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Functional Language Networks in Sedentary and Physically Active Older Adults

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Abstract

Functional magnetic resonance imaging (fMRI) studies have identified consistent age-related changes during various cognitive tasks, such that older individuals display more positive and less negative task-related activity than young adults. Recently, evidence shows that chronic physical exercise may alter aging-related changes in brain activity; however, the effect of exercise has not been studied for the neural substrates of language function. Additionally, the potential mechanisms by which aging alters neural recruitment remain understudied. To address these points, the present study enrolled elderly adults who were either sedentary or physically active to characterize the neural correlates of language function during semantic fluency between these groups in comparison to a young adult sample. Participants underwent fMRI during semantic fluency and transcranial magnetic stimulation to collect the ipsilateral silent period, a measure of interhemispheric inhibition. Results indicated that sedentary older adults displayed reductions in negative task-related activity compared to the active old group in areas of the attention network. Longer interhemispheric inhibition was associated with more negative task-related activity in the right and left posterior perisylvian cortex, suggesting that sedentary aging may result in losses in task facilitatory cortical inhibition. However, these losses may be mitigated by regular engagement in physical exercise. (*JINS*, 2013, *19*, 625–634)

Keywords: Cognitive aging, Physical activity, Functional magnetic resonance imaging, Semantic fluency, Attention network, Transcranial magnetic stimulation

INTRODUCTION

Age-related cognitive decline results from changes in brain structure and function that occur with advancing age (Hasher & Zacks, 1988; Obler & Albert, 1980; Park & Reuter-Lorenz, 2009; Salthouse, 1996, 2001). Consistent brain activity patterns have been identified in the neurocognitive aging literature through the use of functional magnetic resonance imaging (fMRI) techniques, which are associated with cognitive performance during various tasks in healthy aging (For a review see Park & Reuter-Lorenz, 2009). These include (a) increased or less focal positive task-related activity (activity above baseline during a task) in older adults compared to young adults, especially in prefrontal cortex within the non–task-dominant hemisphere (Cabeza, 2002); and (b) age-related reductions in negative task-related activity (activity below baseline during a task) in midline and temporo-parietal regions that are associated with attentional resource allocation and overlap with the so-called "default mode network" (areas that are more active during rest and may reflect self-focused rather than task-focused attention), which we will refer to as the "attention network" (Buckner, Andrews-Hanna, & Schacter, 2008; Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Park, Polk, Hebrank, & Jenkins, 2010; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007; Raichle et al., 2001). The functional

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implications of age-related increases in positive activity are controversial; however, many studies suggest that it represents compensation for age-related brain decline (Park & Reuter-Lorenz, 2009). Other studies have shown that decreased negative activity in areas of the attention network is associated with poor performance on non-verbal spatial judgment tasks (Park et al., 2010) and compromised reallocation of attentional resources during verb generation in seniors (Persson et al., 2007). Furthermore, increased positive and decreased negative task-related activity has been associated with worse performance during word-retrieval in older adults (Meinzer et al., 2012).

Interestingly, age-related brain changes can be mitigated through exercise, which leads to increases in brain volume, normalized brain activity, and better cognitive performance in older adults (Colcombe et al., 2006; Colcombe & Kramer, 2003; Colcombe et al., 2004; Erickson et al., 2011; Ruscheweyh et al., 2011). Although studies of exercise in aging have focused on investigating the neural substrates of executive function (Colcombe, et al., 2004; Voelcker-Rehage, Godde, & Staudinger, 2011) and memory abilities (Erickson et al., 2009, 2011; Ruscheweyh et al., 2011), they have neglected its effects on word-retrieval tasks, such as semantic fluency. In neuropsychological testing, semantic fluency is the generation of a list of words based on their semantic category and it has been shown to decline with age (Schaie, 1997). In the present study, we were interested in the effects of aging and exercise on the functional activity of the attention and language networks during a semantic fluency task.

A recent study investigated age-related change in the attention and language networks during semantic fluency (Meinzer et al., 2012). Compared to young controls, healthy older adults displayed higher levels of positive task-related activity in non–task-dominant frontal regions (right BA 10 and 46) and reduced negative task-related activity in areas related to attentional resource allocation (right BAs 3/40 and 7/31). Importantly, the decreases in negative activity were associated with poorer semantic fluency performance in older adults. It is unknown, however, if increased physical activity alters aging-related differences in positive and negative task-related activity during semantic fluency. The present study was designed to approach this question by comparing a cross-section of physically active older adults with a sedentary age-matched cohort.

