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Physical activity and neural correlates of aging: A combined TMS/fMRI study

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Abstract

Aerobic exercise has been suggested to ameliorate aging-related decline in humans. Recently, evidence has indicated chronological aging is associated with decreases in measures of interhemispheric inhibition during unimanual movements, but that such decreases may be mitigated by long-term physical fitness. The present study investigated measures of ipsilateral (right) primary motor cortex activity during right-hand movements using functional magnetic resonance imaging and transcranial magnetic stimulation (TMS). Healthy, right-handed participant groups were comprised of 12 sedentary older adults, 12 physically active older adults, and 12 young adults. Active older adults and younger adults evidenced longer ipsilateral silent periods (iSP) and less positive BOLD of ipsilateral motor cortex (iM1) as compared to sedentary older adults. Across groups, duration of iSP from TMS was inversely correlated with BOLD activity in iM1 during unimanual movement. These findings suggest that increased physical activity may have a role in decreasing aging-related losses of interhemispheric inhibition.

Keywords

Aging; Physical activity; fMRI; TMS; Interhemispheric communication

1. Introduction

Physical fitness has long been proposed to serve as a potential buffer against cognitive and physical decline associated with normal aging [1,2]. Recent research has focused on the

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effects of physical activity on the nervous system using advanced neuroimaging. These techniques, particularly magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI), have begun to provide valuable information about the positive effect exercise may have on brain integrity. Exercise has been associated with increases in overall brain volume [3], preserved gray matter density [4], and may contribute to increased density in brain white matter [5,6]. Recent work has even indicated that the beneficial effect of exercise on the mass and integrity of neural substrates can be shown in healthy preadolescent participants [7,8]. Findings from studies employing cognitive tasks during functional magnetic resonance imaging (fMRI) have revealed differences in patterns of cortical activity in older adults as a function of physical fitness [9–11]. That is, older adults with higher levels of cardiovascular fitness evidence better performance [11] and patterns of recruitment in the frontal lobes more similar to young adults than sedentary age cohorts during attentionally demanding executive function tasks [9,11]. Recent evidence has shown that patterns of motor-related neural activity in older adults may also be altered by regular engagement in physical exercise [10,12].

Across age groups, volitional unimanual hand movement will almost invariably result in increased metabolic activity in the primary motor cortex contralateral to the moving hand [13–15]. However, the activity of the ipsilateral cortex during such movements may vary according to one's chronological age or level of physical conditioning. In young adults, increasing evidence from fMRI studies indicate that, during unimanual tasks, activity in the ipsilateral primary motor cortex (iM1) is suppressed or deactivated, as indicated by a negative BOLD response (decreased T2* signal to levels below that of resting baseline conditions) in this area [12,14–17]. In contrast, during similar movements, older adults appear to recruit the ipsilateral motor (iM1) cortex, indicated by the presence of a positive BOLD response in this area [12,16,18–21]. However, the recruitment of the ipsilateral cortex in older adults may vary as a function of their physical fitness level. Recently, Voelcker-Rehage et al. reported that older adults with higher levels of motor (muscle strength and coordination) and physical fitness, evidenced decreases in ipsilateral BA4 activity relative to baseline during a unimanual button response task (Flanker task) [10].

fMRI has yielded interesting findings in the investigation of interhemispheric cortical motor processes, but as a methodology, its use in this respect is somewhat novel. For some time, transcranial magnetic stimulation (TMS) has been the accepted standard for the study of interhemispheric communication, particularly in the assessment of inhibitory processes [22]. TMS involves the application of a brief magnetic pulse to specific sites at scalp areas just above the motor cortex. Changes in muscle activity (as measured by electromyography) after stimulation can reveal information about the underlying neural circuitry depending on the stimulation protocol in use. Paradigms in TMS assessing interhemispheric inhibition have revealed analogous results to fMRI in that the performance of unimanual movements by young adults is associated with deactivation of the ipsilateral primary motor area [23–25]. Further, aging-related TMS studies of interhemispheric communication across both paired pulse [26–28] and single pulse methodologies (i.e., the ipsilateral silent period) [29,30] have reported that chronological age may indeed be associated with a loss of interhemispheric inhibition.

Physical activity, specifically aerobic exercise, may serve to influence changes in interhemispheric activity associated with healthy aging. For example, Voelcker-Rehage et al. recently reported that physically fit older adults fit showed BOLD decreases (relative to baseline) in ipsilateral motor cortex (iM1) during a unimanual fMRI task while sedentary adults in the study recruited iM1 (see also [12]). In TMS, [31] reported that physical activity was associated with increased cortical reactivity. To date, however, we are unfamiliar with

any studies that have assessed the effects of physical activity on interhemispheric inhibition using a combination of the two modalities.

To test the hypothesis that regular exercise affects interhemispheric communication dynamics within the aging motor system, the present research used fMRI and TMS to compare patterns of cortical motor activity across elderly adults who were either physically active or sedentary. A group of young adults was also included in the current investigation for comparison purposes. We hypothesized that older adults engaging in regular bouts of exercise (physically active) would exhibit patterns of interhemispheric activity similar to those shown in the young group, given the reported benefits of exercise on the aging brain. Further we predicted that the sedentary older adult group would display evidence of loss of inhibition on measures of interhemispheric communication.

