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Cardiorespiratory fitness: A predictor of cortical plasticity in multiple sclerosis

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Deficits in cognitive abilities are commonly observed among individuals with multiple sclerosis (MS). Recent neuroimaging studies have provided evidence for the existence of cortical plasticity in MS, with cognitively impaired participants recruiting additional brain areas to perform challenging tasks. The existence of altered cerebral activations in MS provides hope for the utilization of neural resources to reduce cognitive deficits that challenge everyday living in MS by employing alternative interventions such as cognitive and fitness training. In this study, we examined whether higher physical fitness levels enhance cognitive and neural plasticity in MS patients. The present study is the first to investigate the impact of cardiorespiratory fitness on cerebrovascular functioning of MS patients. 24 participants with relapsing–remitting MS were recruited for the study. All participants went through a fitness assessment and were scanned in a 3 T MRI system during the Paced Visual Serial Addition Test (PVSAT). Higher fitness levels were associated with faster behavioral performance and greater recruitment of right IFG/MFG, a region of the cerebral cortex recruited by MS patients during performance of PVSAT to purportedly compensate for the cognitive deterioration attributable to MS. In contrast, lower levels of fitness were associated with enhanced ACC activity, suggestive of the presence of greater interference and the potential for error in lower fit MS participants. These results are promising, suggesting the need for further investigation of the utility of aerobic fitness training as a possible method to support the development of additional cortical resources in an attempt to counter the cognitive decline resulting from MS.
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Introduction

Multiple sclerosis (MS) is the most common neurological disease among young and middle-aged adults, affecting an estimated 1,000,000 individuals worldwide (Kantarci and Wingerchuk, 2006). This autoimmune disease involves demyelination and axonal damage in the central nervous system. The demyelination and axonal damage interfere with neuronal conduction and are associated with MS-related symptoms of which cognitive impairment is a prominent symptom that is reported in 45–65% of people with MS (Rao et al., 1991; Bobholz and Rao, 2003). Deficits are frequently seen in working memory (processing of information in temporary storage), executive control functions (planning, scheduling, and task coordination), attention and concentration, and speed of information processing. The deficits in cognitive function coincide with declines in brain structure (reductions in white and grey matter volume) and function (Bobholz and Rao, 2003). The decrements in cognitive function influence the quality of an individual's life, leading to disease-related unemployment, reductions in activities of daily living, and compromised social relationships. Consequently, development of strategies to maintain or enhance cognitive function in MS is an important public health goal.

In addition to the necessity of developing training programs that target amelioration of cognitive deficits in the MS population, recent neuroimaging studies have provided evidence for the existence of cortical plasticity in those with MS (Staffen et al., 2002; Penner et al., 2003; Filippi et al., 2004; Audoin et al., 2005). These studies, using a wide variety of cognitive tasks, have examined and found altered patterns of brain activation in MS. Most of these studies have reported similar brain areas to be activated by healthy controls and MS patients, but also report that MS patients show a greater extent of overall activation, thereby arguing for a compensatory mechanism of the recruited brain areas. Despite the cortical adaptability evidenced by MS patients research on the management of cognitive impairment in this population has been limited (Bobholz and Rao, 2003; Heesen et al., 2006). Current symptomatic treatments are cognitive rehabilitation (e.g., cognitive exercises/drills) and pharmacological management (e.g., disease-modifying agents). To date, there is limited scientific evidence that those treatments are effective, the treatments are often costly and time intensive, and pharmacological management,

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in particular, is associated with unwanted side effects. Hence, identifying alternative methods for mitigating MS-related cognitive impairment through interventions such as cardiorespiratory fitness training would be beneficial for the MS population.

The initial foundation for examining the relationship between fitness and cognitive impairment in MS is based on the aging, neurocognition, and cardiorespiratory fitness literature. Among older adults, cardiorespiratory fitness has demonstrated a protective effect against age-related declines in cognitive function. Indeed, a meta-analysis of 18 intervention studies conducted between 1966 and 2001 examined aerobic fitness training effects on cognitive function among older adults (Colcombe and Kramer, 2003). The analysis indicated a moderate benefit of fitness training across a broad set of cognitive processes for older adults.

