Journal of the International Neuropsychological Society (2011), **17**, 986–997.

doi:10.1017/S1355617711001093

SYMPOSIUM

Physical Activity Associated with Increased Resting-State Functional Connectivity in Multiple Sclerosis

Ruchika Shaurya Prakash,[1] Beth Patterson,[1] Alisha Janssen,[1] Amir Abduljalil,[2] AND Aaron Boster[3]

[1]Department of Psychology, The Ohio State University, Columbus, Ohio
[2]Department of Radiology, The Ohio State University, Columbus, Ohio
[3]Department of Neurology, The Ohio State University, Columbus, Ohio

(RECEIVED December 15, 2010; FINAL REVISION July 8, 2011; ACCEPTED July 8, 2011)

Abstract

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system, resulting in physical, cognitive and affective disturbances, with notable declines in the ability to learn and retain new information. In this study, we examined if higher levels of physical activity in MS individuals were associated with an increased resting-state connectivity of the hippocampus and cortex, resulting in better performance on a task of episodic memory. Forty-five individuals with a clinically definite diagnosis of MS were recruited for the study. Consistent with previous reports, hippocampus was functionally connected to the posteromedial cortex, parahippocampal gyrus, superior frontal gyrus, and the medial frontal cortex. Higher levels of physical activity in MS patients were associated with an increased coherence between the hippocampus and the posteromedial cortex (PMC). The increased connectivity between these two regions, in turn, was predictive of better relational memory, such that MS patients who showed an increased coherence between the left (not right) hippocampus and the PMC also showed better relational memory. Results of the study are interpreted in light of the challenge of disentangling effects of physical activity from effects of disease severity and its neuropathological correlates. (*JINS*, 2011, *17*, 986–997)

Keywords: Hippocampus, Resting-state functional connectivity, Episodic memory, Multiple sclerosis, Posteromedial cortex.

INTRODUCTION

Cognitive impairment is considered to be an important hallmark of multiple sclerosis, with deficits noted across multiple domains (Prakash et al., 2008) and observed early in the disease course (Audoin et al., 2006). Behavioral (Prakash et al., 2008) and neuroimaging studies consistently provide evidence for largest decrements in tasks of memory and learning, along with functional (Bobholz, Gleason, & Miller, 2008) and structural (Benedict, Ramasamy, Munschauer, Weinstock-Guttman, & Zivadinov, 2010; Sicotte et al., 2008) alterations in the medial temporal cortices in individuals with MS. In a recent study, Roosendaal et al. (2010) also reported reduced resting-state hippocampal functional connectivity in individuals with MS, relative to healthy controls. This reduced connectivity was observed in the absence of a decline in memory abilities, thus providing evidence of a reduction in the functioning of hippocampus before any observable behavioral deficits.

One of the most exciting findings of rehabilitation research is the consistent evidence that physical activity has the capability to influence the functional and structural properties of the hippocampus, thereby playing a vital role in exercise-induced improvements in learning and memory (Creer, Romberg, Saksida, van Praag, & Bussey, 2010; Erickson et al., 2009, 2010; van Praag, Christie, Sejnowski, & Gage, 1999; van Praag, Kempermann, & Gage, 1999). Non-human animal research has provided evidence for an increase in neurogenesis through cell proliferation in the hippocampus following exercise training, along with increasing hippocampal-dependent learning and memory processes as assessed by Morris water maze and radial arm maze performance (Anderson et al., 2000; Fordyce & Wehner, 1993; van Praag, Shubert, Zhao, & Gage, 2005; Vaynman, Ying, & Gomez-Pinilla, 2004).

Human research, through epidemiological, cross-sectional, and randomized controlled trials has also provided evidence for a beneficial influence of physical activity, combining both

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Correspondence and reprint requests to: Ruchika Shaurya Prakash, Department of Psychology, The Ohio State University, 1835 Neil Avenue, Columbus, OH 43210. E-mail: prakash.30@osu.edu

low-intensity, and high-intensity exercises on the functional and structural properties of the brain. Physical activity as assessed through a self-report questionnaire was found to moderate the age-related decline in the volume of medial temporal cortices in a cross-sectional investigation (Bugg & Head, 2009) and was also found to predict the rate of volume decline in the hippocampus 9–13 years later in a prospective examination (Erickson et al., 2010). Cardiorespiratory fitness, a physiological surrogate of physical activity enhanced primarily through aerobic exercises, has also been found to be associated with the volume of the hippocampus in both elderly participants (Erickson et al., 2009) and in pre-adolescent children (Chaddock et al., 2010). Through randomized controlled trials, there is also preliminary evidence that aerobic exercise is associated with an increase in the volume of the hippocampus (Erickson et al., 2011), and increased cerebral blood volume in the dentate gyri of the hippocampus (Pereira et al., 2007). An empirical question in this rich field has been the extent to which increases in aerobic fitness mediate the relationship between physical activity and cognition and while there is some support for this hypothesis through cross-sectional (Erickson et al., 2009, Prakash et al., 2011) and RCT investigations (Erickson et al., 2011; Pereira et al., 2007), two meta-analytic reviews directly testing this hypothesis failed to find support for increases in aerobic capacity to mediate the beneficial impact of physical activity interventions on cognitive functioning (Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008; Etnier, Nowell, Landers, & Sibley, 2006). In addition, a growing body of research on resistance training also provides evidence for a prophylactic influence of such exercises on executive control tasks (Liu-Ambrose et al., 2010) and episodic memory tasks (Cassilhas et al., 2007), possibly mediated by an increase in the production of nerve-growth factors, like IGF-1 (Borst et al., 2001, Cassilhas et al., 2007), and decrease in the concentration of serum homocysteine (Vincent, Braith, Bottiglieri, Vincent, & Lowenthal, 2003). Thus, there is some preliminary support for both low-intensity and high-intensity exercises to improve cognitive functioning, brain structure, and function.

