Depression and Cognitive Dysfunction in Multiple Sclerosis: The Effect of Physical Activity

A Senior Honors Thesis

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By

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Abstract

Multiple sclerosis (MS) is a neurodegenerative disease of the central nervous system. MS has been found to have a negative impact on memory functioning and hippocampal volume. Additionally, there is a high prevalence of depression among this population, which is associated with an exacerbation of these deficits. However, cardiorespiratory fitness is linked with cognitive improvement and gray matter volume preservation. This study investigated physical activity as a moderator in the relationship between depression and cognitive functioning as well as depression and hippocampal volume. Fifty-two MS participants completed the Selective Reminding Task (SRT) to assess memory performance and an MRI session to obtain hippocampal volumes. Contrary to our hypotheses, depression was not associated with reduced memory functioning or greater hippocampal atrophy. However, physical activity had a marginally significant main effect on hippocampal volume. Further research is necessary to understand the nature of both depression and cognitive dysfunction is the MS population. This study provided preliminary evidence that both high and low intensity activity may buffer against hippocampal degeneration in MS.

Keywords: multiple sclerosis, cognition, physical activity, depression, hippocampus

Multiple sclerosis (MS) is a neurological disease that is likely of autoimmune etiology. It is characterized by demyelination and axonal damage in the central nervous system (CNS) and is known to afflict nearly 1 in every 1,000 individuals in Western countries (Chwastiak & Ehde, 2007). MS results in damage to the myelin sheath that lines nerve fibers as well as axonal transection in new MS lesions (Brassington & Marsh, 1998; Trapp et al, 1998). Sclerotic plaques, which are lesions where the axonal damage has occurred, disrupt and distort the normal transmission of nerve impulses (Brassington & Marsh, 1998). This disruption of the signals results in many of the symptoms that are seen in MS, including weakness in limbs, spasticity, bladder dysfunction, fatigue, numbness, and emotional changes (Brassington & Marsh, 1991). Individual symptoms can exacerbate or lead to other symptoms, causing a collection of interrelated symptoms (Crayton, Heyman, & Rossman, 2004). Research recognizes that the clinical manifestations of MS vary significantly in every patient (Brassington & Marsh, 1998), with significant individual differences in the nature and severity of the symptoms. While many of the symptoms are physical ailments, cognitive and psychiatric problems can cause much of the distress for individuals with the disease (Brassington & Marsh, 1998).

One of the most commonly observed problems of MS is a significant decline in cognitive functioning. A meta-analytic review of the deficits in cognitive function in individuals with MS provided evidence for significant impairments in the domains of working memory, processing speed, executive control, and attention (Prakash et al, 2007). A recent study found that MS patients were significantly slower on tasks of simple and choice reaction time (Janculjak et al, 2002). Likewise, increased difficulty on the Stroop task, a task of inhibitory control, was associated with more frontal parietal lesions in MS (Pujol et al, 2001). Both secondary progressive multiple sclerosis (SPMS) patients and relapsing-remitting multiple sclerosis

(RRMS) patients performed worse on word-list learning which is known to involve the hippocampus. RRMS is characterized by episodes of acute worsening with recovery and a stable course between relapses. SPMS is characterized by gradual neurologic deterioration with or without acute relapses in a patient who previously had relapsing-remitting multiple sclerosis (Rudick et al, 1997). Both RRMS and SPMS patients needed significantly more attempts to learn the word lists than the group of healthy controls.

In addition to evidence of a decline in cognitive functioning, recent research has also provided evidence for a significant reduction in the gray matter volume in MS patients compared to normal control subjects (Prakash et al, 2010). Cerebral atrophy increases in individuals with multiple sclerosis when compared to a healthy population (Bermel et al, 2002). In addition, Fisher et al (2008) found that gray matter atrophy in MS is moderately correlated with both the Multiple Sclerosis Functional Composite (MSFC) as well as the Expanded Disability Status Scale (EDSS). EDSS is the primary measure of functional disability in MS such that higher scores indicate increased disability (Kurtzke, 1983). MSFC, however, is a functional measure that is becoming increasingly popular because of its demonstrated ability to detect small changes in patients' functioning that EDSS does not detect (Cutter et al, 1999). Fisher and colleagues also found a greater rate of gray matter atrophy as the stage of MS advanced (Fisher et al, 2008). Additionally, in a longitudinal MS study, T2 lesion burden of disease on MRI had a negative correlation with performance on attention and working memory tasks (Sperling et al, 2001). In the Sicotte et al (2008) study mentioned above, the RRMS and SPMS groups had a significant decrease in hippocampal volume compared to the healthy controls. In a post-mortem study by Guerts et al (2007), fifteen out of nineteen cases of progressive MS involved a high number of hippocampal lesions, providing evidence that the integrity of this brain structure is often

compromised in MS (Guerts et al, 2007).