The literature on aging, fitness and neurocognitive function has further examined aerobic exercise and cardiorespiratory fitness effects on human brain structure and function. For example, in a cross-sectional study of humans ranging in age from 55 to 79 years, the trajectory of age-related declines in cortical tissue density was significantly reduced as a function of cardiorespiratory fitness level, with the greatest effects observed in the frontal, prefrontal, and parietal cortices (Colcombe et al., 2003). Subsequent research demonstrated that highly fit or aerobically trained older adults exhibited greater task-related activity, reflected in changes in fMRI activation, in the regions of the prefrontal and parietal cortices that were involved in spatial selection and inhibitory functioning respectively, compared with low-fit or untrained older adults (Colcombe et al., 2004). In a recently completed randomized controlled trial, our research group compared the effects of participation in an aerobic exercise program designed to enhance cardiorespiratory fitness with a stretching/toning control condition, on brain structure and function. Participants in the aerobic conditioning group demonstrated increases in regional grey matter volume and, more importantly, these changes took place in the frontal regions of the cortex, regions that are associated with a broad array of higher order attentional control and memory processes (Colcombe et al., 2006). Further, our intervention resulted in increased white matter volume for the aerobic fitness training condition in the region of the anterior white matter tracts. These white matter tracts facilitate communication between the left and right hemispheres of the brain and deterioration of these tracts are associated with age-related cognitive decline. The results of human studies are consistent with a rapidly expanding animal literature, which has begun to explicate the influence of fitness training on brain structure, function and neurochemistry (Cotman and Berchtold, 2002).

Overall, the extant literature on cognitive function and cardiorespiratory fitness suggests that aerobic exercise and cardiorespiratory fitness can have a beneficial effect on cognition and brain function. There is emerging emphasis to conduct research that examines exercise and physical activity effects on neurocognition among people with MS (for a review see Heesen et al., 2006). Herein, we examined the relationship between cardiorespiratory fitness, brain function and cognition in a group of 24 relapsing–remitting multiple sclerosis patients (RRMS). Participants were scanned in a MRI system while they performed the Paced Visual Serial Addition Test, the visual version of the Paced Auditory Serial Addition Test (PASAT), which is used as a core measure of the multiple sclerosis functional composite (MSFC). PVSAT, a task of working memory, has been extensively studied with both the MS population (Staffen et al., 2002; Chiaravalloti et al., 2005) and healthy controls (Fos et al., 2000; Lazeron et al., 2003) with a number of studies consistently implicating activation of the left frontal and parietal lobes during task performance in healthy controls. In addition to the regions of the left hemisphere, MS patients recruit the right frontal and parietal regions (Audoin et al., 2005; Chiaravalloti et al., 2005) presumably to assist in task performance. In our study, we hypothesized that higher levels of cardiorespiratory fitness would be associated with better task performance in terms of faster reaction time and reduced errors on the PVSAT. In addition we predicted that increases in cardiorespiratory fitness would be coupled with greater recruitment of regions of the right hemisphere that are recruited by MS patients during performance of the PVSAT, thereby suggestive of a compensatory mechanism to counter the effects of the neural disease.

Methods

Participants

We recruited 24 right-handed females (mean age = 44.71, range = 29–53, SD = 7.07) diagnosed with definite relapsing–remitting MS with a mean Expanded Disability Status Score (EDSS (Kurtzke, 1983)), of 2.61 (SD = 1.76). Refer to Table 1 for participant demographics. Participants were excluded from the study if they met any one of the following criteria: a score below 51 on the Modified Mini-Mental State Examination (mMMSE, highest score = 57; Stern et al., 1987), lack of consent from their primary physician, or any other neurological diseases. The visual acuity of all participants was screened requiring 20/30 vision, with corrective lenses provided in order to achieve visual acuity of at least 20/30. The University of Illinois Institutional Review Board approved the study, and all participants provided informed consent.