Most fMRI studies of age-related changes in cognitive functions do not inquire as to potential physiologic mechanisms driving changes in brain activity. Recently, it has been shown that aging is associated with loss of interhemispheric inhibition (Fujiyama, Garry, Levin, Swinnen, & Summers, 2009; McGregor et al., 2012, 2011; Sale & Semmler, 2005; Voelcker-Rehage, Godde, & Staudinger, 2010), and this loss of inhibition may have deleterious effects on task performance (Bernard & Seidler, 2012; McGregor et al., 2012). However, the relationship between language functions and measures of interhemispheric communication has yet to be explored.

The present study investigated whether brain activity during a semantic fluency task differed between young, sedentary old, and physically active old adults using fMRI. We hypothesized that the sedentary older adults would exhibit functional activity patterns consistent with aging, such as those observed by Meinzer and colleagues (2012) (i.e., increased positive and decreased negative task-related activity in the language and attention networks), whereas physically active old adults would resemble the young group. In addition, we aimed to investigate a possible physiologic mechanism underlying these differences. To this end, we collected the ipsilateral silent period (iSP), a measure of interhemispheric inhibition, using transcranial magnetic stimulation (TMS) on a subset of participants. We hypothesized that the iSP would correlate negatively with brain activity in areas of the attention/language networks, which would provide support for a possible underlying mechanism (loss of interhemispheric, and possibly intrahemispheric, inhibition) driving the reduction of negative task-related activity in old age.

METHODS

Participants

Young and community-dwelling older adults from the University of Florida and the Gainesville, Florida, region participated in this study. Older adults were recruited from existing aging research registries at the University of Florida and throughout the community *via* advertisements. Younger participants were recruited from the University of Florida and the Gainesville community *via* advertisements. Older adults were divided into Physically Active Older (PAO) and Sedentary Older (SO) groups based on self-reported physical activity level during a phone interview (refer to the Physical Activity Assessment and Group Assignment section). There were 15 participants in the PAO group (ages 60–85) and 12 in the SO group (ages 63–81), which was matched for age and education to the PAO group. Fourteen young adults (ages 19–37) comprised the Young Adult (YA) comparison group. Signed informed consent was obtained from all participants according to guidelines established by the Health Science Center’s Institutional Review Board at the University of Florida. Participants were compensated for their participation in the study. Refer to Table 1 for participants’ demographic and physical activity/fitness characteristics.

Inclusion Criteria

All participants were right-handed, native English speakers who were deemed eligible for MRI scanning following an extensive screening protocol (e.g., no cardiac pacemaker, ferrous metal implants, or claustrophobia). Participants were apparently healthy and reported no history of diagnosed neurological conditions, head trauma with loss of consciousness, cardiac conditions, learning disabilities, attention deficit disorder, alcohol or drug abuse, or psychiatric conditions. Older adults currently prescribed beta-blockers for hypertension management and those with a resting heart rate >120 beats/min, a systolic blood pressure >180, or a diastolic blood pressure >100 were excluded from the study. All participants scored ≥27 on the Mini-Mental State Examination [MMSE; (Folstein, Folstein, & McHugh, 1975)]. Forty-nine participants were originally enrolled in the study; out of which 47 completed participation (2 were withdrawn due to inability to complete the imaging protocol). Of the remaining 47, 1 SO participant was removed from analyses due to evidence of an ischemic event on MRI scan; 1 YA was excluded for non-compliance during the imaging session, and 4 participants were removed due to image artifacts (1 YA, 2 SO, 1 PAO). The total sample comprised 41 participants (15 PAO, 12 SO, 14 YA) with 38 having iSP measures.

Physical Activity Assessment and Group Assignment

As we were interested in physical activity level over time (years), we chose to use self-report to differentiate groups rather than only a single direct fitness assessment (which was instead used as a validating measure). Participants were enrolled into the physically active group (PAO) if they reported continuous engagement of moderate to strenuous activity (at least 3 weekly 45-min exercise sessions) on a regular basis for more than 3 years contiguous to the report. Participants were enrolled into the sedentary group (SO) if they reported fewer than 45 min/week of moderate to strenuous weekly physical exercise. All younger participants were assigned to the young adult (YA) comparison group irrespective of their self-reported physical activity levels.

To confirm self-reported physical activity levels and group assignment, all participants were asked to undergo a 12-min distance challenge and to monitor their physical activity levels over a period of 7 days using a modified version of the Leisure-Time Exercise Questionnaire [LTEQ; (Godin, Jobin, & Bouillon, 1986; Godin & Shephard, 1985)]. The LTEQ is a three-item scale that asks participants to rate how often they engaged in mild, moderate, and strenuous leisure-time exercise. The instrument is a reliable and valid measure of leisure-time physical activity behavior in adults (Jacobs, Ainsworth, Hartman, & Leon, 1993). For the purposes of this study, we calculated the total number of minutes spent in moderate and strenuous physical activity to validate self-reported group membership (See Table 1). During the distance challenge, participants were instructed to cover as much ground as possible on a treadmill by walking, jogging, or running for 12 minutes. Distance traveled in 12 minutes (self-paced, variable speed) served as the fitness measure to confirm self-reported physical activity levels.