One of the most prominent psychiatric symptoms seen in MS is depression. The lifetime prevalence of depression in this clinical population is considered to be at 50% (Siegert & Abernethy, 2005). This is much higher compared to the lifetime prevalence of depression in the general non-clinical population of about 16% (Kessler et al, 2003). There has been a variety of research that has focused on both cognitive and structural differences between MS patients with depression and MS patients without depression. While most individuals with MS have some degree of cognitive deficits, depression is linked to an increased severity of these cognitive impairments (Demaree, Gaudino, & DeLuca, 2001). Studies have found that depression in MS is correlated with increased deficits in processing speed, sustained attention, and working memory. Arnett et al (1999) established a relationship between depression in MS and both capacity-demanding memory and attentional functioning by recruiting both depressed MS patients and non-depressed MS patients along with healthy controls. Depressed MS patients performed significantly worse compared to the non-depressed MS patients on speeded attentional tasks and tasks of working memory, including the Paced Auditory Serial Addition Test (PASAT), Symbol Digit Test, and the Visual Elevator Test. However, the non-depressed patients did not differ significantly from the healthy controls on any of the capacity-demanding tasks (Arnett et al, 1999). Other studies too have reported significant differences between depressed MS individuals and non-depressed individuals on tasks of verbal learning and memory (Demaree et al, 2003), and executive task of planning as seen in the Tower of London task (Arnett, Higginson, & Randolph, 2001). In addition to cognitive differences, researchers have investigated structural differences in MRI between depressed MS patients and non-depressed MS patients, though the results from these studies have been mixed. While researchers seem to agree that there are

structural differences in depressed MS patients, they do not agree on the nature of the specific differences. According to a study by Berg et al (2000), patients with depression were found to have higher lesion load in the temporal lobes and the left frontal lobe. There was also a significant correlation between the severity of depression and lesion load in the right temporal lobe (Berg et al, 2000). In addition, depressed MS patients showed significantly more atrophy in the hippocampus, spiecifically the Cornu Ammonis 2-3/Dentate Gyrus (CA23DG) subregion as compared to non-depressed MS patients (Gold et al, 2010).

These results are consistent with the existing literature examining the association between depression and hippocampal volume in clinically depressed individuals. Bremner et al (2000) examined the volume of the left and right hippocampus in healthy controls relative to individuals with clinical depression and found that the left hippocampal volume was smaller in individuals with clinical depression, with patients having a 19% reduction in volume than controls (Bremner et al, 2000). Another study found similar results such that the volume of the left hippocampus in depressed patients was significantly smaller compared to controls, while the reduction in the right hippocampus of depression patients approached significance (Mervaala et al, 2000). Interestingly, a study with healthy women found that enhanced emotional memory was predicted by a decrease in the left hippocampal volume. These results support the idea that this decrease in left hippocampal volume might predispose women to engage in stronger emotional responses when shown negative stimuli (Matsuoka et al, 2007). This is consistent with research that has found that a group of individuals with depression are more likely to remember words associated with depression when compared with a group of individuals with anxiety and a healthy control group (Bradley, Mogg, & Williams, 1995). Research has demonstrated that rumination, or repetitively thinking about negative emotions and focusing on the symptoms of one's distress,

seems to predict the onset of depressive episodes (Nolen-Hoeksema, 2000; Nolen-Hoeksema et al, 2008). Additionally, when ruminating in the context of depressed mood, participants recall more negative life events from their memory (Lyubomirsky et al, 1998). Because of this clear connection between depression, rumination, and enhanced memory, it is not surprising that both depression and emotional memory are associated with a decrease in left hippocampal volume.

There has been a variety of research done in the field of multiple sclerosis to investigate and develop new methods of managing and alleviating both physical and depressive symptoms. Many patients utilize various cognitive exercises, but there is limited research to demonstrate that these are significantly effective. Patients are also prescribed different medications, but these can be expensive and have negative side effects. For these reasons, researchers are investigating cost-effective interventions to improve the quality of life for multiple sclerosis patients. (Prakash et al, 2007).

