The Relationship Between Diffuse Axonal Damage and Fatigue in Multiple Sclerosis

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Background: Fatigue is a common and distressing symptom for patients with multiple sclerosis (MS). There is growing evidence that fatigue in MS has a central nervous system component. We hypothesized that diffuse cerebral axonal damage could be associated with fatigue and used proton magnetic resonance spectroscopy to noninvasively measure axonal damage or loss in the brains of patients with MS.

Objective: To assess the strength of the relationship between central brain N-acetylaspartate and fatigue.

Design: Data from 73 patients who had undergone proton magnetic resonance spectroscopy imaging and completed the Fatigue Severity Scale questionnaire were analyzed.

Results: The N-acetylaspartate–creatine ratio (NAA/Cr) was significantly lower in the high-fatigue group than the low-fatigue group (mean±SD, 2.69±0.29 and 2.99±0.33, respectively. P=.003). Independent of the Kurtzke Expanded Disability Status Scale, T2 lesion volume, age, and disease duration, NAA/Cr was significantly lower in the high-fatigue group as compared with the low-fatigue group. There was a statistically significant linear correlation between the Fatigue Severity Scale scores and NAA/Cr (Spearman rank ρ =−0.361, P=.02).

Conclusions: The results of this study, combined with those of others, suggest that widespread axonal dysfunction is associated with fatigue in MS. Increased recruitment of cortical areas and pathways in response to brain injury may be responsible for the patient's sense that the effort required to perform actions is disproportionately high.

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Fatigue is a common complaint of patients with multiple sclerosis (MS) and is considered by many of them to be one of their most disabling symptoms.1-4 A recent study demonstrated that fatigue in patients with MS was associated with impaired quality of life after accounting for physical disability.2 Fatigue can be the initial symptom of MS,3 the main feature of a relapse,4 or it can be associated with deconditioning, spasticity, or depression.5-9 Fatigue has been defined as a "subjective lack of physical and/or mental energy that is perceived . . . to interfere with usual and desired activities."10,11 It is 1 of the 2 major reasons for unemployment among people with MS.10 Patients suffering from fatigue complain of a lack of energy and a sense of tiredness not related to muscle weakness.11 The pathophysiology of fatigue is poorly understood. A number of mechanisms have been implicated, including reduced efficiency of action-potential propagation in partially demyelinated or degenerated central motor axons or intracortical circuits,12 reduced muscular oxidative capacity due to poor physical conditioning,13 and increased energy demands for muscle activation due to impaired recruitment of a motor neurons because of corticospinal involvement or spasticity.14,15

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There is growing evidence that fatigue in MS has a central nervous system component caused by corticosubcortical interconnection damage or by disseminated demyelination.12,13,16 Assessing event-related potentials during the performance of auditory memory tasks, Sandroni et al12 found that fatigue in patients with MS was associated with a slower reaction
time that was not explained by a change in pyramidal tract conduction times. They postulated that the underlying problem was in the neural processes intervening between stimulus evaluation and the initiation of motor events. A recent electroencephalographic study, which required patients with MS to execute a voluntary movement, revealed overactivity in cortical structures involved in motor programming and reduced activity of inhibitory circuits acting on the motor cortex after movement termination in patients complaining of fatigue.\textsuperscript{10} Using fluorodeoxyglucose positron emission tomography, Roelcke et al\textsuperscript{17} have demonstrated reduced cerebral glucose metabolism in a number of areas in patients with MS who reported fatigue as compared with those who did not. These areas include the basal ganglia, the internal capsule, the posterior parietal lobe, the temporo-occipital lobe, and the prefrontal area and its adjacent white matter. These results suggest a central etiology for fatigue.

In recent years, studies of patients with MS have emphasized the association between extrapleural white matter abnormalities and clinical disability.\textsuperscript{20-24} Therefore, we hypothesized that fatigue could be associated with diffuse cerebral axonal damage. Proton magnetic resonance spectroscopy can be used to noninvasively measure cerebral axonal damage. Proton magnetic resonance spectroscopy imaging examinations of the brain were performed using a Philips Gyroscan ACS II operating at 1.5 T (Philips Medical Systems, Best, the Netherlands). A transverse dual-echo, turbo spin-echo sequence repetition time \( [\text{TR}] / \text{echo time} \ [\text{TE}] \ = \ 2075/3290 \) milliseconds, and 200-mm field of view was used. Proton density-weighted and T2-weighted images with 20-mm slab thickness were obtained using a double spin-echo excitation method (TR 2000, TE 272 milliseconds).\textsuperscript{37} Suppression of the intense water resonance was done by placing frequency-selective excitation pulses at the beginning of the magnetic resonance spectroscopy imaging sequence. To allow for correction of B\textsubscript{0} inhomogeneity during post-processing, a quick magnetic resonance spectroscopy image without water suppression was also acquired (TR 850 milliseconds, TE 272 milliseconds, 16×16 phase-encodes, 250×250-mm field of view, 20-mm slab thickness) using a double spin-echo excitation method (TR 2000, TE 272 milliseconds).\textsuperscript{37}