Magnetic Resonance Image Acquisition

All images were acquired on a 3 Tesla Achieva whole-body scanner (Philips), with an 8-channel head coil, at the McKnight Brain Institute of the University of Florida. Head motion was reduced using memory foam padding. Structural Turbo Flash Echo (TFE) T1-weighted images were acquired before functional runs for 160 × 1 mm sagittal slices [field of view (FOV) = 240 mm; repetition time (TR) = 3.685 ms; echo time (TE) = 8.057 ms; flip angle (FA) = 8 degrees; matrix = 256 ×256; voxel size = 1.0 × 0.938 × 0.938 mm). Gradient echo, echo planar images (EPI) were acquired using 39 × 3.75 mm sagittal slices (FOV = 240 mm; TE = 30 ms; TR = 2000 ms; FA = 70 degrees; matrix = 64 × 64; voxel size = 3.75 × 3.75 × 3.75). All stimuli were presented using a surface mirror system projected to a screen located at the rear of the scanner bore (pixel resolution = 1024 × 768) using E-Prime software (Psychology Software Tools, Pittsburgh, PA).

fMRI task: Semantic Fluency

The imaging task consisted of three runs of blocked, covert semantic fluency production. Each run contained eight semantic categories (e.g., furniture, birds, colors) for a total of 24 categories inside the MRI scanner. During the active period, participants saw a word representing a category (2 s) in the center of the video screen and were instructed to silently produce as many members of the category as possible. After 20 s of silent word production a stop sign appeared on the screen (2 s), cuing participants to stop producing category members for that semantic category. During rest (20 s), participants were asked to stop performing the task and fixate gaze on a screen-centered crosshatch until the next trial. Active and rest periods alternated in a blocked manner for 6 min and 8 s per run, for a total time of 18 min and 24 s.

To assess the accuracy and number of category members produced, each participant completed an overt semantic fluency task outside the MRI environment. This task consisted of 3 more runs of 8 new categories each, for a total of 24 categories outside the MRI scanner. Outside the scanner, categories were verbally presented to participants by the experimenter. All participants were given 20 s per category to overtly produce as many items as possible. These categories were different from those presented inside the scanner and all runs were balanced for difficulty level and number of animate/inanimate objects. All runs were counterbalanced such that each of the 48 categories was presented an equal number of times inside and outside the scanner in a randomized manner.

Single-Pulse Transcranial Magnetic Stimulation

For the TMS procedure, participants sat in a comfortable chair within a stereotactic positioning frame. Electromyography (EMG) was recorded from the first dorsal interosseous (FDI) muscle on both hands. Muscle activation was monitored with oscilloscope software. A Magstim 200 magnetic stimulator with a 70 mm figure-of-8 coil was used to stimulate the left primary motor cortex during the initial mapping procedure to identify the site of lowest motor threshold (LMT) or "hotspot." Neuronavigation to a standardized brain image was completed using BrainSight software (Rogue-Research, Montreal). The TMS protocol is similar to that used in our previous work (McGregor et al., 2011). To assess the iSP duration, the participant produced isometric pinch grip at 30–50% maximal voluntary contraction, determined by pinch grip dynamometer while TMS was delivered concurrently at 150% LMT to the left primary motor area FDI hotspot. EMG was monitored from the right FDI. Ten consecutive trials were performed for the iSP assessment. After every five trials, the participant was given a brief rest to allay fatigue. During iSP assessment, the participant was instructed to maintain the non-active hand in a prone, resting position. EMG baseline was taken as mean of the EMG signal 20 ms pre-stimulus during pinch grip. The first of five consecutive data points after MEP that evidenced a minimum decrease of 50% 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 50% of prestimulus mean levels identified termination of the silent period.

PROCEDURE

Participation occurred over two sessions. After physician's clearance, participants were scheduled for the first study session in which they underwent cognitive testing followed by the distance treadmill challenge.

Participants then entered a monitoring period of 7 days during which they completed the LTEQ daily to summarize activity. Participants returned their completed LTEQ upon arrival for their second session, which involved the TMS and fMRI testing.

ANALYSES

Semantic Fluency Outside the Scanner

Analysis of variance (ANOVA) was conducted using SPSS17 software (Chicago, IL) to compare mean level of performance between the three groups during overt semantic fluency.