2. Methods

2.1. Participants

Forty-five right handed participants (15 young [ages 18–37], 30 elderly [ages 60–85]) enrolled in the current study and were reportedly healthy at the time of screening and study participation. Elderly individuals (60–85 years of age) were divided into two categories, sedentary and physically active, based on self-reported exercise activity on a physical activity inventory. Nine participants (3 young, 3 sedentary elderly, and 3 physically active elderly) were removed from study consideration due to scheduling difficulties (2 young), artifacts (head movement, spiking artifacts) in MRI (1 young, 2 sedentary, 2 active) or the presence of mirror motor activity (1 sedentary, 1 active) during unimanual pinch grip assessments. The first group ($n = 12$) of elderly adults was comprised of healthy individuals that engaged in voluntary cardiovascular exercise for fewer than 45 total minutes per week and was termed the “sedentary group”. The second group of elderly adults ($n = 12$) was comprised of healthy individuals who reportedly engaged in bouts of voluntary aerobic (swimming, bicycling, jogging, etc.) exercise lasting at least 30 min at least three times per week. Additionally, these older adults, termed the “physically active group”, were required to have engaged in active exercise patterns for over five consecutive years. Physical activity inventories were also completed for the third group consisting of young adults, but not used as a criterion for exclusion or differentiation within the age group.

All elderly participants were required to obtain a physician’s clearance prior to participation in the submaximal exercise assessment. We excluded individuals with cardiac history (angina, prior cardiac arrest, uncontrolled hypertension) contraindicating tests of aerobic fitness. We also excluded individuals with contraindications to MRI including metal implants, a history of dementia, alcohol or drug abuse, neurological disorder (tremor, stroke, motor disorders, multiple sclerosis), major psychological disorder, or hearing difficulties. A medication history was taken for each participant. Persons on medications that were contraindicated for fitness testing (beta blockers) or MRI (calcium channel blockers) were also disqualified from the study. Cortical activation characteristics in primary motor cortex may be altered by skilled [32,33] or repeated digit movement practice [6] so we excluded participants if they reported that they engaged in repeated skilled finger practice (musical instruments, expert typing, etc.) with practice specified as at least three one-hour training sessions performed on a weekly basis. Study personnel completed the informed consent process with each participant following protocols approved by the University of Florida’s Institutional Review Board (IRB).

Participant characteristics are listed in Table 1. Group comparisons of handedness using the Edinburgh Handedness inventory [34] did not reveal significant differences between any of the groups.

2.2. Sessions and procedures

Participation for the study occurred over two sessions separated by at least 8 calendar days but not more than 21 days. We attempted to schedule both sessions at the same time of day to avert potential differences due to circadian cycles. Participants were asked to refrain from drinking caffeinated beverages at least three hours prior to each session to prevent potential signal alteration in imaging.

2.3. First session: motor assessment and exercise measures

2.3.1. Motor assessment—During the first session, participants completed three motor assessments consisting of an index finger tapping speed assessment, a simple visuo motor reaction time test, and a hand grip force assessment. To test index finger tapping speed, the participant placed their right hand on a flat surface and was asked to maintain contact with the surface with the palm of their hand while pressing a keypad button with the index finger of the right hand in 60-s activity blocks. During the visuomotor reaction time test, the participant maintained a similar surface contact with the right hand and depressed a keypad button, on a computer, when a pseudorandomly timed target stimulus was presented on the screen. Hand grip force was measured using a 30-psi squeeze bulb dynamometer.

2.3.2. Aerobic endurance—Participants underwent a 12-min distance challenge on a treadmill. Researchers instructed participants to travel as far a distance as possible for 12 min after a brief warm-up period involving slow-paced ambulation. Greater distance achieved has been found to be associated with a higher fitness level [35]. Study staff members instructed participants to travel (walk, run or jog) as far a distance as possible for 12 min after a brief warm-up period involving slow-paced ambulation. All participants were required to exhibit postural stability on the treadmill prior to data recording. The participant's heart rate was continuously monitored for signs for tachycardia, the presence of which would have triggered cessation of the test (this occurred in no participants tested). Distance traveled was recorded and used for analysis.

2.3.3. Physical activity monitoring—To calculate subjective time spent in physical activity during a monitoring period of one week, all participants completed the Leisure-Time Exercise Questionnaire (LTEQ), which is a three-item scale that asks participants to rate how often they engaged in mild, moderate, and strenuous leisure-time exercise [36]. The LTEQ is a reliable and valid measure of leisure-time exercise behavior in adults [37] that allows for calculation of metabolic equivalent of task (MET) scores using the following formula: $[3(\text{duration of mild activity}) + 5(\text{duration of moderate activity}) + 9(\text{duration of strenuous activity})]$. Although typically used as a seven-day recall of physical activity behavior, in the present study the LTEQ was used as a measure in which time spent daily in physical activity was summed to derive a weekly leisure activity survey (WLAS).

2.4. Second session: transcranial magnetic stimulation and functional MRI

After at least eight calendar days, the participant was scheduled for the second and final participation session at which time they were to return the log of their weekly exercise activity (LTEQ). Immediately after arrival, the participant provided informed consent for the session's procedures.