One recent hypothesis that could help in alleviating cognitive symptoms is the environment enrichment hypothesis. This hypothesis focuses on the extent to which an individual's behaviors and lifestyle influence cognitive functioning (Hertzog et al, 2009). Rather than using expensive and potentially ineffective cognitive rehabilitation programs and possibly harmful pharmacological treatments, environment enrichment places emphasis on how people can change their own behaviors and optimize their cognitive functioning (Hertzog et al, 2009).

One of the lifestyle changes in environment enrichment that has been extensively studied is one's own level of physical fitness. Exercise has recently been shown to have a both structural, functional, and cognitive benefits for patients diagnosed with MS (Prakash et al, 2007, Prakash et al, 2010). In a recent study by Prakash et al (2007), MS patients with high levels of cardiorespiratory fitness had faster times on the Paced Visual Serial Addition Test (PVSAT),

demonstrating the benefit of fitness on cognitive functioning. In an additional study by Prakash et al (2010), higher levels of cardiorespiratory fitness have also found to be associated with lower lesion load in MS patients. Individuals with higher levels of cardiorespiratory fitness also had a larger volume of gray matter in structures that deteriorate because of MS. Lastly, increased fitness was found to be associated with higher integrity of the myelin sheath, which is commonly damaged in MS (Prakash et al, 2010).

In addition, exercise has also been found to have a beneficial effect on depression in general populations. In one study by Camacho et al (1991), individuals completed questionnaires about physical health and psychological aspects of health at two different time points. Individuals with a low level of physical activity at the first time point were found to be at a significantly higher risk of depression at the follow-up than those who had reported high levels of physical activity at the baseline. This study also found that even with low levels of physical activity at the first time point, simply increasing the levels of physical activity could lower the risk of depression (Camacho et al, 1991). In a follow-up study with this population, researchers used a 12-item scale based on the typical frequency of physical exercise, taking part in active sports, taking long walks, and swimming. This study found that at 0.1 increase in the physical activity scale was associated with a nearly 20% reduction in the likelihood of becoming depressed in later years (Strawbridge et al, 2002). Overall, studies have found that there are no significant differences in the effectiveness between exercise and cognitive therapy (Blumenthal et al, 2007). Exercise has also been found to be useful in the management of non-responders to depression medication (Trivedi et al, 2006).

Physical activity is also shown to have a beneficial effect on brain structures as well. One study using mice found that the level of BDNF protein was significantly increased in wild

type mice after thirteen days of exercise. This physical activity increased the proliferation and neurogenesis, which correlated with an improvement of object exploration and discrimination (Lafenetre et al, 2010). Another study found that in older adults, there was a significant age-related decrease in the volume of the medial temporal lobe of individuals who participated in low levels of physical activity, as compared to individuals who participated in higher levels of physical activity (Bugg & Head, 2009).

In the current study, we combined different areas of research to further investigate the relatively under-studied topic of depression in MS patients. We applied the cognitive enrichment hypothesis to the study of multiple sclerosis patients and investigated whether certain lifestyle behaviors have a positive impact on the cognitive decline that is associated with depression. We hypothesized based on existing literature that depression will be associated with decreased performance on cognitive tasks and lower hippocampal volume. Secondly, we hypothesized that physical activity will be associated with better performance on cognitive tasks and increased hippocampal volume. Lastly, we examined if physical activity moderated the relationship between depression and cognitive dysfunction such that MS patients with higher depression and higher physical activity would have increased task performance and hippocampal volume when compared to patients with higher depression and lower physical activity.

Methods

Participants

We recruited 52 right-handed MS patients ages 30-59 (mean age=45.79, SD=8.30) from the Columbus community for the current study. Participant demographics are shown in Table 1. All participants met criteria for McDonald's revised criteria (Polman et al, 2005) of multiple sclerosis. Forty-eight of these participants were diagnosed with relapsing-remitting MS, three

participants were diagnosed with primary progressive MS, and one participant was diagnosed with secondary progressive MS. All participants were required to satisfy a number of inclusionary criteria: a score greater than 23 on the Mini-Mental Status Examination (MMSE) (maximum score=30; Folstein, Folstein, & McHugh, 1975), corrected (near and far) acuity of 20/40 or better, right-handedness as assessed by the Edinburgh Handedness Inventory, no corticosteroid use in the previous month, EDSS of no more than six to ensure ambulation. In addition, participants with a previous history of any other neurological disorder other than MS, or psychiatric disorder with the exception of depression and mild anxiety were excluded from the study. All participants were prescreened for suitability in the magnetic resonance imaging environment, e.g. 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.