FMRI Image Processing

All functional images were pre-processed using Analysis of Functional NeuroImages Software (AFNI) (Cox, 1996) and FMRIB Software Library (FSL) version 4.1 (Smith et al., 2004). EPI data were registered, orthogonalized for linear trends, spatially smoothed (5 mm FWHM), and scaled to percent signal change. Deconvolution of estimated hemodynamic response (HDR) functions was completed using AFNI's 3dDeconvolve program. Area under the curve (AUC) of the estimated HDR function was computed for each voxel after deconvolution. The AUC measure was used as the dependent variable in the within- and between-subject analyses described below. All structural and functional images were non-linearly registered to the standard 2 mm MNI152 template using FSL tools FLIRT (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001) and FNIRT (Andersson, Jenkinson, & Smith, 2007a, 2007b). AFNI's AlphaSim program was used to calculate the probability of false detection at a voxel threshold level of $p < .01$ and minimum cluster size threshold of $p < .05$ (minimum cluster threshold = 624 mm^3; 5000 iterations). The Harvard-Oxford cortical and subcortical brain atlases included in FSL (Desikan et al., 2006) were used to localize clusters of interest, which were also corroborated by the authors *via* visual inspection.

Within-group comparisons against baseline

For each of the three groups, AUC of each voxel's estimated HDR from the 10-lag deconvolution was entered into voxelwise within group t tests (AFNI's 3dTtest) against an assumption of no change from baseline to represent the areas of positive and negative task-related activity during semantic fluency.

Between-group comparisons

Between-group comparisons were carried out using AFNI's 3dANOVA, with AUC as the dependent variable. This analysis was conducted to elucidate areas that were differentially active between the groups during semantic fluency. Contrasts between YA-PAO, YA-SO, and SO-PAO were conducted and are reported at the $p < .01$ level, cluster size corrected.

ROI Analyses

Given our *a priori* interest in areas of the attention and language networks, which should exhibit negative and positive task-related activity respectively, we extracted the estimated HDR function for each participant's right and left hemisphere in the following regions of interest (ROIs) as defined by the Harvard-Oxford cortical and subcortical brain atlases: inferior frontal gyrus (RIFG and LIFG), posterior cingulate cortex and precuneus cortex combined (PCC), angular gyrus, supramarginal gyrus, posterior middle temporal gyrus, lateral occipital cortex (RLOC and LLOC), basal ganglia (RBG and LBG), and thalami (RTh and LTh). The HDR function for the angular, supramarginal, and posterior middle temporal gyri were averaged to create a right and left posterior perisylvian ROI (RPPS and LPPS). We will refer to these ROIs as those comprising the attention and language networks.

To investigate the differences in the attention and language networks between the groups, the AUC value for each ROI was averaged within groups. We then used the non-parametric Fisher Exact Test using a 2×3 implementation by evaluating the direction (positive/negative) of AUC response in each region across groups. In this manner, the 11 region attention-language network can be evaluated for differences across groups. We then tested specific group comparisons using the non-parametric binomial test. The binomial test designates if likelihood of a binary outcome over a series of comparisons is due to chance or a non-chance factor. We tested whether the AUC value in each region of interest was larger in one group as compared to another. Statistical probability for this test was set to .05 and evaluated the number of times one group showed higher AUC values over all of the regions. We hypothesized that sedentary older adults would

Table 1. Participant demographics and behavioral characteristics

	Young ($N = 14$)		Active Old ($N = 15$)		Sedentary Old ($N = 12$)	
	M	*SD*	*M*	*SD*	*M*	*SD*
Age	24.21*^	4.81	68.6^	6.77	69*	5.27
Education	16.86	2.41	16.53	2.23	15.83	2.79
Gender	5 female		8 female		9 female	
Fitness	1.53*^	.25	.63+^	.21	.42*+	.16
PA	147.14^	79.07	312+^	239.14	128.19+	128.91
BMI	22.84	5.24	23.45	3.21	27.05	4.75
MMSE	28.93	.62	29.27	.59	28.67	1.15
Fluency	8.86*^	1.14	7.67^	1.05	7.52*	1.10

Note. +SO ≠PAO; *YA ≠SO; ^YA ≠PAO, Bonferroni corrected, $p < .05$. No significant gender difference between the groups was found χ^2 (2) = 4.01, $p = .14$. *M* = mean; *SD* = standard deviation; PA = physical activity level (LTEQ no. of minutes of strenuous and moderate physical activity per week); Fitness = distance traveled on treadmill in 12 minutes (miles); BMI = body mass index; MMSE = Mini-Mental State Examination score; Fluency = semantic fluency performance.

show a larger amount of positive task-related activity in the language network as well as more positive (or less negative activity) in the attention network during semantic fluency.