2.5. Single-pulse transcranial magnetic stimulation

For the TMS procedure, participants sat in a comfortable chair within the confines of a stereotactic positioning frame. Electromyography (EMG) was taken from the first dorsal interosseous (FDI) muscle on both hands. Muscle activation was monitored with a real-time oscilloscope software package (Scope 4.0, ADInstruments Ltd., Colorado Springs, CO). A

Magstim 200² magnetic stimulator (The Magstim Company Ltd., Carmarthenshire, UK) with a 70 mm figure-of-8 coil was used to stimulate the left primary motor cortex during the initial mapping procedure. Navigation of the stimulator coil to target cortex was accomplished using coil registration to a standardized brain image provided by BrainSight software (Rogue-Research, Montreal, Quebec). During stimulation, the coil was placed tangential to the scalp with the handle pointing backwards and 45 degrees away from the midline. The scalp site (“hotspot”) corresponding to the lowest stimulator output sufficient to generate a magnetic evoked potential (MEP) of at least 50mV in six out of ten trials was defined as the area of lowest motor threshold (LMT). This hotspot was the single site of stimulation for all measures in the current investigation, which are described below.

Two single-pulse TMS measures were considered for the current study: LMT value and ipsilateral silent period (iSP). To assess the ipsilateral silent period, the right FDI muscle was contracted via pinch grip at 40–50% maximal voluntary contraction (MVC), determined by grip dynamometer, and a 150% LMT TMS stimulus was delivered to the left primary motor area FDI hotspot. Ten consecutive trials were performed for iSP assessment. Prior to silent period assessment, the participant was instructed to maintain the non-active hand in a prone, resting position.

2.6. Functional imaging

After the TMS session, participants were given a rest of approximately 30 min during which time they were instructed on the tasks to be carried out during MRI. After acknowledging understanding of the MRI procedures, the participant was brought to the imaging facility.

2.6.1. Parameters—Magnetic resonance images were acquired on a 3 Tesla Achieva Whole-Body Scanner (Philips) using an 8-channel SENSE head coil. Head motion was minimized using foam padding. Before functional imaging sequences, structural images were also acquired (160 mm×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 planar functional images (EPI) were acquired using 57 mm×2 mm thick axial slices and the following parameters: TE = 30 ms; TR = 4000 ms; FA = 87; FOV = 192 mm × 192 mm × 114 mm; Matrix = 96 × 96; SENSE factor = 1.5. Two dummy EPI acquisitions were acquired and discarded to allow for signal equilibration.

Stimuli were presented on a first surface mirror presentation system situated at the rear bore aperture of the magnet. Stimuli were sent via personal computer (PC) to an Optoma projector (Optoma Inc., Milpitas, CA) at a field of 1024 × 768 pixels.

2.6.2. Imaging tasks—A block-design, right-hand motor task was used to evaluate interhemispheric cortical activation patterns. Blocks consisted of seven images (28 s) for both rest and active conditions. Six cycles (alternating between 7 rest images and 7 active images) comprised each run (5 min 36 s). In the scanner, participants engaged in two runs of the motor task and all performance data (accuracy, reaction times) was saved for later analysis. Participants were trained on the task inside the scanner prior to data acquisition. Between runs, participants again 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 ipsilateral primary motor cortex (M1) in young adults [15,16]. Performance of similar tasks in sedentary elderly samples, however, shows positive BOLD responses in ipsilateral M1 [12]. Stimuli were presented using E-Prime software (PST Software, Pittsburgh, PA). Button responses were made on a RP04U button response unit (BRU) manufactured by MagConcept (Sunnyvale, CA) 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 participant was 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 response 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 2 runs. Blocks were cued by the change of fixation cross varying between the word "Squeeze" (movement condition) or the word "Rest" (rest condition). During the movement condition, participants were instructed to time button presses with the flashing visual stimulus (2 Hz). Trials were briefly practiced in the scanner prior to image acquisition. Researchers in the scanner operation room monitored subject performance during the task. Mirror movements of the left hand were noted if visible.

2.7. Analysis

2.7.1. Behavioral measures—Group data for behavioral measures were compared using between-subjects Student's *t*-test and *p*-values. 0.05 were considered statistically significant. Statistical analyses were completed using the application JMP 7.0 (SAS Institute, Cary, NC), unless otherwise specified.

2.7.2. Physical activity—Different aspects of aerobic fitness have been reported to vary between participants both highly fit and sedentary [38]. As such, the current study indexed physical exercise using two measures (activity survey, 12-min treadmill test) rather than a single assessment.

2.7.3. fMRI task measures—Performance accuracy on the fMRI task (tapping rate) was compared between groups. Errors on fMRI tapping were defined as omitted or multiple button presses at each interval of the visual tapping cue (500 ms response window).

2.7.4. Mirror movements—As a criterion for data exclusion, we also included the presence of mirror movements during unimanual muscle contraction at the TMS session. We assessed such movements during 10 unimanual contractions each of both the left and right first dorsal interosseous (FDI) muscle (via submaximal force pinch grip) using electromyography (EMG). A mirror score for each hand was calculated for each trial by taking the root mean square of the EMG in the mirror hand and dividing by the median EMG root mean square value (over the 20 contractions) in the voluntary hand. This procedure was adapted from previously reported work [39,40]. The mirror scores for the trials were then averaged within each hand squeeze condition. Individuals exhibiting a mirror score greater than 0.20 were removed from study consideration.