Cardiorespiratory fitness assessment

Participants performed an incremental exercise test on an electronically braked cycle ergometer to measure peak oxygen consumption ($\dot{V}O_{2peak}$). Initially, participants were fitted to the cycle ergometer. The participants were then provided with standardized, tape-recorded instructions for correctly using the overall perceived exertion (Borg 6–20 scale; 4) scales. An investigator described the maximal exercise test procedures to all participants. After inserting a mouthpiece for collecting expired gases, the participants performed a 5-min warm-up at 0 W, and then the power output continuously increased at a rate of 15 W min^{-1} until the participant reached volitional fatigue. Using an open-circuit spirometry system, ventilation ($\dot{V}_E$), oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and respiratory exchange ratio (RER) were measured every 20 s. Heart rate, rating of perceived exertion, and power output were recorded during the last 10 s of every min during the test of peak oxygen consumption.

Table 1
Demographic Information for MS participants ($n = 24$)

Demographic factor	Mean	SD	Range
Age (years)	44.71	7.07	29–53
EDSS	2.61	1.76	0–6
MS duration (years)	8.02	5.07	1–18
Education (years)	15.33	2.01	12–21

$\dot{V}O_{2peak}$ was defined as the highest recorded $\dot{V}O_2$ value when two of three criteria were satisfied: (1) RER≥1.10; (2) peak heart rate within 10 beats min^{-1} of age-predicted maximum (i.e., ~1 SD); or (3) peak rating of perceived exertion≥18.

Neuropsychological assessment

The cognitive status of participants was established using a battery of neuropsychological tests. The test battery included the K-Bit (verbal); a computerized version of the Wisconsin Card Sort Test (WCST) and Rao's Brief Repeatable Battery (BRB) of neuropsychological tests. The BRB includes five subtests: the Selective Reminding Test (SRT), a measure of verbal learning and delayed recall of a list of 12 paired words; the Spatial Recall Test which measures visuospatial learning and delayed recall; the Symbol Digit Modalities Test (SDMT), which is a measure of sustained attention, working memory, and information processing speed; and the Word List Generation (WLG), a verbal fluency test. The neuropsychological and fitness assessments were completed in the first session of the study.

Functional MRI (fMRI) parameters and cognitive task

For the second session, all participants performed the PVSAT task while being scanned in a 3 T Siemens Allegra head-only magnetic resonance imager. PVSAT has been extensively used to evaluate the cognitive abilities in MS patients and is a measure of sustained attention, information processing speed and working memory (Nagels et al., 2005; Rachbauer et al., 2006). In this task, participants were presented with four blocks with eight different digits in each block. Participants were required to add each digit to the one immediately preceding it and asked to respond by depressing the rightmost button of the left pad with their left index finger if the sum was less than or equal to 10, and the leftmost button of the right pad with their right index finger if the sum of the two digits was greater than 10. Each block was presented for a period of 45 s followed by 21 s of a rest period. Trials were first-order counterbalanced such that all integers between 1 and 9 were used equally, and the two responses of less than 10 (or equal to 10) and greater than 10 occurred uniformly.

The fMRI data were acquired using a T2*-weighted echo planar imaging (EPI) protocol (28 horizontal slices; TR=1500 ms; TE=25 ms; ascending slice acquisition; 80° flip angle; 4 mm isotropic thickness). High-resolution structural images were also collected for each participant using a spoiled gradient sequence (256×256 mm FOV; 1.3 mm thick slices, with a 1.3×1.3 mm in-plane resolution) for spatial registration.

Data analyses

Neuropsychological analyses

The VO_{2peak} scores of all participants collected during the first session were used as a continuous variable to investigate the impact of cardiovascular fitness on neuropsychological test performance. Partial correlations (pr) between VO_{2peak} scores and neuropsychological tests were computed while removing variance associated with age, education and duration of illness.

Behavioral analyses

The behavioral data (reaction time and accuracy) were analyzed by correlating VO_2 peak scores with reaction time and accuracy with age, education and duration of illness as covariates. This was done in order to insure that the impact of cardiorespiratory fitness on behavioral performance was not confounded by these demographic variables. For reaction time analysis, only correct trials were included. Behavioral data were analyzed using SPSS 11.0.3 for Mac.