To better understand the relationships among the variables and whether there was a negative association between the iSP and positive/negative task-related activity, the AUCs for all ROIs described above were correlated with the iSP as well as with age, physical activity, fitness, and semantic fluency *via* Pearson two-tailed correlations.

To further validate our findings, we used previously published data as a "reference" for task-positive and task-negative activity during semantic fluency based on Meinzer and colleagues (2012). This latter study used word-repetition as the baseline state. To accomplish this validation, published coordinates from Meinzer's supplementary Tables 1 and 2 were used to extract the AUC from those regions (8 mm-radius spherical ROIs) that were positively or negatively active during semantic fluency in the young group.

RESULTS

Confirmation of Self-Reported Physical Activity Levels

Distance travelled during the treadmill test and number of minutes spent in moderate and strenuous physical activity over seven days (modified LTEQ) confirmed the older participants' self-reported sedentary or physically active status assessed during the phone screening. See Table 1 for significant differences between the groups on several variables.

Semantic Fluency Outside the Scanner

Refer to Table 1 for overt semantic fluency performance values for each group. There was a significant difference among the groups' semantic fluency performance, $F(2,38) = 6.08$, $p < .01$. Bonferroni-corrected *post hoc* tests indicated that the YA group produced more category items than either of the older adult groups ($p < .05$). There was no significant difference in the average number of items produced by the SO and PAO groups, even though they differed significantly on the fitness and physical activity measures.

FMRI Task: Semantic Fluency

Group comparisons

Results of the between-group comparisons are depicted on Figure 1 at a family-wise error corrected threshold of $p < .05$ (voxel-wise $p < .01$, 624 mm^3 clusters). See Table 2 for a list of significant clusters and locations. There were more areas of differential activity between the YA and SO groups than between the YA and PAO adult group (see Figure 1A and 1B)

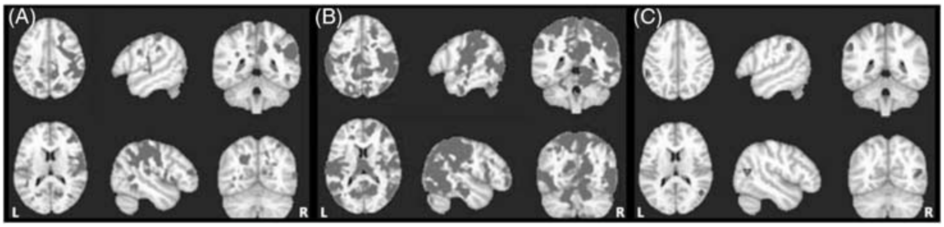

Fig. 1. Between-group comparisons during semantic fluency. (1A): YA – PAO; (1B): YA – SO; (1C): SO – PAO. Blue represents areas of significant difference in which older adults displayed more activity than the young adult group. The differences in brain activity between the YA and the PAO adults (1A) are less extensive than the differences between the YA and SO groups (1B). Figure 1C represents the areas of significant difference between the PAO and SO groups (right angular gyrus/lateral-occipital cortex and left supramarginal gyrus). YA = Young Adult; PAO = Physically Active Older; SO = Sedentary Older.

Table 2. Between-group comparisons

		Left hemisphere			Right hemisphere		
	Cluster	μL	*t*	X, Y, Z	μL	*t*	X, Y, Z
SO-PAO	SMG	918	4.63	143,81,109	0	—	—
	LOC, AG	0	—	—	799	3.89	39,65,85
YA-PAO	Left PCC, precuneus, PCG, Right PCG, posterior MTG, LOC, AG, SMG	733	−4	101,87,109	61797	−5.07	37,75,77
	Postcentral gyrus, insula, SMG, PCG, SPL	13253	−4.82	131,99,69	0	—	—
	Precuneus, LOC	4738	−4.24	135,55,71	0	—	—
	Frontal pole, IFG	0	—	—	2007	−4.45	51,162,81
	Amygdala, basal ganglia	0	—	—	2986	−4.53	67,125,59
	Frontal pole, paracingulate gyrus	0	—	—	1693	−4.39	67,185,73
YA-SO	Postcentral gyrus, LOC, precuneus, SPL, SMG	116358	−5.87	153,111,97	167983	−5.73	71,186,81
	Frontal pole, MFG, SFG	1319	−3.93	119,151,109	0	—	—
	Insula, putamen	1869	−4.18	117,139,71	0	—	—
	Occipital pole	192	−3.5	91,23,79	194	−3.54	89,24,79
	Frontal pole	765	−4.12	135,173,67	0	—	—
	PCG & SFG	0	—	—	653	−3.77	63,115,135
	Caudate	354	2.95	100,131,89	0	—	—