2.7.5. TMS—Two measures were analyzed from TMS: lowest motor threshold (LMT) and duration of ipsilateral silent period (iSP). Scope 4.0, JMP 7.0 and Microsoft Excel 2007 software were used to complete this analysis. This procedure was modified from [41]. All EMG data was rectified and normalized to baseline of prestimulus EMG prior to analysis. EMG baseline was taken as mean of the 20 ms pre-stimulus waveform during pinchgrip. The latency of MEPs was measured from the onset of the stimulus presentation to the onset of the MEP. The first of five consecutive datapoints after MEP that evidenced a minimum decrease of 80% from mean EMG values from the 20 ms prestimulus recording period were taken as the silent period onset. Conversely, the first of five consecutive data points

evidencing a return to greater than 20% of prestimulus mean levels was set as the point of termination of the silent period. Group comparisons of TMS measures were analyzed using between-subjects Student's *t*-test and *p*-values < 0.05 were considered statistically significant.

2.7.6. fMRI—Functional images were analyzed and overlaid onto structural images with the Analysis of Functional Neuroimaging (AFNI) program [42]. To mitigate spatial deviation from the structural to functional images, a local Pearson correlation registration procedure was implemented with AFNI's 3dAllineate program [43]. To minimize the effects of head motion, timeseries images were spatially registered in 3-dimensional space to the first functional image using a linear rigid-body transform as implemented by AFNI's 3dvolreg. A subject's data was excluded from further analyses if any time series of a subject is judged, from visual inspection, to contain a significant number of images with gross artifacts or residual motion. Signal timeseries were then Z-normalized within runs to mitigate signal intensity variance between runs and participants. To control for multiple comparisons, a False Discovery Rate correction [44] procedure was utilized on fMRI statistical maps using AFNI's 3dFDR program with a *q* value set to .05.

2.7.7. fMRI within group analyses—We hypothesized that sedentary elderly adults would show a positive BOLD response in their right motor cortex (rM1), while young adults and physically active elderly adults would show a negative BOLD response in this region. To assess this hypothesis, we performed a within-group analysis of average hemodynamic response functions in primary motor cortex. For this procedure, functional images were spatially smoothed using a 5mm full-width half-maximum (FWHM) Gaussian filter to compensate for variability in structural and functional anatomy across participants. Anatomic and functional images were then interpolated to volumes with 1mm³ voxels and converted to stereotaxic space of Talairach and Tournoux [73] as implemented by AFNI. Estimates of hemodynamic response functions (HRF) were generated from a 12-lag deconvolution procedure, as implemented by AFNI's 3dDeconvolve [74], for each participant. Deconvolution is a model-free signal analysis technique that can create an estimate of the hemodynamic response function (HRF). We selected this procedure due to the expected differences between groups of the HRF. To assess group differences on this measure, we took that area under the curve (AUC) of the estimated hemodynamic response function for each voxel. For each of the three groups, AUC of each voxel's estimated HRF during active response were entered into a voxel-wise *t*-test (AFNI's 3dttest) against a null hypothesis of no change from baseline during the functional task.

2.7.8. fMRI between group analyses—Comparisons were made between groups of estimates of hemodynamic response functions (HRF) derived from the above-described deconvolution analysis. Area-under-the-curve (AUC) of each Talairach transformed voxel's estimated HRF was entered into a voxel-wise between-subjects *t*-test (using AFNI's 3dttest) for each pair-wise comparison of the three groups for each functional task.

2.7.9. M1 hemodynamic response function analysis—The group analysis described above is sensitive to magnitude of differences in voxels across groups, but relatively insensitive to the specific profile of the BOLD response. As deconvolution analysis, even in a block design, is sensitive to possible changes in the profile of the hemodynamic response [74]. The hypothesis that sedentary and physically active elderly adults evidence directional changes in the profile of the hemodynamic response in motor cortex ipsilateral to the moving hand was tested. This region was identified on a Talairach-registered structural image by locating the following key landmarks. First, in sagittal view of the medial wall of the right hemisphere, the ascending marginal ramus of the cingulate sulcus was located.

Second, the next sulcus forward passing over the crest of the brain was taken as the candidate for central sulcus. Third, from sequential axial views or from a volumetric rendering, the precentral sulcus was located by its T-shaped intersection with the superior frontal sulcus, and the next sulcus back was taken as the candidate for central sulcus. Fourth, on a high axial view, the candidate central sulcus was confirmed if it showed an inverted omega-shaped “hand knob” [45] deep from the lateral surface. The cortex anterior to the central sulcus at this area was defined as primary cortex (M1). A spherical region of interest mask with a radius of 5 mm at the hand knob was then used at the center of the motor hand area of iM1. This mask was used for all participants and was derived from a Talairach averaged brain. HRF values constrained to this mask were then compared between groups using a mixed-model multivariate ANOVA (group as between-subjects factor, HRF lag values as within-subjects factor).

2.7.10. Regression analysis of iSP with AUC fMRI data—Additional regression analyses were completed with the fMRI data from each task to account for the contributions of behavioral and neurophysiological measures towards fMRI amplitude change as estimated by the area-under-the-curve values derived from deconvolution. To this end, AFNI’s 3dRegAna application was employed using linear regression with the ipsilateral silent duration in prediction of AUC values. Hypothesis testing was completed for iSP duration on AUC from fMRI using a *t*-test with statistical significance was held to $p < .05$, FDR corrected.

2.7.11. Correlation analyses—We completed correlation analyses of reaction time (RT), iSP duration and AUC measures for right motor cortex from fMRI. AUC measures were derived using the same M1 region of interest mask used for the hemodynamic response analysis.