fMRI processing and analyses

Neuroimaging data were analyzed using FSL version 3·2 (http://www.fmrib.ox.ac.uk/fsl) and FEAT (fMRI Expert Analysis Tool) Version 5.43. The 220 images that were collected while the participants performed the PVSAT were slice-time corrected, motion corrected using a rigid-body algorithm in MCFLIRT (Jenkinson, 2003), and temporally smoothed with a Gaussian low-pass (1.5-s cut-off) and high-pass (100-s cut-off) filter. Spatial smoothing was done with an 8 mm (Full Width at Half Maximum: FWHM) 3-dimensional Gaussian kernel. Following this, all images were skull-stripped using a robust deformable brain extraction technique (BET) (Smith et al., 2002). These skull-stripped images for each participant were spatially registered using a 12-parameter affine transformation—to a common stereotaxic space that was specifically created for the study in order to avoid potential biases due to structural differences between participants. This was done by: (a) warping each participants' high-resolution scan to MNI space, (b) creating an average of these registered images, and (c) spatially smoothing the average image with a 10 mm (FWHM) Gaussian kernel. This study-specific template was subsequently used for spatial registration.

Correct trials for each participant were modeled in FILM (FMRIB's Improved Linear Model) using a double gamma function with temporal derivatives. In addition, six motion correction parameters and error trials were treated as covariates of no interest within this first level analysis. This resulted in voxel-wise parameter estimates for each participant that represented the fit of the model with the underlying time series. The parameter estimate maps and variance maps for each participant were then forwarded into a whole-head second level analysis whereby inter-participant 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 were significantly active during task performance across participants. The resulting statistical maps were thresholded using voxels with a $z>4.1$ and a (corrected) cluster significance threshold of $p<0.01$ (Worsley et al., 1992; Friston et al., 1994; Forman et al., 1995). The regions that survived this thresholding were used as *a priori* ROIs by drawing a 10-mm sphere around each of the peak voxels within each cluster. The average percent signal change from these regions was then extracted and examined in order to investigate the effects of cardiorespiratory fitness. Specifically, VO_{2peak} scores were treated as a continuous variable by calculating partial correlations between VO_2 peak scores and percent signal change in each of the ROIs after removing variance associated with age, education and duration of illness.

In addition to the above analyses, participants were divided into a high-fit (mean $VO_{2peak}=25.41$ ml^{-1} kg^{-1} min^{-1}, SD=4.82) and a low-fit group (mean $VO_{2peak}=16.68$ ml^{-1} kg^{-1} min^{-1}, SD=2.13) based on the median split of their VO_{2peak}. The average percent signal change in the clusters that was found to be significantly active as a function of fitness in the above analysis was then used as a

Table 2
Neuropsychological data for all participants

Neuropsychological test	Mean	SD	pr	*p*-value
mMMSE	54.92	1.79	0.23	0.16
K-BIT (Verbal)	107.07	8.78	0.07	0.37
WCST (Perseverative Errors)	11.83	6.98	−0.06	0.41
Brief Repeatable Battery				
Selective Reminding Test	40.88	10.76	−0.22	0.17
Spatial Reminding Test	23.33	6.28	−0.12	0.29
Symbol Digit Modalities Test	45.08	10.72	0.17	0.24
Paced Auditory Serial Addition Test	42.54	10.85	0.42	0.03
Word List Generation Test	8.86	1.81	0.30	0.09

Partial correlation (pr) coefficients between the neuropsychological variables and cardiorespiratory fitness were calculated after removing variance associated with age, education and duration of illness.

dependent variable in a one-way ANOVA with cardiorespiratory fitness scores of all participants as the independent variable. All images were rendered in Mri3DX version 5.

Results

Neuropsychological results

The results from the partial correlation analysis between VO_{2peak} and each of the neuropsychological variables are presented in Table 2. We found that only the scores on the PASAT were significantly correlated with VO_{2peak} ($pr=0.42$, $p<0.03$). Cardiorespiratory fitness was not significantly related to MMSE or K-BIT (verbal) performance, suggesting that fitness does not have an influence on these measures of general cognitive functioning and crystallized intelligence.

Behavioral results

Mean RT for our sample of MS participants for the PVSAT task was 1173.17 ms (SD=277.73). Reaction time data were significantly correlated with the VO_{2peak} scores of the participants ($pr=-0.51$, $p<0.02$). Higher levels of fitness were associated with faster responding on the PVSAT. Mean error rates were found to be quite low across the entire sample (6.67%) and did not co-vary with CRF.

