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Research Report

Aerobic fitness is associated with gray matter volume and white matter integrity in multiple sclerosis

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A B S T R A C T

Alterations in gray and white matter have been well documented in individuals with multiple sclerosis. Severity and extent of such brain tissue damage have been associated with cognitive impairment, disease duration and neurological disability, making quantitative indices of tissue damage important markers of disease progression. In this study, we investigated the association between cardiorespiratory fitness and measures of gray matter atrophy and white matter integrity. Employing voxel-based approaches to analysis of gray matter and white matter, we specifically examined whether higher levels of fitness in multiple sclerosis participants were associated with preserved gray matter volume and integrity of white matter. We found a positive association between cardiorespiratory fitness and regional gray matter volumes and higher focal fractional anisotropy values. Statistical mapping revealed that higher levels of fitness were associated with greater gray matter volume in the midline cortical structures including the medial frontal gyrus, anterior cingulate cortex and the precuneus. Further, we also found that increasing levels of fitness were associated with higher fractional anisotropy in the left thalamic radiation and right anterior corona radiata. Both preserved gray matter volume and white matter tract integrity were associated with better performance on measures of processing speed. Taken together, these results suggest that fitness exerts a prophylactic influence on the structural decline observed early on, preserving neuronal integrity in multiple sclerosis, thereby reducing long-term disability.

1. Introduction

Multiple sclerosis (MS), a neurodegenerative, inflammatory disease is associated with focal areas of demyelination (lesions) in the central nervous system (Devins and Seland, 1987, Charil et al., 2007, Lester et al., 2007). These demyelinating lesions are accompanied with pathology in both normal appearing white matter (NAWM) and normal appearing gray matter (NAGM), suggesting that brain tissue damage in MS extends beyond the abnormal appearing white matter and significantly impacts multiple cortical structures (Amato et al., 2004, Bermel et al., 2002, Chard et al., 2004, Cifelli et al., 2002, DeStefano et al., 2003, Sailer et al., 2003, Prinster et al., 2006, Ciccarelli et al., 2008, Vrenken et al., 2006a, Roosendaal et al., 2009). Weak correlations between demyelinating lesions and neurological disability (Barkhof, 2002, Vrenken et al., 2006b), indicate that

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pathophysiological processes happening outside the white matter lesions explain some of the variance in disease progression (DeStefano et al., 2001, Fisher et al., 2000, Chard et al., 2002). With advances in neuroimaging techniques and analyses, in vivo abnormalities of the NAWM and NAGM have been studied extensively (Miller et al., 2003, Filippi et al., 1995, Dehmeshki, et al., 2003, Cercignani et al., 2001, Werring et al., 1999, Chard et al., 2002, Vrenken et al., 2005, Ranjeva et al., 2006, Audoin et al., 2006), with research focusing on both the nature of pathology seen in GM and WM structures and their subsequent association with clinical and demographic factors.

Diffusion tensor imaging (DTI) is increasingly being used to detect disease related injury in the NAWM and provides information on the local properties of white matter tracts (Pierpaoli and Basser, 1996). Fractional anisotropy (FA), reflecting the preferential directionality of water diffusion, is the most commonly studied diffusion parameter and ranges from isotropic diffusion (FA value equal to zero) to anisotropic diffusion (FA value equal to 1). Reduced FA values have been reported in the WM lesions (Bammer et al., 2000, Tievsky et al., 1999) as well as the NAWM (Ciccarelli et al., 2001). Damage within the NAWM has been studied through many approaches such as ROI-based approaches (Ciccarelli et al., 2003, Hasan et al., 2005, Vrenken et al., 2006b), voxelwise approaches (Roosendaal et al., 2009, Dineen et al., 2008) and through histogram analyses (Rovaris et al., 2002a, Vrenken et al., 2006b). Voxelwise approaches, in contrast to the other approaches, have the advantage of investigating group differences in local structures in a more exploratory manner. Using tract-based spatial statistics (TBSS, Smith et al., 2006), a relatively new approach to conducting voxelwise statistical analyses of FA data, Roosendaal et al. (2009) reported differences in MS individuals relative to healthy controls in a number of brain regions including the corona radiata, fornices, inferior longitudinal fasciculus and optic radiation in both hemispheres, and parts of the corpus callosum. FA reductions in these tracts were associated with neurological disability and cognitive impairment, providing direct evidence for the impact of NAWM degeneration on the clinical progression of MS.

