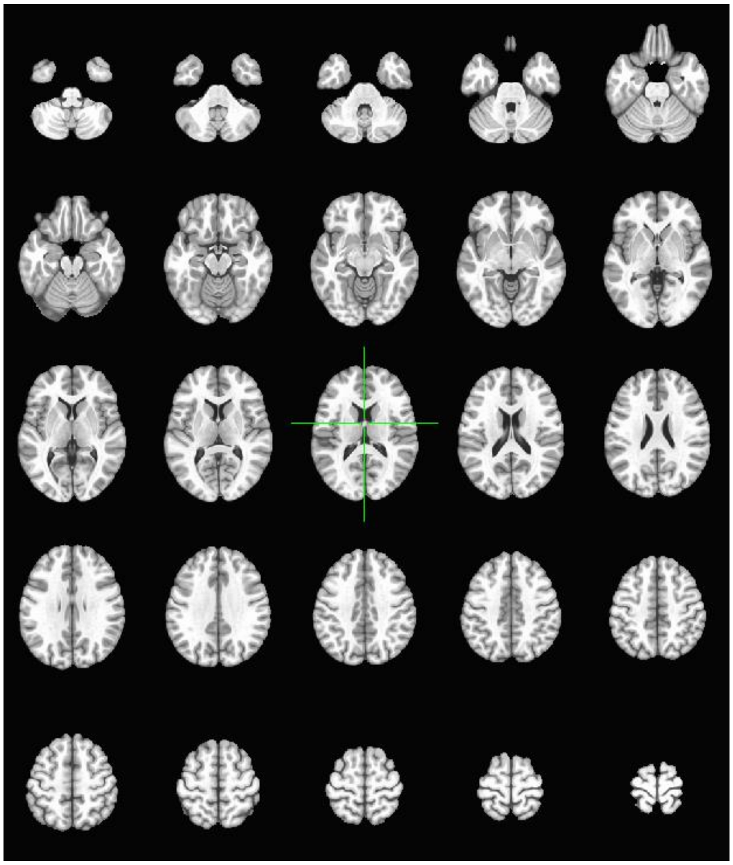
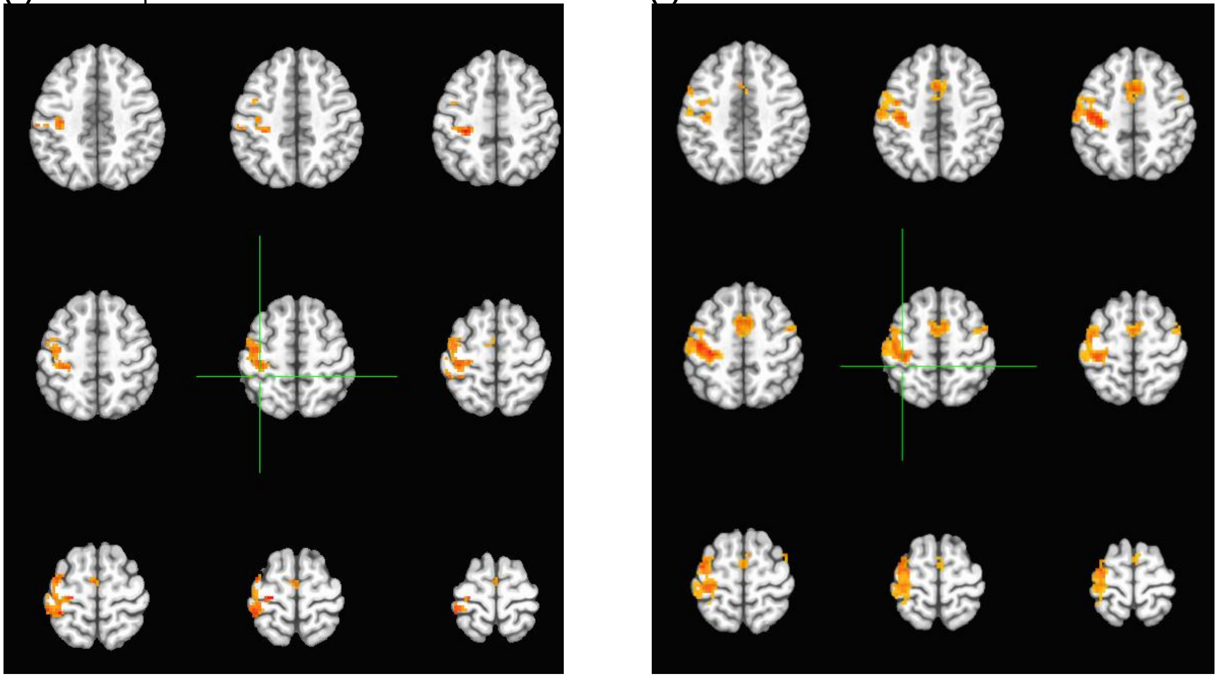