Depression Assessment

Participants completed the Mood and Anxiety Symptom Questionnaire (MASQ: Watson & Clark, 1991; see Appendix) in order to assess their mood within the past two weeks. The MASQ is typically a 90-item questionnaire that measures characteristics unique to both anxiety and depression, as well as shared characteristics. There are two subscales that specifically measure characteristics of anhedonic depression and anxious arousal. Anhedonic depression (AD) is the inability to experience pleasure (e.g., “felt like nothing was very enjoyable”). This scale represents a pure measure of anhedonia, the unique, identifying feature of depression that separates it from anxiety (Watson et al, 1995). Anxious arousal (AA) is a negative emotional state with feelings of worry, nervousness, and apprehension (e.g., “heart was racing or pounding”). This scale represents a pure measure of anxious arousal, which is the identifying

feature of anxiety (Watson & Clark, 1991; Watson et al, 1995). Participants completed the AD and AA scales for a total of 39 items. The AD scale had 22 items while the AA scale had 17 items. The MASQ is a Likert-type scale with questions rated from 1 ("not at all") to 5 ("extremely"). Given that the focus of our study was examining the effects of depression on cognition and hippocampal volume, we primarily considered the score on the anhedonic depression scale for all of our analyses.

Physical Activity Assessment

In order to assess physical activity, participants were asked to wear an ActiGraph GT3X accelerometer. The accelerometer recorded steps and activity levels measures dependent upon predetermined parameters. The device was programmed to take measurements at an epoch of 60 seconds. Activity levels were measured in "counts", which is the summation of all changes in acceleration [dA/dt] during the programmed epoch. The physical activity data was collected linearly dependent upon the intensity of the activity. Previous research has found evidence that accelerometers generate reliable physical activity data for the MS population (Sosnoff et al., 2010).

Participants were instructed to wear the accelerometer for a seven consecutive days during waking hours, except when showering or swimming. They wore the belt on their left hip in order to allow for measurement of core body movement and completed a log on which they recorded any times during the day that they did not wear the accelerometer. We summed each count for the total amount of activity over the seven days, and divided this number by the number of days that the unit was worn. This allowed for a measurement of the average amount of activity per day, where larger measurements were indicative of greater activity.

Neuropsychological Assessment

To measure short-term and long term memory, participants completed the Selective Reminding Task (SRT). In this task, the experimenter verbally presented participants with a list of twelve words. Participants then recalled as many of the words as they could remember on one trial. The experimenter would then selectively remind participants of each word they were unable to recall on that trial and the participants were then instructed to recite the entire list again. Participants had a total of six recall trials to learn all of the words before the task was terminated. However, if they were able to recall all twelve words in less than six trials, the task was terminated after the successful trial where all twelve words were recalled and each of the remaining trials was scored with a perfect score. Both long-term storage (LTS) and consistent long-term retrieval (CLTR) were scored for this task. LTS was defined as the ability to successfully recall a word in two consecutive trials, while CLTR was defined as the successful recall of a word across all trials.

Hippocampal Segmentation

Hippocampal volumes were calculated using Freesurfer image analysis, a free automated segmentation program that is available for download online (http://surfer.nmr.mgh.harvard.edu). The technical details are described in Fischl et al, 2002. We loaded the high-resolution MPRAGE images into Freesurfer, which mapped each participant's data into MNI standard space. All of the reconstructed images were first reviewed for proper white matter and pial boundaries, proper segmentation, and proper skull stripping. If necessary, manual changes were made to problem areas before resubmitting the corrected data through Freesurfer. The segmentation was once again reviewed before analyzing the specific hippocampal volumes for each participant (Figure 1).

MRI Parameters

Participants were scanned at the Wright Center of Innovation using a 3T Philips full body scanner in which they were demetaled and instructed to lie still for 25 minutes. High-resolution structural images were collected for each participant using a 3D Magnetization Prepared Rapid Gradient Echo Imaging (MPRAGE) protocol with 160 contiguous sagittal slices (TE/TR/TI 3.7/8.1/1005 ms), collected in an ascending fashion parallel to the anterior and posterior commissures using a spoiled gradient sequence (240 × 240 mm FOV; 1 mm thick slices, with a 1 × 1 x 1 mm in-plane resolution) with a flip angle of 8 degrees.