3. Results

3.1. Behavioral measures

Table 2 shows group means and *t*-test comparisons for behavioral measures significant at $p < .05$. Significant differences existed between all levels of age and activity group in regards to the physical activity scores (Weekly Leisure Activity Survey [WLAS], exercise challenge). The young group showed the highest assessed level of physical activity and the sedentary older group showed the lowest. The Active Elderly scored significantly higher on both fitness measures than the Sedentary Elderly, but these two groups did not differ from each other on motor measures. fMRI tapping error rate was below 2% for all participant groups. Groups did not differ in years of education.

3.2. Mirror movement assessment

Omitted from the study were two participants (elderly adults: 1 sedentary, 1 physically active) evidencing mirror movements beyond the threshold criterion during pinch grip assessment in the TMS session (described above). During fMRI, no participants evidenced overt mirror movements (monitored by visual observation) or reported such movements after inquiry.

3.3. Transcranial magnetic stimulation

Presented in Table 3 are group data from TMS with associated *t*-tests and significance. Young adults evidenced the longest ipsilateral silent periods and showed significant differences between both elderly groups. Physically active older adults evidenced significantly longer ipsilateral silent periods as compared to sedentary older adults, but also significantly shorter ipsilateral silent periods than young adults.

3.4. fMRI

3.4.1. Primary motor cortex: group comparisons—Presented in Fig. 1 are data from an AUC analysis of active block activity taken against a null baseline. A motor mask has been applied from a Talairach template. During the tapping task, both young adults and physically active older adults evidenced decreased AUC values relative to baseline in the hand knob [45] of right motor cortex while sedentary older adults showed increased AUC values in the right hand knob. Activity in Fig. 1 is depicted at $p < .05$, False Discovery Rate (FDR) corrected.

Group comparisons on AUC of estimated hemodynamic response profiles during motor tapping tasks are presented in Fig. 2. Hue in the figure indicates minimum significance at $p < .05$, False Discovery Rate corrected. Peak voxel coordinate for associated comparisons are presented in within the figure for each comparison respectively. Fig. 2A depicts a t -test comparison between sedentary elderly adults against active elderly adults with orange indicating higher AUC values in sedentary elderly adults and, oppositely, blue indicating higher AUC values in the active elderly group. Fig. 2B indicates comparison of sedentary elderly against young adults with similar color-significance indication as in Fig. 2A (orange indicates higher AUC in sedentary). Finally, Fig. 2C indicates comparison between active elderly adults against young adults; again with similar color-significance (orange indicates higher AUC in active elderly). As compared to sedentary older adults, both physically active older adults and young adults evidenced significantly lower values of AUC relative to baseline in the hand knob of right motor cortex during the tapping task.

Group averages of Talairach-transformed estimated HRF from right primary motor area are presented in Fig. 3A. A multivariate ANOVA indicated significant (Wilks' Lambda = .06, $F(22,58) = 8.01$, $p < .01$) differences between all three groups across the hemodynamic response profile over time. A one-way ANOVA comparing group HRF means at lag time intervals yielded significant group differences ($p < .05$) at timepoints (lag) 2–8 of the 12-lag HRF (denoted by asterisks in Fig. 3A). Younger adults and physically active older adults evidenced a decrease in BOLD signal relative to baseline while sedentary older adults showed BOLD signal increases relative to baseline. Fig. 3B presents a bar graph of the data in percentage signal change for the peak voxel values along the hemodynamic response within the same region of interest as Fig. 3A.

3.4.2. Regression analysis of iSP with AUC fMRI data—Regression analysis of ipsilateral silent period with the fMRI data showed that AUC values in rM1 were negatively associated with ipsilateral silent period duration across all participants. That is, lower ipsilateral silent period duration predicted larger AUC values in rM1. These data are presented in Fig. 4 with a $p < .05$ threshold (False Discovery Rate corrected).

3.4.3. Correlation analyses—Due to the influence of RT outliers, the non-parametric spearman ρ (rho) was used to correlate iSP duration with right motor AUC and RT with right motor AUC across groups. A significant negative correlation ($\rho = -.33$, $p < .05$) was found between iSP duration and AUC of rM1 during the tapping task. While not statistically significant at the .05 level, a positive trend ($\rho = .29$, $p = .08$) was found in correlations of serial RT (outside scanner) with AUC measures of right motor cortex. iSP duration and RT did not significantly correlate ($\rho = .15$, ns).

4. Discussion

The current study investigated the effects of physical activity on measures of interhemispheric inhibition previously shown to differ across age groups. During unimanual activity (finger tapping), AUC measures of the estimated hemodynamic response in right

motor cortex showed decreases relative to baseline (i.e., negative BOLD) in young adults. In contrast, AUC from right motor cortex in sedentary older adults evidenced positive BOLD activity relative to baseline. As with young adults, active older adults showed decreases in AUC in right motor cortex, though to a lesser degree than young participants. Group comparisons of AUC in right motor cortex during unimanual task activity show significant differences between physically active and sedentary older adults. Significant group differences were also found when comparing the ipsilateral silent period between the physically active and sedentary older adult groups. A negative correlation was found between AUC in right motor cortex during tapping and the ipsilateral silent period, indicating an inverse relationship between BOLD activity and the iSP. This correlation and a subsequent regression analysis indicated that negative BOLD changes were generally associated with longer iSPs, and that positive BOLD changes during motor activity generally were associated with shorter iSPs.