Within MS focused research, our laboratory, has been systematically examining the association of cardiorespiratory fitness with cognitive and brain functioning (Prakash et al., 2007; Prakash, Snook, Kramer & Motl, 2010; Prakash, Snook, Motl, & Kramer, 2010). Extending this line of research to physical activity that involves both aerobic and anaerobic components, we examined the association between activities during waking hours and functional connectivity of the hippocampus during quiet wakefulness, along with better performance on an item and relational memory task.

Investigating intrinsic, spontaneous, low-frequency fluctuations in regional cerebral blood flow during resting state has marked the emergence of a new era in the field of neuroimaging (Damoiseaux & Greicius, 2009). In here, the connectivity between different regions of the brain is examined in the absence of external stimulation, resulting in well-characterized functional networks of the brain. These intrinsic brain networks have been implicated in Alzheimer's disease (see Greicius, 2008 for a review) and predict the magnitude of task-induced BOLD activation (Mennes et al., 2010). Individual differences in resting-state connectivity have been linked to working memory and executive control (Damoiseaux et al., 2008; Voss, Erickson, et al., 2010), and episodic memory (Wang et al., 2010) in healthy older adults.

Given the significant decline in the ability to learn and retain new information in MS (Thornton & Raz, 1997), much of which depends on the intact functioning of the hippocampus (Ranganath, Heller, Cohen, Brozinsky, & Rissman, 2005), we examined whether higher levels of physical activity in individuals with MS was associated with increased low-frequency fluctuations between the hippocampus and regions of the cortex during quiet wakefulness, which in turn, was predictive of better memory performance. Based on the existing literature, we hypothesized a positive relationship between physical activity and hippocampal connectivity in MS individuals. Furthermore, we also predicted higher levels of physical activity to be associated with better performance on a task of relational memory, known to be dependent on the intact functioning of the hippocampus.

METHODS

Participants

Forty-five participants (34 females and 11 males), with a clinically definite diagnosis of multiple sclerosis, according to the revised McDonald criteria (Polman et al., 2005) were recruited to participate in this study. Participants were recruited via advertisements in the local media, promotional flyers, Ohio State University's MS center, and through advertisement in NARCOMS. All participants were required to satisfy a number of inclusionary criteria: a score greater than 23 on the MMSE (maximum score = 30; Folstein, Folstein, & McHugh, 1975), corrected (near and far) acuity 20/40 or better, right-handedness as assessed by the Edinburgh Handedness Inventory, between the ages of 30 and 59, no corticosteroid use in the previous month, and an Expanded Disability Status Scale (EDSS) score of no more than 6 to ensure ambulation. In addition, participants with a previous history of any other neurological disorder other than MS, or psychiatric disorder were excluded from the study. All participants were prescreened for suitability in the magnetic resonance imaging environment, for example, no metallic implants that could interfere with the magnetic field or cause injury, no claustrophobia, and no history of head trauma. The Ohio State University Institutional Review Board approved the study and all participants provided informed consent.

Forty-two of these participants had relapsing-remitting MS, while the remaining three had primary progressive MS. Additional information on participant demographics and pertinent clinical factors is presented in Table 1. All participants gave approval to collect protected health information from their neurologists, who confirmed diagnosis of MS, criteria used, type and duration of MS, and current medications. Participants also filled out the self-reported version of EDSS, which has been shown to have a high correlation with

Table 1. Presents the demographic and clinical characteristics of the MS sample included in the current study

	Descriptives		
Demographic/Clinical Factor	Mean	*SD*	Range
Age (years)	45.18	8.28	30–58
Education (years)	15.58	2.24	12–20
Mini-Mental Status Examination	29.16	1.12	26–30
Expanded Disability Status Scale	4.08	1.27	2–6
Duration of MS (years)	10.13	6.68	1–29
Average activity over a 7-day period (counts/day)	180,894.87	104,866.62	61,015–526,445

physician-reported EDSS ($r = 0.87$, Bowen, Gibbons, Gianas, & Kraft, 2001).

Physical Activity Assessment

Physical activity was measured using the Actigraph GT3X accelerometer^{TM} (model 7164 version, Health One Technology, Fort Walton Beach, FL). The accelerometer recorded steps and activity level dependent upon predetermined specifications. The parameters for this study were to take measurements at an epoch of 60 seconds for 7 days. Activity level was defined as the summation of change in acceleration [dA/dt] during the specified cycle, once every minute. The acceleration measurement set for the accelerometer was 16 milliGs/s at 75 Hz, and the physical activity data collected was linearly dependent upon the intensity of the activity. Previous studies assessing the reliability of accelerometry data have provided evidence for the validity and efficacy of using these accelerometers to reliably generate physical activity data in MS (Gosney, Scott, Snook, & Motl, 2007; Prakash, Snook, Kramer, et al., 2010; Sosnoff, Goldman, & Motl, 2010).