Data Analyses

Statistical analyses were completed using SPSS 19.0 for Mac OS X. All dependent variables in the regression analyses discussed later were tested for normality. Residual terms in the regressions reported below were tested for homoscedasticity by inspecting the Q-Q plots and Levene's test of equality of error variances. None of the residual terms in the regressions reported below violated the assumption of homoscedasticity.

To examine the association of depression and physical activity with cognitive performance and hippocampal volume, we conducted two separate multiple regression analyses. Given that for the domain of episodic memory we had multiple measures (LTS and CLTR), we created a multivariate dependent variable vector for this construct. Similarly, for the second multivariate multiple regression we created a multivariate dependent variable vector for the left and right hippocampal volume. In these analyses, age, gender, and education were included as covariates and depression, physical activity, and the interaction between the two variables were included as continuous independent variables. For each of the multivariate regression analyses,

we first report the significance of the overall multivariate model, followed by the results of the separate univariate analyses.

Results

Selective Reminding Task

In order to examine the association of depression and physical activity on cognitive performance, we conducted a multivariate multiple regression, with two measures from the selective reminding task as the dependent variables. In addition, in the model, age and education were entered as the continuous covariates and sex was entered as the categorical covariate. The overall multivariate model was not significant for either depression (Wilks's Λ=0.99, $F_{(2,44)}$=0.06, p>0.05, μ^2=0.003) or physical activity (Wilks's Λ=0.84, $F_{(2,44)}$=0.15, p>0.05, μ^2=0.007) or the interaction between depression and physical activity (Wilks's Λ=0.98, $F_{(2,44)}$=0.43, p>0.05, μ^2=0.02). Given that the overall multivariate model was not significant for the dependent vectors, no separate univariate analyses were conducted.

Hippocampal Volume

In addition to memory performance, we also investigated physical activity as a moderator between depression and hippocampal volume. In this model, in addition to age, education, and gender as covariates of no interest, we also added intra-cranial volume (ICV) as a covariate. The overall multivariate model was not significant for depression (Wilks's Λ=0.96, $F_{(2,43)}$=0.80, p>0.5, μ^2=0.04) but was marginally significant for physical activity (Wilks's Λ=0.88, $F_{(2,43)}$=2.74, p= 0.07, μ^2=0.11). The interaction of depression and physical activity was not significant (Wilks's Λ=0.98, $F_{(2,43)}$=0.28, p>0.05, μ^2=0.01), suggesting that physical activity did not moderate the association between depression and hippocampal volume.

Following the marginally significant multivariate analysis, we conducted separate univariate regressions to examine the effects of physical activity on the left and right hippocampal volumes. Similar to before, the variables age, gender, education, and ICV were added as covariates of no interest. Physical activity was significantly associated with the volume of the right hippocampus ($F_{(1,44)}$=4.339, $p<0.05$, μ^2=0.090) and accounted for about 9% of the variance in right hippocampal volume over and above that of age, gender, education, and ICV. The relationship between physical activity and left hippocampal volume, although in the positive direction, was not found to be significant ($F_{(1,44)}$=1.3, $p>0.05$, μ^2=0.03), with physical activity accounting for 3% of the variance in left hippocampal volume. These results are shown in Figure 2.

Discussion

Cognitive dysfunction has recently become an area of interest in MS literature. Previous research has demonstrated that MS patients perform significantly worse than healthy controls on tasks of cognitive functioning (Janculjak et al, 2008; Sicotte et al, 2008). This cognitive deficit is further exacerbated in individuals with MS who have also been diagnosed with clinical depression (Arnett et al, 1999, 2001). This finding is particularly troubling because of the high prevalence of depression in the MS population. In addition to cognitive differences, previous research has also found structural disparities between not only MS populations and healthy controls (Sicotte et al, 2008), but also between depressed and non-depressed MS patients (Gold et al, 2010). While researchers have described a variety of structural differences, research has recently focused specifically on the hippocampus because of its vital role in memory.

Recent promising results that suggest cardiorespiratory fitness is not only correlated with improved cognitive functioning (Prakash et al, 2007), but it is also associated with increased gray

matter volume and white matter tract integrity (Prakash et al, 2010). However, these beneficial influences have not been investigated in relation to levels of depression. The purpose of this study was to expand the MS literature and further investigate the influence of physical activity for patients with MS. Particularly, we were interested in the depression component and whether there was preliminary evidence that physical activity could potentially buffer the increased degenerative effects that depression has on both cognitive functioning and hippocampal volume in depressed MS patients.