Neuroimaging results

Consistent with other neuroimaging studies of MS (Staffen et al., 2002; Audoin et al., 2005), participants in our study activated a number of regions in the prefrontal, parietal, temporal and occipital lobes in response to the PVSAT (see Fig. 1 and Table 3). Peaks in these regions were then used to create masks to compute average percent signal change in each of these regions for every participant (see Methods section). Correlational analysis between average percent signal change and VO_{2peak} scores resulted in a significant correlation of fitness with two main regions. Cardiorespiratory fitness was positively correlated with right IFG/MFG (BA 9; $pr=0.46$, $p<0.03$) and negatively correlated with ACC (BA 32; $pr=-0.44$, $p<0.04$). See Table 4.

Thus, higher levels of fitness were associated with a greater recruitment of right IFG/MFG during task performance along with a reduction in activity in the ACC. These results are consistent with results from other studies of fitness on brain function (Colcombe et al., 2004), which showed a similar reduction in the activity of ACC with increased fitness levels.

In addition to the above analysis where VO_{2peak} was treated as a continuous variable, we did a post hoc analysis whereby participants were divided into high-fit and low-fit groups based on a median split of their VO_{2peak} scores. The two groups differed statistically in terms of their VO_{2peak} scores ($t(24)=5.74$, $p<0.0001$), even though were statistically similar in terms of age, education level, duration of

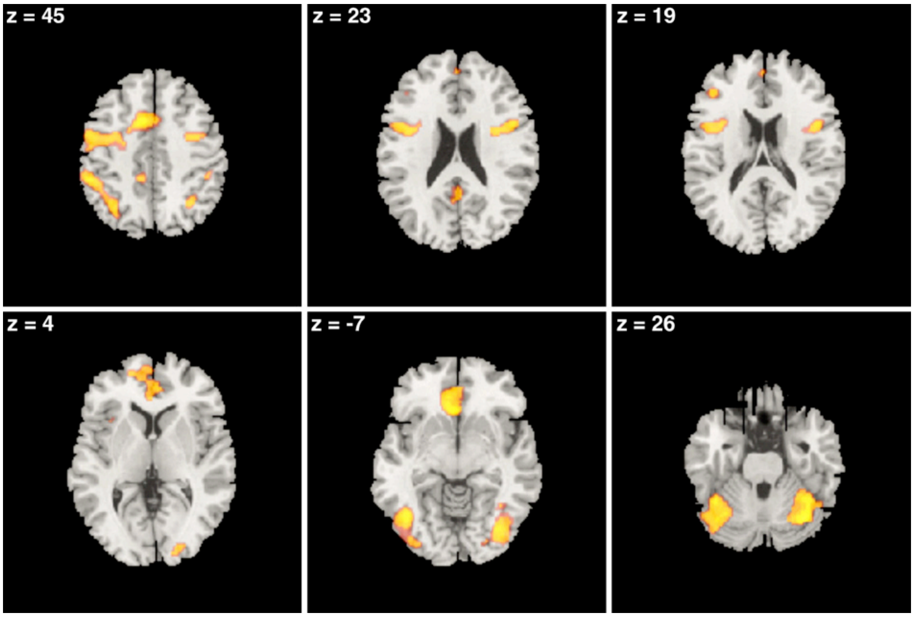

Fig. 1. Activation in frontal, parietal, temporal and occipital lobes during performance of PVSAT collapsed across all participants. All statistical maps were thresholded at a $z>4.1$ and a (corrected) cluster threshold of $p<0.01$. Images are presented in neurological convention (R=R; L=L).

Table 3
Cortical Regions that were recruited by the MS participants while performing the PVSAT