Participants were requested to wear the accelerometer for 7 days during waking hours, except for when swimming, bathing, or showering. The device was worn on the participant's left waist/ hip area throughout the time period. This allowed for measurement of the participant's core body movement indicative of daily activity levels. All participants were also asked to complete a daily log, recording any times throughout the day when the accelerometer was not worn. We summed the minute-by-minute counts across each of the 7 days and then averaged the total daily movement counts across the 7 days. This yielded accelerometer data in total movement counts per day, with no upper limits for the average total movement counts per day, with higher scores representing greater physical activity. Thirty-two of the 45 participants wore the accelerometer for all 7 days, 12 participants wore the accelerometer for 6 days, and 1 participant wore the accelerometer for 4 days. Given that that the independent variable of interest was the average activity, we decided to include all participants for the current study.

Cognitive Assessment

Participants were administered the Mini Mental Status Examination (Folstein et al., 1975) to determine eligibility for participation. To assess functioning in the domain of episodic memory, an item and relational memory task was administered to all participants. The task used in the current study was a modification of the item and relational memory task used by Dennis et al. (2008) to study age-related differences in source and relational memory. This task was presented in a separate behavioral session, outside the scanner to all participants.

The task consisted of non-verbal, visual stimuli, where faces were superimposed on a scene background for all blocks to maintain constant visual stimulation and participants were asked to respond with the right index and the left index fingers, depending upon task instructions. For all study-test blocks, participants were instructed to remember as many stimuli as possible in an encoding condition, and were made aware of the recognition condition, that followed the encoding trials. Throughout the experiment, accuracy, over speed was emphasized. We had three study-test blocks in this task, each of which were repeated twice, once the entire sequence was completed. Each study-test block comprised of an encoding condition, where 16 stimuli were presented to the participants and they had to make superficial judgments about the stimuli. Following the encoding condition, participants were given a recognition condition, which comprised of 16 test trials, 8 of which were old stimuli from the encoding condition, and the remaining 8 were new stimuli. We had the following study-test blocks: (1) Face Block – Participants were presented with 16 faces on a constant scene background and were asked to remember as many faces as possible, followed by a recognition block of 16 test trials, 8 of which were old face stimuli from the encoding condition, and the remaining 8 were new stimuli; (2) Scene Block – Participants were presented with 16 scenes on the background of a constant face and were asked to remember as many scenes as possible, followed by a recognition block of 16 test trials, 8 of which were old scenes from the encoding condition, and the remaining 8 were new scenes; and (3) Face-Scene Block – Participants were presented with 16 combinations of face-scene pairings, and were instructed to remember the specific pairing of the face and the scene, followed by a recognition block, where 8 pairings were repeated from the encoding condition, and the remaining 8 were new re-pairings of the face and scene stimuli used in the encoding conditions. Therefore, our entire task had six study-test blocks in which the encoding condition within the block, was followed by the recognition condition, with the following sequence: FACE BLOCK, SCENE BLOCK, FACE-SCENE BLOCK, FACE BLOCK, SCENE BLOCK, AND FACE-SCENE BLOCK. For all the recognition trials, participants had to depress the "M" key if they had seen the stimulus before and responded with the "X" key if the stimulus on screen was a new item. All stimuli in the encoding and recognition blocks were presented for three seconds, with an inter-trial interval of two seconds. There was also a delay of 10 seconds between the encoding and the recognition blocks for each of the study-test blocks.

All faces and scenes were standardized for luminosity, and contrast. Face stimuli were taken from the FACES database (Ebner, Riediger & Lindenberger, 2010), a set of 171 naturalistic young and old faces, displaying six facial expressions. For our study, we matched stimuli based on age, gender, and emotional expression, and ensured an equal representation of the two age groups, gender, and emotional expressions. Scene stimuli were gathered from the internet and consisted of indoor and outdoor scenes. Since participants were asked to make judgments on whether the scene had water or not, we had an equal number of scenes with water and without water in the study and test blocks. Face-scene pairs were created with MATLAB to superimpose the faces on scenes.

Face and scene blocks involving recognition of individual items, were used to calculate item memory, whereas the face-scene block, involving pairing of the two stimuli, and dependent on the activity of the hippocampal formation was used to assess relational memory. Reaction time and accuracy data were collected for each participant, however, we primarily used the accuracy scores as described below in all our analyses.

Functional and Structural MRI parameters

Participants were scanned at the Wright Center of Innovation on Ohio State campus using a 3 T Philips full body scanner. Both high-resolution structural images and functional T2*-weighted echo planar images (EPIs) were acquired during resting-state. For details on acquisition parameters, please see Supplementary Materials.

Supplementary Materials

To review details on MRI parameters, behavioral and imaging data analyses and Supplementary Figure 1, please visit journals.cambridge.org/INS, then click on the link "Supplementary Materials" at this article.

Data Analyses

Behavioral analyses

Recognition data collected for the Item and Relational Memory task was analyzed using PASW 18.0. To minimize response bias, a *d'* index based on the accuracy scores was calculated separately for face recognition, scene recognition, and face-scene recognition and used in all subsequent analyses. For details on calculation of *d'* index, please see Supplementary Materials.