In this study, we hypothesized that depression would have a negative influence on both cognition and hippocampal volume. However, we found that there were no significant correlations between these variables. While these results were not what we had expected, this is an important finding because it demonstrates preliminary evidence that for MS patients who are experiencing depression, this clinical diagnosis may not be a driving force behind the cognitive dysfunction or hippocampal atrophy that is often associated with this disease. This may indicate that depression is a secondary symptom and does not have the same structural and cognitive impacts for MS populations that previous research has described for non-MS populations.

We also expected to find a positive influence of physical activity on cognitive functioning, but the present study did not find such a correlation. Previous research from our lab found that there was a positive relationship between cognitive functioning and cardiorespiratory fitness (Prakash et al, 2007). These earlier studies focus on VO_2 consumption, a measurement of a participant's peak oxygen consumption, which occurs with high intensity physical activity. However, many individuals do not regularly partake in high intensity activity, thus never reaching their peak oxygen consumption. This is especially noticeable in a population that has routinely been told not to exercise. Therefore, our interest was whether these earlier findings

could be extended from cardiorespiratory fitness to everyday activity. We wanted to investigate whether both high and low intensity activity would significantly influence performance on cognitive tasks. However, our results did not support this hypothesis. It is possible that in order to produce significant improvements in task performance, a certain level of cardiorespiratory fitness must be reached.

While this study did not find a significant influence of physical activity on memory functioning, there was a significant relationship between physical activity and right hippocampal volume. These results are consistent with previous research that found a positive correlation between levels of physical activity and volume of the medial temporal lobe in older adults (Bugg & Head, 2009). This is an important finding because studies have found that MS patients have a significant decrease in hippocampal volume (Roosendaal et al, 2010; Sicotte et al, 2008), and that this decline is further exacerbated in depressed MS patients (Gold et al, 2010). As noted earlier, previous research within the MS literature found a preservation of both gray matter and white matter tract integrity in highly fit MS patients (Prakash et al, 2010). While this previous study focused on global gray matter volume rather than the volume of subcortical structures, our current study extends this earlier finding to the hippocampus. This study demonstrates evidence that physical activity may have a buffering effect in an area of the brain that recent research has shown is negatively impacted in MS patients.

The results of our study should be interpreted in the context of certain limitations. One of the most basic limitations is that the study employed a cross-sectional design. For this reason we are unable to determine causality for any of the conclusions that we drew from our data. For these particular analyses, we also did not analyze behavioral or structural data of healthy controls. Because these current analyses only provide correlations within an MS population, it

does not allow us to draw concrete conclusions that there are significant impairments in MS patients as compared to other populations.

In addition, our measure of depression may not have had the necessary sensitivity because it only measured anhedonia, the unique identifying feature of depression. We used the MASQ because of its ability to separate out the unique characteristics of anxiety and depression, which enabled us to be sure that higher scores on our questionnaire were due to depression and not due to anxiety. However, there are many overlapping symptoms between depression and anxiety. Because there are symptoms of clinical depression other than anhedonia, if participants scored low on the anhedonic depression subscale it may not have been indicative that they were not clinically depressed. Rather, it may only have indicated that anhedonia was not a significant symptom of depression for these individuals. Because of this, some depressed patients in our sample may not have been accurately represented by the MASQ questionnaire.

It has become increasingly necessary to not only understand the nature of cognitive deficits in multiple sclerosis, but also to develop safe and effective treatments to protect patients' cognitive functioning. Additionally, while there is a high prevalence of depression in MS patients, it is still a relatively understudied area of MS. Researchers have begun paying more attention to this topic because depression is one of the strong determinants in the quality of life for MS patients (Amato et al, 2001). Because much of the research demonstrates that depression is associated with an even further decline in cognition, it is more important than ever to understand the role that depression plays in cognitive dysfunction. Many studies are beginning to focus on finding cost-effective ways to reduce the many symptoms of MS. Our lab has previously found that cardiorespiratory fitness has a positive influence on performance on

cognitive tasks. These findings have provided the groundwork not only for this current study, but also for future studies that are being developed in our lab.