As compared to young adults, older adults, particularly sedentary individuals, evidenced decreases in measures of ipsilateral inhibition from both fMRI (decreased BOLD activity in right motor cortex) during unimanual task performance (finger tapping) and TMS (ipsilateral silent period). While similar findings have been reported from aging-related studies using a single modality (TMS: [29]; fMRI: [16], we are aware of only a single study that has combined fMRI and TMS to assess interhemispheric recruitment using an ipsilateral silent period assessment [23]. This small, but significant study presented fMRI and TMS data from ten participants in young to middle adulthood. The results showed that the adults who recruited the ipsilateral cortex during unimanual movement also lacked an ipsilateral silent period. We found in the present investigation correlations between AUC values in rM1 in fMRI and iSP values from TMS. Based on this correlation and a subsequent regression analysis (Fig. 4) between these measures we propose that negative BOLD in ipsilateral cortex (i.e., right motor cortex) during unimanual movements is indicative of an active inhibition of this area [17,46], which is diminished by the aging process.

The function of interhemispheric inhibition during unimanual movement is a topic of debate. It is possible that the inhibition of the ipsilateral motor cortex may serve to silence potentially task-interfering mirror movements of the non-active hand. The presence of unintended mirror movements (usually identified by EMG or force transduction measures) has been reported in pathological states (e.g., Kallman's Syndrome) [39,47] as well as in healthy adults of advanced age [48–50]. In healthy adults, these movements are typically seen in volitional movement of the non-dominant extremity [51], particularly for right-handed adults [52] and can complicate interpretation of data from unimanual tasks. In the present sample of older adults, EMG during unimanual pinch grip did not reveal the presence of mirror activity in opposite hand muscles in the participants whose data were analyzed (such movements were a criterion for exclusion). As such, it is unlikely that mirror recruitment of muscle groups in the ipsilateral hand could easily explain the aging related changes in interhemispheric inhibition observed in both TMS and fMRI in the present study.

The finding of aging related alterations in interhemispheric inhibition can be considered in light of the HAROLD (Hemispheric Asymmetry Reduction in Older Adults [53]) model of cortical activity changes across the lifespan. The HAROLD model describes a progressive increase in bilateral recruitment of functional activity (typically measured with fMRI) with increasing age during tasks for which one hemisphere is normally dominant. Such bilateral brain activity is not characteristic of the patterns observed in young adults, who tend to recruit only a single hemisphere to complete the same task (see Seidler et al. for recent motor-related review). That older adults in the current study showed lower levels of interhemispheric suppression could indicate that performance on unimanual tasks requires the compensatory recruitment of ipsilateral motor substrates [54–57] to accomplish the task

successfully. However, given the rather simple nature of the motor tasks involved in the current study, it is difficult to determine if ceiling effects on motor assessments limit potential group differentiation based on performance.

In contrast, it is possible that increasingly bilateral patterns of activity in older adults may be the result of a dedifferentiation of neural recruitment and potentially indicate an inefficient “overactivation” of neural substrates [58]. During unimanual motor task execution, bilateral M1 recruitment in older adults may actually confer no benefit towards the successful completion of the task [16,19]. For example, Riecker et al. had older adults perform index finger tapping with incremental increases in tapping rates (difficulty). A compensatory recruitment pattern would likely have been characterized by a corresponding incremental increase in positive BOLD in ipsilateral motor cortex (iM1) during such movements. However, older adults exhibited no differences in M1 recruitment across low to high tapping rates [16]. In addition, in a more recent study [12], we reported no changes in magnitude or direction of BOLD in iM1 in a sample of older adults when comparing externally or internally guided unimanual movements (the latter of which was reported as more difficult). Further, there exists evidence that iM1 over-activation in older adults may be correlated with decreased motor performance and increased reaction time [18]. A trend in this direction was evident in correlations of RT and AUC in rM1 in the current dataset. As such, the increased bilaterality in M1 recruitment for older adults could indicate an aging-related decline in motor function. Future research should involve a broader range of motor assessments to better characterize age-related changes in the motor system.

The most striking findings of the current investigation are the group differences in ipsilateral motor related neural activity during unimanual tasks between physically active older adults and their sedentary counterparts. Physically active older adults showed negative BOLD in iM1 during finger tapping while sedentary older adults, on average, showed a positive BOLD signal. During TMS, physically active older adults displayed a longer duration of ipsilateral silent period in comparison with the sedentary older group. These results indicate that the long-term maintenance of high levels of physical activity could delay or reverse losses of interhemispheric inhibition associated with chronological aging [12,16,28].

While previous work has indicated that aerobic exercise could serve to mitigate age-related cognitive decline [9,11,59–62], less is known of the potential effect of physical fitness on the human motor system. We found that older adults who engage in regular bouts of volitional exercise exhibit greater interhemispheric inhibition in ipsilateral M1, in contrast to their sedentary counterparts. However, the functional significance of this finding is not well understood and considerable variability exists in study reports from related literature. Some studies have reported that aging related loss of interhemispheric inhibition is associated with decreased task performance [18,29], while others have reported no performance gains with increased contralateral recruitment in older adults [16]. The differing findings from such studies likely reflect the variability of many measures in aged populations [63]. This offers an important point in consideration of the current study, which sought to identify a potential source (i.e., physical fitness level) of variance within older adults. In the present study, though sedentary older adults recruited more ipsilateral motor substrates (M1 AUC from fMRI) than physically active older adults, task performance did not differ significantly between the groups. Additional study is warranted to discriminate potential aging related changes in gross and fine motor activity as it relates to measures of interhemispheric communication.