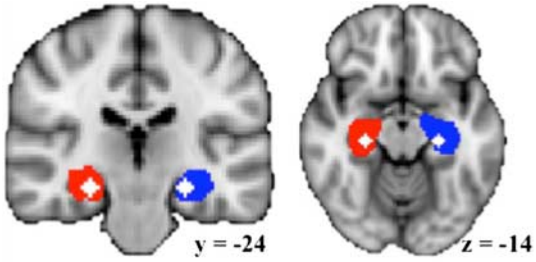

Fig. 1. Presents the right and left hippocampal masks segmented for a representative subject using FIRST. For each participant, the center of gravity in these masks was calculated to create a 10-mm sphere around it. This 10-mm sphere, presented here in white, was used as the seed of interest in the functional connectivity analyses. All images are presented in radiological orientation: R = L; L = R.

Image analyses

Structural MRI preprocessing and FIRST segmentation – All structural data was analyzed using FSL 4.1.4 (Smith et al., 2004, Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). The high-resolution T1 images were used first, to compute the spatial transformation from the mean functional EPI image for the resting state functional scan to the high-resolution MPRAGE image, and the transformation from the MPRAGE image to the standard MNI (Montreal Neurological Institute) template. Second, these high-resolution images were used for segmenting each participant's left and right hippocampus using FMRIB's Integrated Registration and Segmentation Tool (FIRST, Patenaude, Smith, Kennedy, & Jenkinson, 2011) to generate individual-level seeds for seed-based connectivity analyses. For details on the structural preprocessing and FIRST methodology, please see the Supplementary Materials.

Using FIRST, we generated masks for the left and right hippocampus, comprising of the dentate gyrus, the ammonic subfields (CA 1-4), the prosubiculum, and the subiculum for each individual participant. Figure 1 presents masks of the left and right hippocampus for a representative subject. To create seeds for seed-based connectivity analyses, the center of gravity for the hippocampi masks were taken individually for each subject and a 10-mm sphere around the center of gravity was drawn to create the region of interest. These 10-mm left and right hippocampus spheres were used as seeds for the functional connectivity analyses described below. Figure 1 also displays the hippocampi seeds overlaid on the FIRST generated hippocampi masks for a representative subject.

Seed-based functional connectivity analyses – For seed-based connectivity analyses, we used FMRIB's software library (FSL version 4.1.4, Smith et al., 2004) and applied preprocessing as described previously (Voss, Erickson, et al., 2010).

As discussed above, individual seeds of the left and right hippocampus were generated for each participant using FIRST, which were then used as seeds of interest to compute voxel-wise partial correlation with the timeseries of these seeds and the timeseries of each individual voxel. For this, we first extracted the mean timeseries for the left and right hippocampus for each individual participant from the residual functional volumes derived after preprocessing. These timeseries were normalized and entered as independent variables in two separate individual-level analyses, with the residual functional volume being the dependent variable. The resulting voxel-wise partial correlation maps, representing a correlation between the timeseries of the seed and that of every voxel in the brain, were converted to Fisher's Z maps using Fisher's r-to-z transformation (Zar, 1996) to improve normality.

These individual-level maps for the left and right hippocampus were forwarded separately to two higher-level analyses, whereby inter-subject variability was treated as a random variable. Mixed effects analysis was performed using FLAME (FMRIB's Local Analysis of Mixed Effects; Beckmann et al., 2003; Woolrich et al., 2004) to locate regions of cortex that demonstrated a positive and negative correlation with the hippocampus at rest. To correct for the confound of anatomical differences which may manifest itself as functional activations in between-subject comparisons, we inserted on a voxelwise basis, the 3D gray matter partial volume information for each subject at the higher-level analysis as a covariate. This analysis resulted in functional z-stat maps that were independent of anatomical differences and likely represented true functional differences. All parameter estimates were thresholded at a voxel-wise threshold of $Z = 2.33$ ($p < .01$) and for correction for multiple comparison, cluster thresholding at $p < .05$ using Gaussian Random Field Theory was used (Worsley, Evans, Marrett, & Neelin, 1992).

Brain-Behavior Analyses – To examine if individual differences in levels of physical activity were related to differences in the positive connectivity of the hippocampus, regions of interest from the whole-brain analyses were determined based on statistical peaks in separable anatomical regions as demarcated by the Harvard-Oxford cortical atlas that is packaged with the FSL software package (FSL 4.1.4, FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Fisher transformed partial correlation coefficients, representing the positive connectivity of the hippocampus with the region of interest, were extracted to examine associations with physical activity and episodic memory performance, after removing variance associated with age, education, and gender. Additionally, to remove variance associated with the construct of disease severity, we controlled for disease duration in all our analyses, defined in terms of the number of years the participant had been diagnosed with MS. We chose to not use the Expanded Disability Status Scale (EDSS, Kurtzke, 1983) as a proxy for disease severity in our analyses, because of the prime focus of this measure on assessing ambulatory status and ignoring the role of other impairments in calculation of disease severity (Balcer, 2001; Polman & Rudick, 2010). That is, rather than being a measure of symptom severity in the MS population, most of whom experience a host of physical and cognitive symptoms, EDSS focuses excessively on their ability to walk, resulting in this measure being a poor predictor of disease progression, lesion load development, and other clinical characteristics. Given its excessive focus on walking abilities and the accepted knowledge-base in MS literature in this regard (Balcer, 2001; Polman & Rudick, 2010), EDSS scores are a poor covariate for our independent variable of interest, that is, physical activity. Controlling for a measure that assesses walking ability, while we are examining the association between levels of walking ability and brain plasticity, will render our IV of interest theoretically devoid of its full meaning (Miller & Chapman, 2001). Keeping these caveats in mind about controlling for covariates, we chose not to control for EDSS scores as we have done in our previously published studies examining associations between physical activity and brain plasticity in the MS population (Prakash et al., 2007; Prakash, Snook, Motl et al., 2010) showing broad acceptability of our approach.