In addition to WM atrophy, MS is also characterized by significant neuronal loss in GM (Prinster et al., 2006, Chard et al., 2002, 2004, Dalton et al., 2004). Voxel-based morphometric analyses of GM structures have been employed in several studies, which provide evidence of a significant decline in global GM volume of MS participants (Audoin et al., 2006, Prinster et al., 2006, Ciccarelli et al., 2008). Decline in GM volume has been found to be associated with neurological disability as assessed through expanded disability status score (EDSS) and cognitive impairment (Amato et al., 2004; Benedict et al., 2004; Zivadinov et al., 2001, Morgen et al., 2006). Much recent work has also elucidated regional GM structures that show deterioration as a result of the neurodegenerative disease. These include the thalamus and the right lateral prefrontal cortices (Audoin et al., 2006), left prefrontal and temporal cortices (Prinster et al., 2006) and the right pre and post-central gyri (Ciccarelli et al., 2008). Thus, much of the recent research suggests that individuals with multiple sclerosis have a significant deterioration of both GM and WM structures that are not visible through conventional MRI and that deterioration in these cortical structures is associated with significant functional and cognitive limitations (Dineen et al., 2008). Lifestyle factors that moderate the decline of MS on cortical atrophy might help in slowing and even potentially reversing the disease progression in MS. One such factor that might potentially be associated with preserved GM or WM volumes or both is cardiorespiratory fitness.

Cardiorespiratory fitness, a physiological surrogate of physical activity is increasingly being recognized as having a neuroprotective effect on neurological disorders (White and Castellano, 2008). Both initial non-human animal research (Le Page et al., 1994, 1996) and cross-sectional human research (Prakash et al., 2007) provide promising evidence for the possible role of fitness in improving functioning in those with MS. Using functional magnetic resonance imaging, we have provided evidence for an association between increased levels of fitness and activation in the right middle frontal gyrus during performance on the Paced Visual Serial Addition Test (PVSAT), which in turn was associated with better behavioral performance (Prakash et al., 2007). These results provided the first evidence for the association of fitness levels with functional neuronal plasticity in MS patients. In the current study, we were interested in examining the association between cardiorespiratory fitness and structural loss as measured through voxel-based morphometric analysis of GM and tract-based spatial statistical analysis of diffusion tensor data.

We recruited relapsing–remitting MS participants and age, education and gender matched healthy controls for our study. We predicted that consistent with previous literature, we would firstly find differences in both global and regional GM volumes of MS participants relative to healthy controls. Cortical regions of GM loss would in turn be negatively associated with fitness, such that higher-fit MS participants would have less of a decline in these GM structures. Previous studies employing voxel-based approaches to analyses of gray matter decline have provided evidence for a reduction in the volume of midline cortical structures, such as the ACC and the medial frontal gyrus, neuronal regions that are responsible for interconnections between cortical and sub-cortical structures (Charil et al., 2007, Bendfeldt et al., 2009). Based on these results, we expect that the volume of these cortical structures would be positively associated with fitness. In addition, we predicted that higher levels of fitness in our MS participants would also be associated with less reduction in FA values both globally and focally. Further given that the integrity of the white matter tracts and greater GM volumes have been associated with improved cognitive functioning, we predicted that structural areas that might show a preservation with increasing levels of fitness, will also be associated with improved cognitive functioning on measures of processing speed; tasks that often show significant deterioration in individuals with MS (Demaree et al., 1999, Henry and Beatty, 2006).

2. Results

2.1. *Neuropsychological results*

Differences in performance between healthy controls and MS participants on the neuropsychological measures were assessed by Student's *t*-tests. Of all the neuropsychological