Note. Location, volume, and coordinates of peak activity, family-wise error corrected threshold of $p < .05$, 624 mm^3 clusters, voxel-wise $p < .01$.
PCC = posterior cingulate cortex; AG = angular gyrus; SMG = supramarginal gyrus; LOC = lateral occipital cortex; MTG = middle temporal gyrus; STG = superior temporal gyrus; IFG = inferior frontal gyrus; PCG = precentral gyrus; MFG = middle frontal gyrus; SFG = superior frontal gyrus; SPL = superior parietal lobule.

indicating that the PAO were more similar to the YA than the SO group. The SO group showed significantly greater activity than the PAO group in the right angular gyrus/lateral occipital cortex and in the left supramarginal gyrus (Figure 1C).

ROI analyses

To compare regions of interest between the groups, we tested AUC values of the estimated HDR function in ROIs within the attention and language networks using the 2 × 3 Fisher Exact test (positive/negative × 3 groups), which indicated significant differences between groups ($p < .05$ one-tailed). We then compared groups directly based on magnitude of AUC response value in each of the ROIs in the attention and language networks using a 2 × 2 Fisher Exact binomial test. Figure 2 depicts HDR values for regions in the attention and language networks. As hypothesized, the SO group displayed more positive task-related activity in our 11 *a priori* ROIs than either the PAO ($p = .043$) or YA groups ($p < .01$) during semantic fluency in these networks. This pattern was consistent when using Meinzer and colleagues' 28 reference ROIs, where the SO group displayed significantly more positive activity than either the PAO ($p = .044$) or the YA ($p = .0001$) groups.

Age was negatively correlated with semantic fluency ($r = -.48$; $p = .001$) and fitness level ($r = -.82$; $p < .001$) and positively associated with brain activity in the RIFG ($r = .39$; $p = .01$), LPPS ($r = .59$; $p < .001$) and RPPS ($r = .74$; $p < .001$) cortex, RLOC ($r = .58$; $p < .001$), LLOC ($r = .49$; $p = .001$), PCC ($r = .55$; $p < .001$), and the right thalamus ($r = .37$; $p = .02$). Semantic fluency performance was associated with higher fitness level ($r = .34$; $p < .02$), while physical activity level was not significantly correlated to any other measure. Higher fitness level was associated with longer iSP ($r = .57$; $p < .001$), and less brain activity in the RIFG ($r = -.41$; $p = .007$), RPPS ($r = -.61$; $p < .001$), LPPS ($r = -.54$; $p < .001$), PCC ($r = -.55$; $p < .001$), LLOC ($r = -.47$; $p = .002$), RLOC ($r = -.54$; $p < .001$), left ($r = -.33$; $p = .04$) and right ($r = -.39$; $p = .01$) thalami, and right basal ganglia ($r = -.36$; $p = .02$). This indicates that those who are more fit, also exhibit more negative task-related activity in areas of the attention and language networks. The iSP was negatively correlated with brain activity in the LPPS ($r = -.37$; $p = .02$), RPPS ($r = .34$; $p = .04$), and the left ($r = -.37$; $p = .02$) and right thalami ($r = -.33$; $p = .04$), indicating that those with longer iSP showed more negative task-related activity in the attention network, as hypothesized.

TMS results

See Table 3 for ANOVA results indicating significant group differences for the iSP, $F(2,35) = 6.98$, $p < .01$. Younger adults differed significantly from the sedentary old group on the duration of the iSP, but not from the physically active group. Younger adults showed the longest duration of iSP (longer iSP = better interhemispheric inhibition) followed by the active old adults. The sedentary old group showed the shortest iSP duration.

DISCUSSION

The goal of this study was to investigate if age-related brain activity changes (increased positive and reduced negative