RESULTS

Behavioral Results

Recognition data for the episodic memory task is presented in Table 2. MS participants were slower and less accurate on the relational block, relative to the two item memory blocks ($p < .05$ for all paired t tests). We performed partial correlations between physical activity data and *d'* for the three memory conditions, after removing variance associated with age, education, gender, and disease duration. Physical activity was not correlated with face recognition, scene recognition, or face-scene recognition ($p > .05$ for all analyses).

Functional Connectivity Network of Hippocampus

Below we report the results of both positive and negative connectivity of the left and right hippocampus for MS participants. The patterns of functional connectivity for the two seeds were generally similar.

Positive connectivity

Both the left and the right hippocampus showed positive connectivity with the posteromedial cortex (PMC), the

Table 2. Presents the reaction time, accuracy, and d' data for the three recognition conditions.

	Face Recognition	Scene Recognition	Relational Recognition
Reaction Time (ms)	1459.30 (32.51)	1507.58 (32.38)	1777.60 (34.27)
Accuracy (HITS + CR)	0.81 (0.02)	0.81 (0.02)	0.65 (0.01)
d' (z(Hits) – z(False Alarms))	1.65 (0.15)	1.63 (0.15)	0.61 (0.11)

Note. d' index was calculated after adding a constant of 0.05 to both Hits and False Alarms.

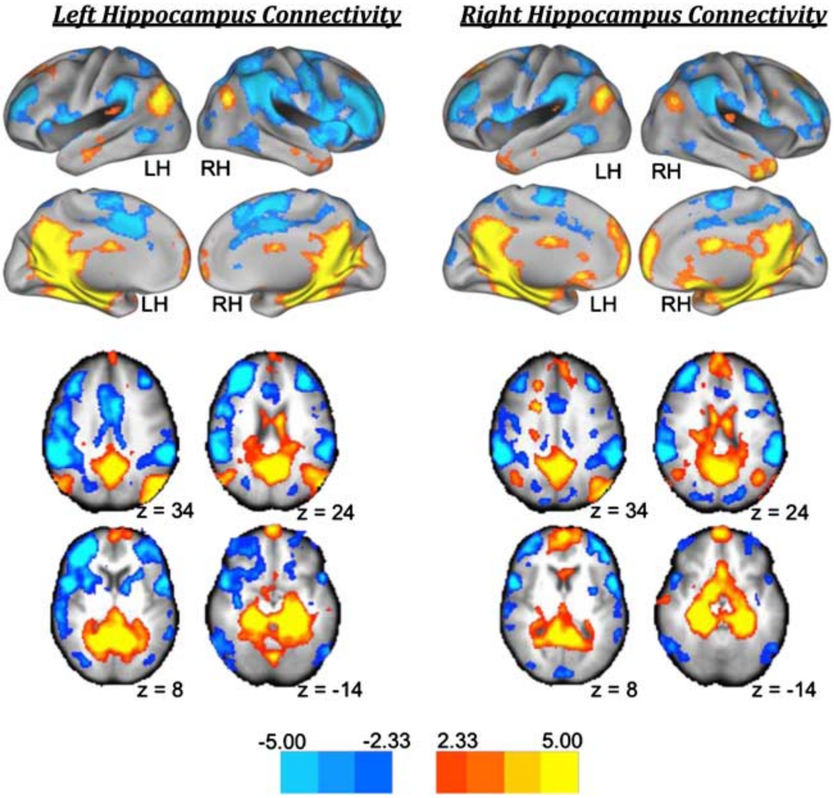

Fig. 2. Presents the positive (in red) and negative (in blue) connectivity maps for the left and right hippocampus. Bilateral hippocampi were found to be positively connected to areas of the default-mode network, and negatively connected to areas of the fronto-executive network. All axial images are presented in radiological orientation: R = L, L = R.

contralateral parahippocampal gyrus, the frontal pole/medial prefrontal cortex, and the ipsilateral superior frontal gyrus (see Figure 2). These regions typically comprise the default-mode network (DMN), with the hippocampal formation being an integral part of the network. Statistical peaks in these regions were identified to examine individual differences in the connectivity of the hippocampus as a function of physical activity. This resulted in four peaks for the left hippocampus and four peaks for the right hippocampus. These included the posteromedial cortex (PMC), frontal pole/medial prefrontal cortex (MPFC), the contralateral parahippocampal grgus (lt. PHG for the right hippocampus, and the rt. PHG for the left hippocampus), and the ipsilateral superior frontal grgus (rt. SFG for the right hippocampus and lt. SFG for the left hippocampus). Table 3 presents the MNI co-ordinates for the statistical peaks for connectivity analyses of the left and right hippocampus. The results for the physical activity-connectivity analyses are reported in the brain-behavior section.