MS is a distressing disease, particularly because of its unpredictability and wide variety of symptoms (Brassington & Marsh, 1998). Supplementary studies are necessary to further understand the nature of depression and cognitive dysfunction in MS. In the near future, our laboratory will be contrasting the data from our MS population with a recently collected data set from a population of healthy controls who have been matched on age, gender, and education. This will provide valuable information about many of the cognitive and structural differences between these two populations. Likewise, functional MRI (fMRI) data will be examined to further identify differences not only within an MS population, but also in comparison to a healthy population. Because there are substantial differences in the progression of the different types of MS, another interesting study would examine how different disease courses impact both depression and cognitive functioning. It would be worthwhile to investigate if there are varying degrees of beneficial influence for the different diagnoses of MS. While there is still much to be researched in order to understand the many complexities of MS, researchers have taken important steps to understand the problems of MS and thereby increase the quality of life for this clinical population.

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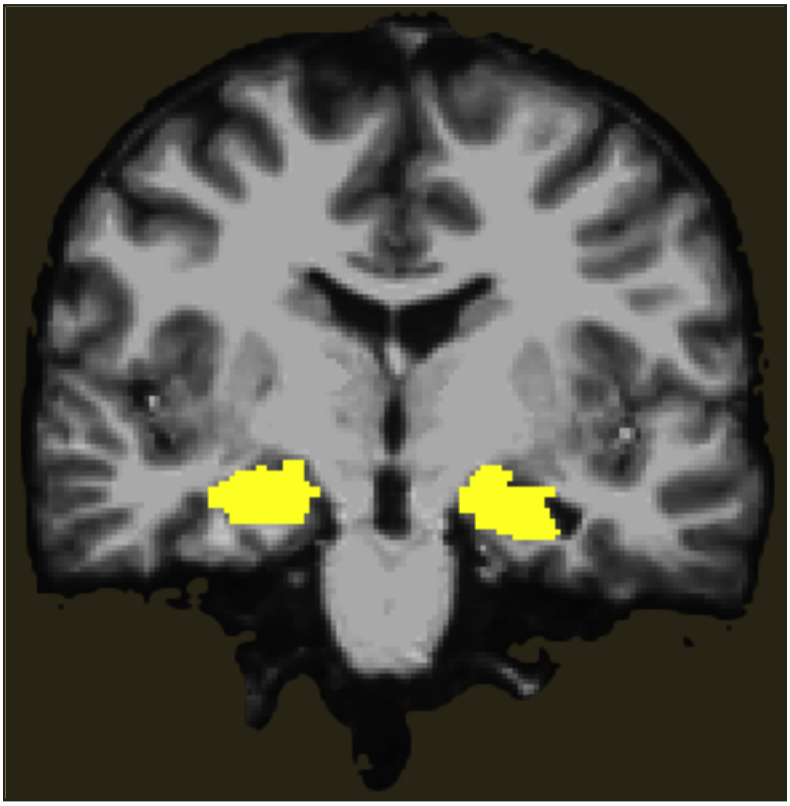
Table 1

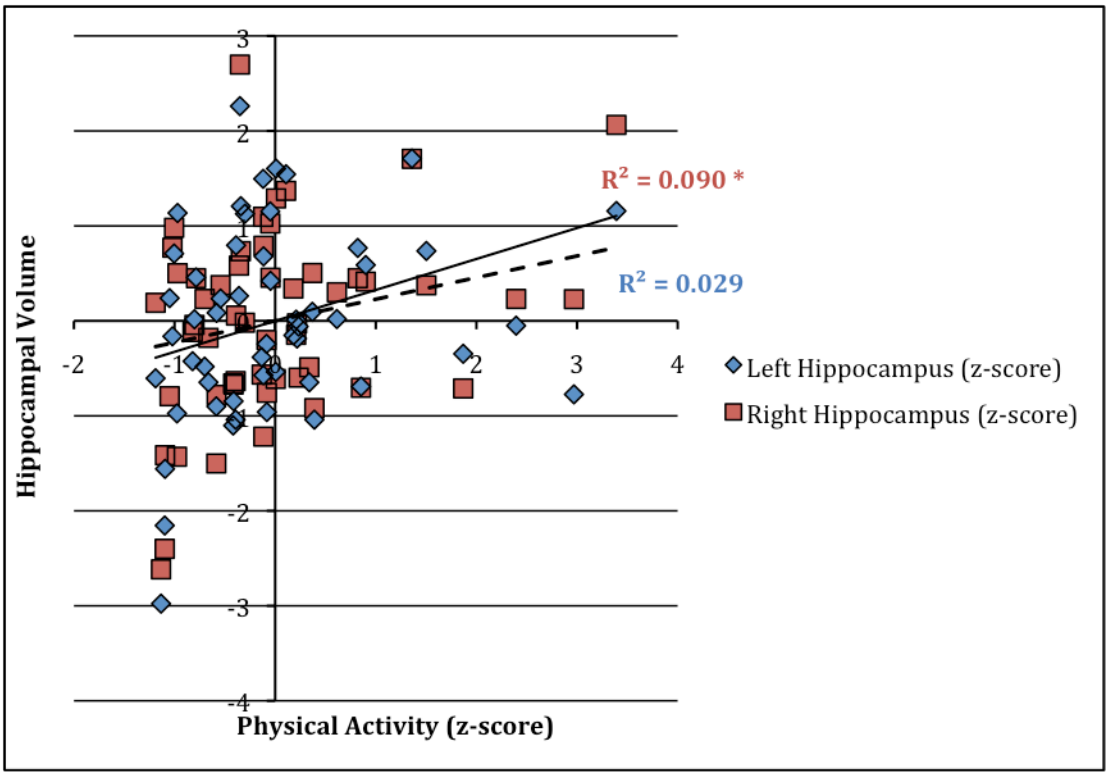
Demographics and clinical descriptives of the MS sample