If indeed the group differences in the present study indicate improvement in motor function with increased physical activity, the results further support the notion that regular aerobic exercise exerts beneficial effects on behavior in healthy aging. Functional MRI also has

been used to investigate differences in brain activity in older adults on tasks involving prefrontal areas between individuals of varying aerobic fitness levels. In a cross-sectional study, Colcombe et al. reported that participants who were more aerobically fit tended to show brain activation during the Erikson Flanker Task more consistent with younger adults. Sedentary older adults on the other hand showed activity in the anterior cingulate cortex, an area associated with behavioral conflict potentially indicating difficulties with attention to the task [9]. More recently, Prakash et al. showed that increased levels of physical fitness may improve task-relevant recruitment of prefrontal areas involved with executive control during such activity. In this study, during execution of the Stroop interference task, an attentionally demanding executive function test, older adults with higher cardiovascular fitness tended to recruit more task-appropriate prefrontal and parietal areas, as compared to more sedentary age cohorts. Moreover, this activity was correlated with better task performance, particularly in the most challenging task conditions [11]. In addition to functional MRI findings, results from aging-related structural MRI studies have revealed the benefits of regular physical activity. For example, in aging related literature, exercise has been associated with increases in overall brain volume [3] and increases in gray matter density [4,62]. Importantly, aerobic fitness has also been associated with increased density in brain white matter [5,6,64] across older adults. Given that the corpus callosum mediates interhemispheric inhibition, as indexed by the cortical silent period [65,66]; white matter changes could be the origin of the differences in interhemispheric inhibition apparent in the current study [46].

It is important to note that the current study involved the assessment of physical activity and not specifically aerobic fitness level. Recent evidence is clear that aerobic exercise is likely the mechanism of change within the physiological system [7,11,62,67]. Increased levels of aerobic activity yield increases in levels of neurotrophic factors (Brain Derived Neurotrophic Factor [BDNF], Insulin-like Growth Factor, Fibroblast Growth Factor) [68,69]. These resulting changes, with particular emphasis on BDNF, have a strong correlation with improvements in both the neural structure and function of the human brain [62,70]. Qualification for inclusion in the current study's physically active group required the regular engagement in regular prolonged bouts of moderate to strenuous exercise, which, in the assessed group, was almost exclusively aerobic (swimming, cycling, elliptical, jogging). Moreover, participants had to engage in this pattern of activity for over five consecutive years prior to the time of assessment. As such, this long term physical activity may have resulted in differential levels of neurotrophic factors in comparison to the sedentary age cohort. Future work should involve the assessment of neurotrophic factor levels, specifically BDNF, via serum assay to better characterize the neurochemical mechanism of change.

One of the strengths of this investigation is that it marks, we believe, the first study to combine both fMRI and TMS to assess the relationship between physical activity and interhemispheric inhibition in aging. While both MRI [58,64,67,71,72] and fMRI [9–11] have been utilized to investigate the effects of physical activity on the human brain, we are aware of only one existing study [31] utilizing TMS measures (paired associative stimulation) in such a context. In this work, Cirillo et al. reported that younger adults (18–37) who engaged in regular bouts of aerobic exercise evidenced higher levels of cortical reactivity and excitability in the motor cortex contralateral (cM1) to the target hand. In the current study, we noted an inverse correlation between ipsilateral silent period from TMS with magnitude of iM1 BOLD response in fMRI in older adults. Although this finding establishes a link between the length of the iSP and the magnitude of the ipsilateral BOLD response, it is uncertain whether the loss of iM1 inhibition and the shortening of the iSP with aging are manifestations of the same underlying phenomenon or whether they indicate a

different set of underlying factors. Continued exploration of the relationship between fMRI and TMS measures with aging populations will help to better understand these factors.

The current study does have some limitations that should be considered. Firstly, we grouped individuals based on self-report on a physical activity questionnaire. The use of self-report presents some challenges to the interpretation of the findings from this work. The gold standard for assessment of physical activity involves the determination of an individual's maximum rate of oxygen uptake (VO₂max) with spirometry measures. Physical activity inventories, while correlated with VO₂max, are not an exacting measure of an individual's physical fitness level. We used a direct measure of physical activity (12 min walking test) to approximate this value as a validative measure of self-report, which had a notable limitation. Some of our physically active participants acknowledged slight discomfort with the treadmill as an exercise apparatus, as their exercise regimen involved low load bearing activities (swimming and cycling, in particular). As such, some individuals rated their tested self-performance as much lower than typical. Future studies should endeavor to include more precise metrics of physical fitness. Secondly, the current study used somewhat basic assessments (e.g., visuomotor reaction time, grip strength, tapping rate) to inventory motor performance. Individual differences in dexterity, interdigit coordination and skilled finger use (other than what was precluded by questionnaire) could account for variation in motor recruitment. Future work should better characterize motor performance with the inclusion of a more robust testing battery. Finally, the cross-sectional approach employed by the current work needs follow up. An aerobic fitness intervention with sedentary individuals would yield more explanatory power in estimation of both the direct effect of physical activity and a time scale of changes.

5. Conclusions

In summary, we have shown that normal aging may confer a loss of interhemispheric inhibition that can be detected with both fMRI and TMS. Further, this loss of inhibition appears to be ameliorated by routine exercise. The full implications of these changes need to be explored across the life span by expanding measures of motor performance and measures of fitness and by examining the rate of change in cortical and motor functions from young to old age. It will also be important to understand whether the changes in motor cortical function reported in this study are unique to the motor system, or if these findings would extend to the neural substrates of perception and cognition.