Negative connectivity

Consistent with previous research (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008) both the left and the right hippocampus showed a negative coherence with regions of the prefrontal and parietal cortices, cortical areas traditionally known to comprise the fronto- executive network (Dosenbach et al., 2007). Figure 2 demonstrates that the bilateral hippocampi exhibited a negative connectivity with the bilateral

Table 3. Presents the statistical peaks for the connectivity analyses of the left and right hippocampus.

		Left Hippocampus				Right Hippocampus			
			MNI Co-ordinates (mm)				MNI Co-ordinates (mm)		
Cortical Area	Label	Max z-stat	X	Y	Z	Max z-stat	X	Y	Z
Posteromedical Cortex	PMC	7.94	−8	−46	6	6.15	6	−54	6
Media Prefrontal Cortex/Frontal Pole	MPFC	3.87	0	62	6	6.07	0	64	6
Parahippocampal Gyrus	PHG	7.62	20	−34	−14	5.97	−20	−30	−20
Superior Frontal Gyrus	SFG	4.43	−22	30	48	5.11	24	34	42

Note. These peaks were then used to create regions of interest to examine associations with physical activity and episodic memory.

middle frontal gryi, bilateral inferior parietal lobules, anterior cingulate cortex, and the bilateral precentral gryi. Individual differences in the negative connectivity of the hippocampus with the attentional network were not examined, given lack of apriori hypotheses regarding the effects of physical activity on negative functional connectivity of the hippocampus at rest.

Brain-Behavior Associations

All associations between physical activity and the strength of functional connectivity between the hippocampus and regions of interest were examined using non-parametric partialcorrelations, after removing variance associated with age, education, gender, disease duration, and gray matter volume. Physical activity was associated with a greater connectivity between the left hippocampus-PMC connection ($pr = 0.31$; $p < .05$) and the right hippocampus-PMC connection ($pr = 0.30$; $p < .05$), after removing variance associated with age, gender, education, disease duration, and gray matter volume (see Figure 3). These results also remained statistically significant after the removal of three outlier participants with physical activity data greater than 2 *SD* units (see Supplementary Figure 1). The association of physical activity with other regions of interest was not significant. Table 4 presents the correlations of physical activity with all regions derived from the functional connectivity analyses.

To examine if the increased functional connectivity as a function of physical activity was associated with better relational memory performance, we performed a series of non-parametric partial correlations between the Hipp.-PMC connection for the left and right hippocampus with *d'* for face recognition, scene recognition, and face-scene recognition, after removing variance associated with age, gender, education, disease duration, and gray matter volume. Greater connectivity between the left hippocampus-PMC was associated with better performance on the relational memory condition ($pr = 0.40$; $p = .006$), but not with face recognition ($pr = 0.01$; $p = .916$) or scene recognition ($pr = 0.10$; $p = .526$). The strength of connection between the right hippocampus-PMC was not associated with memory performance on any of the three conditions. The association between left-hippocampus-PMC and relational memory remained significant after correcting for Bonferroni correction of 6 correlations, $p < .008$.

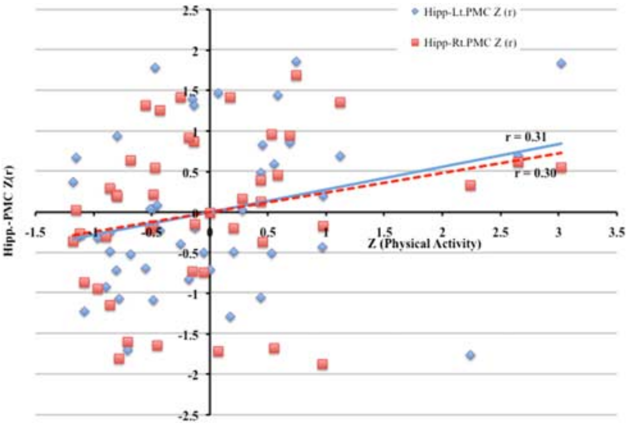

Fig. 3. Scatter-plots of the correlation between standardized physical and fisher transformed hippocampus-posteriomedial connection for the left (in blue) and right (in red) hippocampus.

Table 4. Presents non-parametric partial correlations of physical activity and hippocampal connectivity with the four regions of interest.

	Left hippocampus	Right hippocampus
PMC	0.31* $p = .038$	0.30* $p = .040$
Contralateral PHG	−0.02 $p = .900$	0.07 $p = .611$
Ipsilateral SFG	0.15 $p = .338$	0.04 $p = .820$
MPFC	−0.11 $p = .464$	−0.07 $p = .642$

Note. *indicates $p < .05$.

DISCUSSION

Reduction of cognitive deficits to improve overall quality of life, functional status and employment rates in MS individuals has become a topic of great interest in the MS community. Despite such unequivocal results of an association between cognitive impairments and quality of life (Amato et al., 2001; Cutajar et al., 2000; Gold et al., 2003), there is a dearth of treatment studies designed to reduce the cognitive burden associated with the disease. Over the past few years, we have cross-sectionally examined the effects of cardio-respiratory fitness on cognitive functioning in MS (Prakash et al., 2007; Prakash, Snook, Kramer, et al., 2010; Prakash, Snook, Motl, et al., 2010). Extending this work to the domain of physical activity, which combines both aerobic and non-aerobic components, we examined if physical activity is associated with episodic memory and the functioning of the hippocampus, a sub-cortical region in the medial temporal lobe known to play a critical role in the formation of new associations between previously unrelated information (Davachi, 2006; Eichenbaum & Cohen, 2001; Ranganath et al., 2005). To examine this, we used the left and right hippocampus as seeds of interest to identify patterns of positive and negative connectivity throughout the entire brain.