Figure 4 | Post group differences in BOLD activity for the Aerobic Spin and Baseline conditions. Data was corrected utilizing a voxel-wise cluster size of 100 voxels (t = 3.68; p < .01 holding alpha at .01). Balance condition exhibited increased left MI and SMA activity as compared to the Aerobic Spin condition.



(a) Aerobic Spin Condition

(b) Balance Condition

Figure 5 | Group differences after 3dMVM analysis of post-session imaging data between the Balance and Aerobic Spin conditions accounting for the pre-session. Data was corrected for multiple comparisons with a voxel-wise cluster size of 100 voxels (t = 3.68; p < .01 holding alpha at .01). Reduced left M1 and SMA activity observed in the Aerobic Spin condition as compared to the Balance condition.

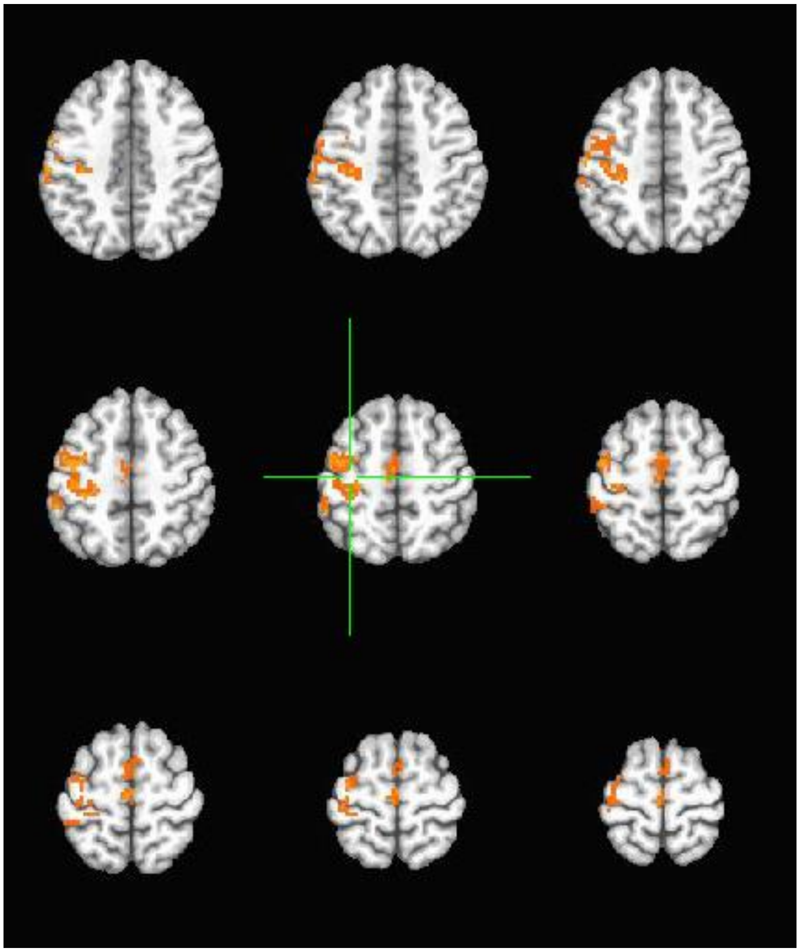


Table 5 | Results from AFNI 3dMVM analysis of group differences (Aerobic versus Balance) in fMRI activity during a unimanual right-handed finger-tapping task for the post session. Data was corrected for multiple comparisons using a voxel-wise cluster size of 100 voxels (t = 3.68; p < .01 holding alpha at .01). Cluster size is in voxels.

Number of Voxels	CM x	CM y	CM z	Peak x	Peak y	Peak z	Region
258	-37.4	-16.6	+56.4	-44.6	-6.1	+57.0	L M1
145	-2.4	-9.8	+61.0	-3.0	-18.0	+63.0	SMA
141	-56.1	-23.1	+47.0	-56.5	+5.8	+39.0	R Precuneus
134	+1.2	-79.7	+19.1	+3.0	-83.4	+15.0	V1
121	+52.1	+17.3	+4.7	+50.5	+14.7	+9.0	R Cerebellum

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