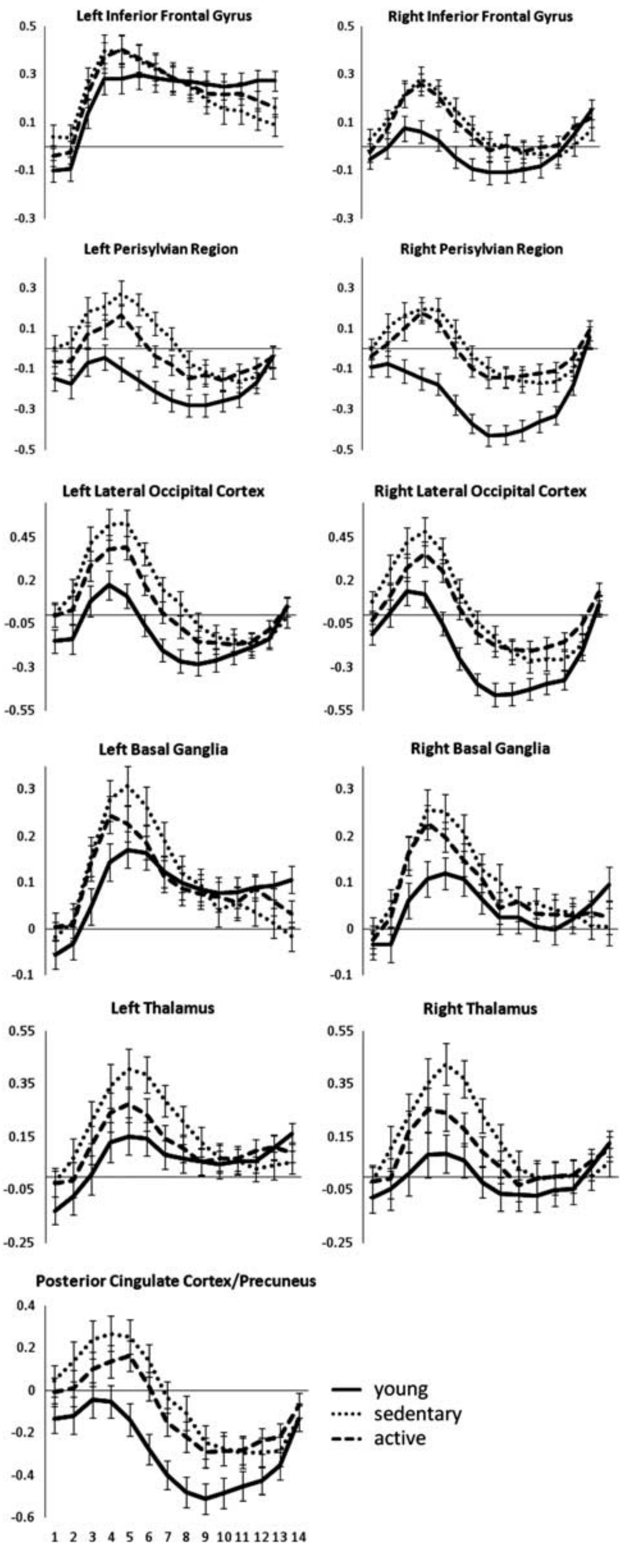

Fig. 2. Hemodynamic response function for *a priori* regions of interest (ROIs) in the attention/language networks. The X-axis depicts time [repetition time (TR) = 2 s] and the Y-axis portrays % signal change from baseline during semantic fluency. Standard error bars are depicted for each group. For most ROIs, HDR time course in the Physically Active Older (PAO) group is intermediate between the Young Adult (YA) and Sedentary Older (SO) groups.

Table 3. Means and group comparisons for iSP measures

	Active old	Sedentary old	Young
iSP Duration (ms)	43.25 (10.79)	36 (4.7)*	50.9 (9.88)*

Note. Cell values denote group means in milliseconds. Parentheses indicate standard deviation within cell. Analysis of variance contrast significance at $p < .05$ denoted by: * = Young *vs.* Sedentary.
iSP = ipsilateral silent period.

task-related activity) in language and attention networks would be mitigated by fitness level in older adults compared to young adults. Furthermore, we aimed to investigate a possible mechanism (interhemispheric inhibition) underlying these changes. While extensive attention has been afforded to the effects of exercise on executive function and memory, we believe this to be the first study investigating brain activity for word retrieval as a function of physical fitness in old age. Furthermore, exercise studies have not yet reported on age-related differences between positive and negative task-related activity, which have been shown to change with age and are associated with performance differences (Meinzer et al., 2012; Park et al., 2010; Persson et al., 2007).

There are two main findings in the current study. The first is that during a semantic fluency task sedentary aging appears to be related to increased positive task- related activity in attention and language processing regions typically suppressed in younger adults. It appears exercise may alter these changes in network activity, as the time course of the HDR function in areas involved with attention and language processing differed between physically active and sedentary older adults. The second finding was that longer ipsilateral silent period, a measure of interhemispheric inhibition, was associated with higher fitness level and more negative fMRI activity in areas of the attention network in the current sample.

Our findings are consistent with those of Meinzer and colleagues (2012) who reported that healthy older adults, compared to young adults, display increased positive task-related activity and reductions in negative task-related activity during semantic fluency, which in their study, were associated with poor performance. Our study is unique, however, in that the same patterns of brain activity reported by Meinzer and colleagues as a consequence of age can be attributed, at least in part, to differences in physical activity level in the current sample of older adults. In the current study, physically active older adults showed brain activity patterns similar to the young group in Meinzer and colleagues, while our sedentary old group resembled Meinzer's older adult group. The observed brain activation patterns occurred in the absence of semantic fluency performance differences between the older adult groups. This suggests that the differences in brain activity observed between the older groups are not attributable to differences in task difficulty level. Although we did not find significant relationships between brain activity and performance during semantic fluency in the current study, the young group did outperform both older adult groups while also displaying the largest amount of negative task-related activity and least amount of positive task-related activity.