Our results confirmed previous investigations of resting-state connectivity in young adults (Buckner, Andrews-Hanna, & Schacter, 2008; Greicius, Krasnow, Reis, & Menon, 2004; Shannon, Snyder, Vincent, & Buckner, 2006; Shulman et al., 1997), where the hippocampal formation was functionally connected to areas of the default-mode network (DMN). In our analyses with MS participants, we found the left and right hippocampus to be positively connected to areas of the DMN, including, the posteromedial cortex, medial prefrontal cortex, parahippocampal gyrus, and the superior frontal gyrus providing evidence for the spontaneous oscillations between these areas and the hippocampal formation in MS patients. The default-mode network (DMN) has been investigated for its functional properties in healthy (Binder et al., 1999; Grady et al., 2010) and clinical populations (Lowe et al., 2002;

Zhou et al., 2007) and consistently shows deactivation during exogenous processing, and activation during endogenous processing (Fox et al., 2005; Fransson, 2005, 2006; Kelly et al., 2008), resulting in anti-correlation with the task positive networks (Kelly et al., 2008). Indeed, one of the observations of the current study was a negative connectivity of the bilateral hippocampi with areas of the dorsolateral prefrontal cortices, and the superior parietal lobule, cortical regions traditionally known to be involved in the fronto-executive network (Dosenbach et al., 2007). These two analyses thus provide evidence for the intact integrity of the two main networks in individuals with MS, however, given the lack of a healthy control group, we will refrain from speaking on the magnitude of connectivity of these networks as a function of the disease.

We found higher levels of physical activity in MS individuals to be associated with an increased functional connectivity between the left and right hippocampus and the posteromedial cortex, including the posterior cingulate gyrus, precuneus, and the retrosplenial cortex. These results are interesting given that these two cortical areas, while being critical to the DMN are often involved in declarative memory, enabling associations and integration between stimuli (see Wagner, Shannon, Kahn, & Buckner, 2005, for a review). Notably, activation of the hippocampus and deactivation of the PMC has been linked to successful encoding (Daselaar, Veltman, & Witter, 2004; Otten & Rugg, 2001), whereas activation of the PMC during retrieval has been associated with successful recall (Daselaar et al., 2009; Kim, Daselaar, & Cabeza, 2010). In contrast to these opposing patterns during active task performance, studies of resting-state connectivity have demonstrated a positive functional connection between these two regions in the absence of external stimulation (Greicius et al., 2004; Kahn, Andews-Hanna, Vincent, Snyder, & Buckner, 2008), and in a recent study, the strength of connection between the hippocampus and PMC was predictive of better memory performance in older adults (Wang et al., 2010). Taken together, much of the literature seems to suggest the involvement of these two regions of the DMN in our ability to form and learn new associations. Indeed, one of the main hypotheses regarding the functionality of the DMN is its involvement in processes of internal mentation (Buckner et al., 2008), which underlies much of our ability to self-reflect, remember personal events from the past, take the perspective of others and make moral decisions, thereby enabling us to look beyond the immediate perspective, and simulate the perspective of others. Critical to this ability, is the capacity to integrate information and form associations between items to aid the process of mental exploration, subserved largely by one subsystem of the DMN, namely the connection between the hippocampal formation and the PMC. Physical activity may thus be one lifestyle factor influencing the connection between our intrinsic brain networks to facilitate interaction between core areas, and improve behavioral performance. Contrary to our hypothesis, we did not find physical activity to be directly associated with better episodic memory performance. These results were surprising given the existing animal and human literature demonstrating a positive relationship between physical activity interventions and memory performance (van Praag, Christie, et al., 1999; Erickson et al., 2010). However, differences in the type of memory paradigms used across studies could be one explanation of null findings. In our study, we included an item and relational memory task that has been previously shown to be dependent on the integrity of the hippocampus (Chaddock et al., 2010, Dennis et al., 2008), while animal research has primarily included measures of spatial learning and memory, such as the water maze tasks (Nichol, Parachikova, & Cotman, 2007; van Praag, Christie, et al., 1999; van Praag et al., 2005). In addition, much of the direct benefit on cognition has been demonstrated by chronic exercise interventions, however, our study using a physical activity measure, combining both low-intensity and high-intensity exercises could be another potential explanation for a lack of direct association between physical activity and cognition.