Region	Tailarach coordinates			Max *z*-score
	X	*Y*	*Z*	
Frontal				
L. medial frontal gyrus	−9	−9	48	6.57
R. medial frontal gyrus	1	7	52	5.95
L. superior frontal gyrus	−6	5	54	6.52
R. superior frontal gyrus	1	3	56	5.95
L. anterior cingulate	−1	27	−4	6.59
R. anterior cingulate	1	25	−5	6.04
L. posterior cingulate	−5	−53	24	4.32
R. posterior cingulate	5	−47	24	4.37
R. cingulate gyrus	3	−45	30	5.49
L. cingulate gyrus	−9	6	50	6.57
L. inferior frontal gyrus	−46	1	30	5.45
R. inferior frontal gyrus	45	7	23	5.43
L. middle frontal gyrus	−25	−9	52	5.44
R. middle frontal gyrus	29	−1	48	4.87
Temporal				
L. inferior temporal gyrus	−45	−63	−5	5.43
R. inferior temporal gyrus	49	−51	−18	4.84
L. middle temporal gyrus	−43	−61	−4	4.89
Parietal				
L. precuneus	−29	−63	36	5.48
R. precuneus	1	−49	30	5.46
L. angular gyrus	−31	−63	36	5.48
R. angular gyrus	33	−55	36	4.34
L. inferior parietal lobule	−33	−59	38	5.47
R. inferior parietal lobule	35	−53	41	4.88
L. supramarginal gyrus	−33	−51	33	4.93
R. supramarginal gyrus	33	−53	34	4.35
L. superior parietal lobule	−30	−59	44	4.89
R. superior parietal lobule	29	−57	44	4.31
Occipital				
L. inferior occipital gyrus	−39	−69	−8	4.88
R. inferior occipital gyrus	35	−71	−11	5.98
L. middle occipital gyrus	−41	−67	−9	5.44
R. middle occipital gyrus	35	−71	−12	5.98
L. fusiform gyrus	−39	−49	−19	5.41
R. fusiform gyrus	37	−57	−15	5.98
R. lingual gyrus	33	−71	−12	5.41

All statistical maps were thresholded at $z > 4.1$ and a (corrected) cluster threshold of $p < 0.01$.

illness and IQ scores (see Table 5). We then performed a one-way ANOVA to investigate differences in activation between high-fit and low-fit participants in regions that were found to correlate with cardiorespiratory fitness in the previous analysis. As expected from the preceding results, high-fit participants showed a greater percent signal change than the low-fit participants in the right IFG/MFG, whereas the low-fit participants recruited more of the ACC (see Fig. 2). Greater recruitment of ACC by low-fit participants is indicative of the greater need for executive control due to higher interference from the preprogrammed response (the last addition).

Table 4
This table provides a description of regions for which we found a main effect of cardiorespiratory fitness

Region	Tailarach coordinates			Max *z*-score	pr	*p*-value
	X	*Y*	*Z*			
rt IFG/MFG[a]	51	7	25	4.89	0.46	0.03
ACC[b]	−9	6	50	6.01	−0.44	0.04

[a] rt IFG/MFG was positively correlated with fitness scores and the cluster had its peak in the rt IFG and extended to the rt MFG, [b] ACC was negatively correlated with VO_2 peak scores and the cluster had its peak in lt ACC and extended to lt SMA.

Table 5
Demographic Information of high-fit and low-fit groups

Demographic factor	High fit		Low fit		*t*-Statistic	*p*-value
	Mean	SD	Mean	SD		
VO_{2peak} scores	25.41	4.82	16.68	2.13	5.75	0.0001
Age (years)	43.67	8.36	45.75	5.69	−0.72	0.48
Education (years)	15.83	2.33	14.67	1.55	1.44	0.16
Duration of illness (years)	8.63	5.01	7.42	5.28	0.75	0.57
IQ (K-BIT (verbal))	108.33	8.71	106.00	9.07	0.74	0.46

Discussion

This study is, to our knowledge, the first to establish a relationship between cardiorespiratory fitness, cerebrovascular functioning and cognition in MS patients. Higher cardiorespiratory fitness was found to be associated not only with improved task performance but greater recruitment of the right IFG/MFG, a region of the cerebral cortex, known to be recruited by MS patients during performance of PVSAT, presumably to compensate for the decline in information processing speed owing to compromised neural function. The activation of the right frontal and parietal regions in MS has been reported in a number of recent neuroimaging studies (Staffen et al., 2002; Audoin et al., 2005; Chiaravalloti et al., 2005), thereby arguing for a compensatory utilization of additional resources of the contralateral hemisphere to meet the demands imposed by a challenging task. In our study the higher fit participants recruited more of this region to meet the demands of the task, which resulted in improved performance. An important point to note, however, is that the results of this study may be task specific and therefore should not be taken to suggest that any additional activation in the right IFG/MFG will always be beneficial to MS patients (see Colcombe et al., 2004, and Erickson