Mean Age (S.D.)	45.79 (8.30)
Mean Education (S.D.)	15.53 (2.20)
Gender	14 male / 38 female
Type of MS	48 RRMS / 3 PPMS / 1 SPMS
Mean EDSS (Range)	4.03 (2-6.5)
Mean Duration of MS (Range)	10.04 (1-29)
Mean Score on SRT – LTS (Range)	44.13 (2-67)
Mean Score on SRT – CLTR (Range)	34.25 (2-64)
Mean Score on the MASQ-AD (Range)	55.52 (26-98)



Y=10

Figure 1. Hippocampal segmentation using Freesurfer. This figure is a coronal slice as seen in the Freesurfer software that displays the right and left hippocampi in yellow.



* $p < .05$

Figure 2. Correlations between physical activity and hippocampal volumes. This figure shows the associations standardized physical activity scores and left and right hippocampal volumes, as well as corresponding effect sizes.

Appendix

Mood and Anxiety Symptom Questionnaire (MASQ)

Below is a list of feelings, sensations, problems, and experiences that people sometimes have. Read each item and then mark the appropriate choice in the space next to that item. Use the choice that best describes how much you have felt or experienced things this way during the past week, including today. Use this scale when answering.

1	2	3	4	5
not at all	a little bit	moderately	quite a bit	extremely

(AD/RS) 1 _____Felt really good about myself

(AD/RS) 2 _____Felt optimistic

(AD/RS) 3 _____Seemed to move quickly and easily

(AD) 4 _____Felt cheerful

(AD) 5 _____Felt really "up" and lively

(AA)) 6 _____Heart was racing or pounding

(AD) 7 _____Felt like nothing was very enjoyable

(AA) 8 _____Was afraid I was going to die

(AA) 9 _____Was trembling or shaking

(AD) 10 _____Felt unattractive

(AA) 11 _____Felt faint

(AA) 12 _____Had to urinate frequently

(AD/RS) 13 _____Felt like I had a lot of energy

(AD) 14 _____Felt like there wasn't anything interesting or fun to do

(AD/RS) 15 _____Felt like I had a lot of interesting things to do

(AA) 16 _____Felt dizzy or lightheaded

(AD/RS) 17 _____Was proud of myself

(AD/RS) 18 _____Felt like I had accomplished a lot

(AA) 19 _____Was short of breath

(AD) 20 _____Felt really slowed down

(AD/RS) 21 _____Felt like I had a lot to look forward to

(AD) 22 _____Felt like it took extra effort to get started

(AA) 23 _____Felt numbness or tingling in my body

(AA) 24 _____Hands were cold or sweaty

(AD/RS) 25 _____Looked forward to things with enjoyment

(AD/RS) 26 _____Felt really happy

(AA) 27 _____Hands were shaky

(AA) 28 _____Startled easily

(AA) 29 _____Had hot or cold spells

(AA) 30 _____Had trouble swallowing

(AA) 31 _____Muscles twitched or trembled

(AD) 32 _____Thought about death or suicide

(AA) 33 _____Had a very dry mouth

(AA) 34 _____Had pain in my chest

(AD) 35 _____Felt really bored

(AD) 36 _____Felt withdrawn from other people

(AA) 37 _____Felt like I was choking

(AD/RS) 38 _____Felt hopeful about the future

(AD/RS) 39 _____Felt like I was having a lot of fun

AD=anhedonic depression scale

AA=anxious arousal scale

RS=reverse-scored item