Above and beyond replicating Meinzer's findings with a sample of active and sedentary older adults, the current study found an association between a measure of interhemispheric inhibition (iSP) and negative task-related activity. Adults who were more fit in the current sample also exhibited more suppression of activity in areas of the attention network. The fact that brain activity in the left and right posterior perisylvian cortex and thalami was negatively associated with the iSP and with fitness suggests that those who are more fit are better able to suppress activity in regions that should be inhibited during a cognitive task, while the sedentary older adults showed decreased suppression in these regions. These findings are consistent with those of McGregor et al. (2011) who found that fit older adults showed a negative blood oxygen level dependent (BOLD) response in ipsilateral motor cortex during a unimanual finger movement task, as did the young group, while the sedentary old group actually recruited the ipsilateral motor cortex. In this study, the iSP also correlated negatively with brain activity in the ipsilateral motor cortex, indicating that longer interhemispheric suppression is associated with a more negative brain response in the opposite hemisphere.

The authors proposed that negative activity in homologue regions of the motor cortex during unimanual movements represents a process of active inhibition, which is reduced with aging, and mitigated by physical fitness. A more recent study by McGregor et al. (2012) reported that this lack of interhemispheric inhibition is associated with poorer motor performance in older adults. A very similar pattern was observed in the current study whereby sedentary older adults showed reduced inhibition in areas of the attention network during a semantic fluency task when compared to the active older adults and the young control group. Hence, the sedentary group may experience more difficulty than the young and active older adult groups with the re-allocation of attention from internal thought or unconstrained processes, to a more constrained, cognitively-oriented action. Relationships between the iSP and language activity in posterior cortices suggest that difficulty in re-allocation of attention may be driven by deficits in active suppression (McGregor et al., 2011; Persson et al., 2007).

Although these patterns have not yet resulted in performance differences, it is possible that the sedentary older adults will exhibit earlier word retrieval deficits while the active older group remains stable over time, as has been the case with memory and executive function (Colcombe et al., 2004; Erickson et al., 2011; Ruscheweyh et al., 2011; Voelcker-Rehage et al., 2011). Interestingly, a recent exercise intervention study found that older adults assigned to a 12-month walking intervention showed reduced fMRI activity on an executive function task following the intervention, which was interpreted as increased processing efficiency (Voelcker-Rehage et al., 2011). This further highlights the premise that exercisers show less positive task-related activity, possibly due to more efficient inhibitory processes.

There are some limitations to the current study. Its cross-sectional nature does not allow us to infer a causal link between physical activity and mitigation of the effects of brain aging, though such a link has been established elsewhere (Colcombe et al., 2006, 2004; Erickson et al., 2011; Ruscheweyh et al., 2011; Voelcker-Rehage et al., 2011). Even though the current sample size was small, group differences were found. It is possible that significant differences in semantic fluency would have emerged given a larger sample. Furthermore, since the BOLD signal measured by fMRI is influenced by age-related changes in brain structure and metabolism (Ances et al., 2009; Fleisher et al., 2009; Huettel, Singerman, & McCarthy, 2001), we cannot rule out the possibility that our findings may be confounded by vascular age-related changes (i.e., cerebral blood flow, oxygen metabolism). To reduce this confound, we excluded participants with hypertension from participating in the study. Future studies should take into consideration age and exercise-related vascular differences by using techniques such as calibrated fMRI to further characterize changes in underlying metabolism across age groups (Ances et al., 2009). On a similar note, the control task used in the current study (fixation cross) was not optimal given that we cannot know for certain if participants were in fact "resting" and not continuing to perform the task. Even though this condition was not optimal, our results are similar to those of Meinzer and colleagues (2012) who performed a semantic fluency task with a repetition control condition (repeating the word "rest"). The fact that our results did not change when using Meinzer and colleagues' ROIs as a reference strengthens the current findings.

In conclusion, the current study was the first to investigate whether physical fitness level mitigates age-related brain changes in the neural substrates of language function, while describing a possible physiologic mechanism underlying these differences. We found that brain function in the physically active older adults resembled that of younger adults, while the sedentary group showed decrements in suppression of areas that should be inhibited during the task. Hence, physical activity may mitigate the effects of brain aging on language functions by helping to maintain a "younger" brain that is better equipped for efficient re-allocation of attention during language processing by suppressing the recruitment of task-irrelevant regions.

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