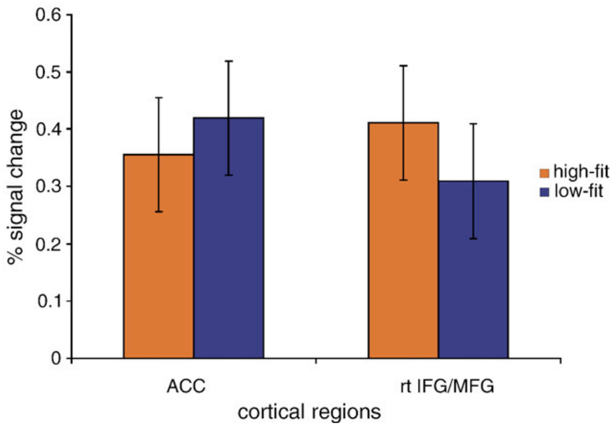

Fig. 2. Average % signal change in ACC and rt IFG/MFG in high-fit and low-fit participants along with standard error bars.

et al., in press, for further discussion of this issue with older adults). Utilization of additional right frontal regions in the performance of a working memory task such as the PVSAT is thought to assist the left frontal regions when activity in such regions is compromised as a result of declines in brain tissue or greater cognitive demands (Reuter-Lorenz et al., 2000; Cabeza, 2002). Thus the benefits of greater activation in the contralateral hemisphere might be dependent on the complementary role played by the particular region in task performance and not just a general function of MS-related decline.

We also found that lower levels of aerobic fitness were associated with enhanced ACC activity. The PVSAT task requires participants to inhibit conflict arising from the previous addition and engage the contents of working memory to perform the new addition (Audoin et al., 2005; Lazeron et al., 2003). Additional ACC activity in low-fit participants can thus be indicative of the presence of a larger amount of conflict and a greater need to engage in top-down attentional control to resolve such conflict (Bush et al., 1998; Smith and Jonides, 1999). An alternative explanation for the increase in ACC activity in low-fit people could be due to increased effort being devoted towards the task. Note that this explanation is not incompatible with our prior explanation. In fact, greater effort to perform the task might be needed in these participants because they experience greater response competition or conflict. Increases in aerobic fitness thus might be able to counter the neural deterioration associated with the disease resulting in a more flexible allocation of cortical resources during cognitive tasks in individuals with MS.

Results of the present study are in line with a number of fitness studies with aging individuals (Colcombe et al., 2004; Hillman et al., 2004) which suggest that higher-fit older adults show greater functional recruitment of task-related areas during performance of cognitive tasks than do lower-fit individuals. Findings from such studies indicate that aerobic fitness training can be beneficial across a number of cognitive processes (i.e., speed, visuospatial, controlled processing, and executive control) but that the effects are often largest for tasks involving executive control processes. Those findings suggest that aerobic fitness may serve to protect against age-related loss of cognitive function (Kramer et al., 1999; Colcombe and Kramer, 2003; McAuley et al., 2004). Taken together with the findings of the present cross-sectional study, the possibility that CRF may be related to cognitive function and brain structure in individuals with MS is an exciting and new area of study.

There are two caveats to the results and conclusions presented above. First, is that the task used in this study has only one contrast, and as a result one might conclude that the differences observed between higher-fit and lower-fit individuals could be attributable to differences in blood flow between the groups rather than differences in neural recruitment. Although the differential activation of brain regions as a function of fitness reduces the possibility of artifactual increases in blood flow in this study (Colcombe et al., 2004), future studies using different cognitive tasks with multiple contrasts will extend these findings and control for any changes due to blood flow.

The cross-sectional nature of the study and the small sample size employed does not allow us to rule out the potential confounding effects of myriad demographic variables. Though the effects of age, education and duration of illness were controlled for in the current study, the impact of other demographic variables cannot be completely ruled out. The design of the study thus does not permit us to examine the causal relationship between CRF and cerebrovascular functioning. Future longitudinal studies examining the impact of fitness training on brain structure and function in MS patients can add to the existing literature and control for the confounding effects of a number of different demographic variables.

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