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Fig. 1.

Motor mask of comparisons of area-under-curve of the deconvolved hemodynamic response during performance of a tapping task taken against a null baseline condition with significance set to $p < .05$, False Discovery Rate corrected (hues: orange indicates positive t -statistic, blue indicates negative t -statistic). Data shown for: (A) young adults, (B) sedentary older adults, (C) physically active older adults. Both physically active older adults and young adults showed a negative to baseline pattern of activity in rM1, while sedentary older adults showed positive to baseline activity in rM1. Anatomical underlay is a skull-stripped standardized (Talairach) T-1 image. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Fig. 2.

Motor mask of group differences in area-under-curve group comparisons on tapping task at $p < .05$, False Discovery Rate corrected (hues: orange indicates positive t -statistic, blue indicates negative t -statistic). Each panel presents three axial slices of the primary motor cortex encompassing the motor hand area. Z-coordinates reflect position in atlas (TT) space for each slice. Additionally present (in white) are peak difference voxel coordinates for each group comparison. Panels present: (A) comparison of sedentary elderly group against active elderly (orange indicates large magnitude area-under-curve (AUC) in sedentary group; blue indicates larger AUC in physically active), (B) comparison of sedentary elderly group against young adults (orange indicates large magnitude AUC in sedentary group), (C)

comparison of physically active elderly group against young adults (orange indicates large magnitude AUC in physically active group). Both physically active older adults and young adults evidenced significantly lower AUC values in right primary motor cortex as compared with sedentary older adults. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Fig. 3.

Panel A presents average estimates of hemodynamic response profiles across 12-image deconvolution interval (Lag, abscissa) for right primary motor cortex (rM1) per group during motor tapping task. Graphs presented are for: (blue) young adults, (red) sedentary elderly adults, and (green) physically active elderly adults. The Z-score transformed data was constrained to areas in rM1 that were coincidentally active across groups ($p < .05$, False Discovery Rate corrected) in area-under-curve analysis. Asterisks on abscissa indicate differences ($p < .05$) between groups at lag interval from one-way ANOVA group comparison of average response value each lag interval. (B) Graph of percentage signal change of estimate of hemodynamic response from primary motor areas per group during

motor tapping task. Bars present average data from left and right motor cortex per group. Error bars reflect standard deviation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article)

Fig. 4. Regression analysis of ipsilateral silent period measures with area-under-curve values on tapping task at $p < .05$, False Discovery Rate corrected (hues: orange indicates positive t -statistic, blue indicates negative t -statistic). Across participants, larger levels of AUC in rM1 are inversely related to duration of ipsilateral silent period. That is, individuals who had a shorter the ipsilateral silent period in TMS, recruited (show positive BOLD) in the ipsilateral cortex during the fMRI tapping task. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Table 1

Participant characteristics.

	Active elderly	Sedentary elderly	Young
Age	68.2 (6.74) [60–85] [^]	70.64 (7.5) [64–83] [*]	24.3 (2.86) [19–37] ^{*,^}
N/gender	12/6 female	12/7 female	12/5 female
Education	16.4 (1.95)	15.4 (3.31)	16.9 (1.82)
MMSE	29.0 (0.57)	28.4 (1.20)	28.8 (0.68)
Mirror score	.024 (.08)	.043 (.08)	.029 (.04)

Cell values denote group means. Parentheses indicate standard deviation within cell. Bracket indicates range. Student's *t*-test contrast significance at $p < .05$ denoted by

* young vs. sedentary

[^] young vs. active

^o sedentary vs. active. MMSE=Mini-Mental Status Examination. Mirror Score=Mirror movement score based on EMG data during unimanual pinch grip.

Table 2

Behavioral measures.

	Weekly leisure activity survey (WLAS)	Exercise challenge (km over 12 min)	Visuomotor reaction time	Maximum right hand squeeze force (bulb)
Active elderly	124.5 (83) ^{^o}	.99 (.26) ^{^o}	361 ms (49.1) [^]	5.8 lbs (2.9) [^]
Sed. elderly	52.4 (47) ^o	.65(.23) ^{*o}	407ms (112.2) [*]	5.6 lbs (3.3) [*]
Young	67.58 (33.6) [^]	1.8 (.29) ^{*^}	270 ms (28.6) ^{*^}	6.8 lbs (2.6) ^{*^}

Cell values denote group means. Parentheses indicate standard deviation within cell. Student's *t*-test contrast significance at $p < .05$ denoted by:

* young vs. sedentary;

[^] young vs. active;

^o sedentary vs. active.

Table 3

Means and group comparisons for TMS measures.

	Active elderly	Sedentary elderly	Young
iSP duration (ms)	37.1 (12.4) ^{^o}	26.3 (7.2) ^{*o}	49.9 (10.5) ^{*^}
LMT	45.2 (10.2)	46.0 (12.1)	41.1 (7.8)

Cell values denote group means. LMT is reported as percentage of maximum stimulator output. Parentheses indicate standard deviation within cell. Student's *t*-test contrast significance at $p < .05$ denoted by:

* young vs. sedentary;

[^] young vs. active;

^o sedentary vs. active.

(Abbreviations: iSP=ipsilateral silent period; LMT=lowest motor threshold value.)