This study was a cross-sectional examination of the association between physical activity and hippocampal connectivity in MS patients, thereby precluding us from making causal inferences on the role of physical activity in serving a prophylactic role within this population. While we controlled for the effects of a host of demographic and clinical variables, one of which included disease duration as a proxy for disease severity, an alternate possible explanation for the observed effects of increased physical activity and hippocampal connectivity could be the role played by severity of MS and its neuropathological correlates on physical activity. That is, MS patients with high disease severity are less likely to be physically active, and thus the neuropathological changes associated with increased MS severity could be one reason for the observed correlation between physical activity and increased connectivity. To address this possible confound, in addition to controlling for effects of disease duration as a proxy for disease severity, we also controlled for the effects of gray matter volume in our analyses, and thus individual differences in gray matter pathology, likely resulting from higher disease severity is not a possible explanation of the observed effects. However, it is likely that a host of other cellular and molecular factors, which are impaired as a function of the disease, which were not included as covariates in the current analyses could possibly serve as an explanation of the observed effects. Thus, factors such as concentrations of brain-derived neurotrophic factor, insulin-like growth factor, or overall lesion load volume could possibly have an influence on our results. Given the shared variance between measures of physical activity and EDSS, future studies should use the Multiple Sclerosis Functional Composite (MSFC) scale as a measure of disability status, which creates a composite disability score based on arm function, leg function, and cognitive function and was recommended by the US National Multiple Sclerosis Society's task force (Polman & Rudick, 2010) to correct for the confound of disease severity. Additionally, future research, using a randomized controlled design, will enable a more conclusive examination of the effects of exercise training on brain plasticity in MS, along with an investigation into the moderating effects of disease severity on the relationship between exercise and brain plasticity within MS.

Our research with multiple sclerosis patients and hippocampal connectivity builds on the recent human work that has found evidence for the hippocampus to be the site of neurobiological changes accompanying fitness and exercise training (Burdette et al., 2010; Erickson et al., 2009; Pajonk et al., 2010; Voss, Prakash, et al., 2010). Through both structural and functional investigations, these studies report changes in the volume and connectivity of the hippocampus as a function of fitness training, thus corroborating previous non-human animal research that has demonstrated exercise-dependent changes in the plasticity of the hippocampus, and the functions subserved by it (Anderson et al., 2000; Fordyce & Wehner, 1993; van Praag et al., 2005; Vaynman et al., 2004). Future research examining changes in the activity and connectivity of the hippocampus, and the associated areas of the declarative memory system during active encoding and independent task states promises to characterize how exercise alters functional brain systems and increases their capacity to interact efficiently under high cognitive demand.

The results of the current study should be interpreted in the context of certain limitations. First, we only included three primary progressive patients, and 42 relapsing-remitting patients, and thus a comparison between the two types of MS was not plausible. Also, we did not include a group of healthy controls, which precludes us from first, investigating if our sample was impaired on the item and relational memory task, and second, from investigating the integrity of the DMN in the MS population, relative to healthy controls.

In our study, we looked at measures of functional connectivity, which again, precludes us from making inferences on the directionality of observed effects between the hippocampus and the posteromedial cortex. Although there have been impressive data on the effects of exercise training on brain volume (Colcombe et al., 2006; Erickson et al., 2011), cortical activation (Colcombe et al., 2004), and functional connectivity (Burdette et al., 2010; Voss, Prakash, et al., 2010), much of this work has been done with healthy older adults, with no cognitive impairments. Within the realm of neurodegenerative disorders, there is no randomized clinical trial examining the effect of exercise training on neural activity and connectivity, despite an impressive literature examining changes in cognitive functioning following exercise intervention (Heyn, Abreu, & Ottenbacher, 2004, Smith et al., 2010). There is a clear need to extend the behavioral literature to understand the neurobiological changes accompanying the effects of such an intervention. Such a study would enable a conceptualization of a more coherent and parsimonious understanding of the effects of exercise on brain processes under cerebral challenge.

This study examined the association between physical activity, dependent upon the intensity of activity, and hippocampal connectivity in the MS brain. Although a high correspondence between an individual's physical activity levels and physical fitness, as measured by a maximal exercise test, has been demonstrated (Jacobs, Ainsworth, Hartman, & Leon, 1993), there is still debate on whether fitness mediates the effects of physical activity on brain and cognitive functioning (Angevaren et al., 2008; Colcombe & Kramer, 2003; Etnier et al., 2006). Through cross-sectional investigations, the results primarily support the cardiovascular hypothesis, which suggests aerobic capacity to be the critical factor influencing brain health (Erickson et al., 2009; Prakash et al., 2007; Voss, Erickson, et al., 2010), but many of these cross-sectional investigations have not included a physical activity measure, thereby precluding a direct comparison between the two measures. Meta-analyses of randomized clinical trials, in older adults, provide evidence against the cardiovascular hypothesis (Angevaren et al., 2008; Etnier et al., 2006), thereby suggesting that it is a factor other than aerobic fitness that mediates the benefits of exercise training on cognitive function. An important direction for future research is to parse out the contribution of physical activity, and cardiorespiratory fitness on cognitive and brain functioning, as this would have critical implications for the public health benefits of exercise and physical activity.

Finally, we examined the connectivity of the hippocampus with the rest of the brain during periods of quiet wakefulness, providing us one context in which physical activity was associated with increased connectivity. It would be interesting to examine these relationships in the context of an active task of episodic memory, both during encoding and retrieval, as that would shed some additional light on whether such enhanced connectivity as a function of activity levels exists primarily in the absence of task demands, or is present when participants are actively engaged in task performance. Similarly, we also restricted our investigation to examining one domain of cognition. For future research it would be important to assess the role of physical activity across the different domains of cognitive functioning and examine the specificity of physical activity in benefitting functioning in MS.

ACKNOWLEDGMENTS

The authors have no conflict of interest. We thank Michelle Voss for help in programming the Item and Relational Memory Task and Jamie Lukac, Daniel Snider, Lyla Mourany, Luke McDonald, Danielle Rickert, and Frank Dossman for their help in data collection.

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