**METHODS**

**PATIENT POPULATION**

This is a retrospective study on patients with MS at the Montreal Neurological Institute and Hospital who are part of an ongoing spectroscopic study that enrolls all patients interested in being followed longitudinally with spectroscopy. The Ethics Committee of the Montreal Neurological Institute and Hospital approved the study and informed consent was obtained from all participants. All patients with a definite diagnosis of relapsing-remitting or secondary progressive MS who had completed an FSS questionnaire between December 1998 and February 2001 were potential subjects. The exclusion criteria were undergoing immunomodulatory therapy at the time of the scan, an attack within 30 days of the scan, or poor-quality spectroscopic data. The study included 73 patients with MS.

**STUDY PROCEDURES AND OUTCOME MEASURES**

This was a cross-sectional study. Each patient's visit comprised an imaging portion, a Kurtzke Expanded Disability Status Scale (EDSS) assessment by a neurologist, and the completion of an FSS questionnaire.

Fatigue was quantified using the FSS,\textsuperscript{3} which assesses subjective, general fatigue. The patients filled out a questionnaire by assigning a number between 1 and 7 to the items listed. A higher score indicated more fatigue. The answers were then averaged, resulting in a global fatigue score for each patient. Patients were asked to complete the questionnaire on the day of their scan. Five patients completed their questionnaire within 2 weeks of their scan, and 6 completed it within 3 weeks. Based on previous work, the patients were divided into 2 fatigue groups determined by their FSS score: the low-fatigue group (FSS \( \leq 4 \)) (n=26) and the high-fatigue group (FSS \( > 5 \)) (n=43). Thirteen patients whose FSS score was between 4 and 5 were excluded from the between-group analysis but were retained for correlation analyses.

The patient's degree of disability was assessed by a neurologist using EDSS,\textsuperscript{35} which is based on neurological testing of 7 central nervous system functional systems: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and mental.

**DATA ACQUISITION**

Proton Magnetic Resonance Spectroscopy Imaging

Combined proton magnetic resonance imaging and magnetic resonance spectroscopy imaging examinations of the brain were performed using a Philips Gyroscan ACS II at 1.5 T (Philips Medical Systems, Best, the Netherlands). A transverse dual-echo, turbo spin-echo sequence repetition time \( [\text{TR}] / \text{echo time} \ [\text{TE}] \) = 2075/3290 milliseconds, and 200-mm field of view was used. Proton density-weighted and T2-weighted images with 20-mm slab thickness were acquired parallel to the plane connecting the anterior and posterior commissures (Figure 1). This was followed by a matching T1-weighted fast field-echo sequence (TR/TE = 35/10 milliseconds). These magnetic resonance images were used to position a spectroscopic volume of interest of approximately 90×90×20 mm\(^3\) to include the corpus callosum and adjacent periventricular white matter. Magnetic resonance spectroscopic images parallel to the anterior and posterior commissures were acquired (32×32 phase-encodes, 250×250-mm field of view, 20-mm slab thickness) using a double spin-echo excitation method (TR 2000, TE 272 milliseconds).\textsuperscript{37} Suppression of the intense water resonance was done by placing frequency-selective excitation pulses at the beginning of the magnetic resonance spectroscopy imaging sequence. To allow for correction of B\textsubscript{0} inhomogeneity during post-processing, a quick magnetic resonance spectroscopy image without water suppression was also acquired (TR 850 milliseconds, TE 272 milliseconds, 16×16 phase-encodes, 250×250-mm field of view, and 1 signal average).\textsuperscript{37}

**Post Processing**

Metabolite resonance intensities of NAA, choline (Cho), and creatine (Cr) were determined using a combination of Xunspec1 software (Philips Medical Systems, Andover, Mass) and locally developed software (AVIS; Samson Antel PhD, Magnetic Resonance Spectroscopy Unit, Montreal Neurological Institute) that integrates fitted peak areas between automatically determined frequency bounds relative to a locally interpolated baseline. Metabolite signals are expressed as ratios to Cr in the same voxel. Creatine is relatively homogeneously distributed throughout the brain, and thus it has been used as an internal reference peak to calculate NAA/Cr and Cho/Cr ratios.\textsuperscript{38} All voxels at the edges of the volume of interest were excluded from analysis owing to potential chemical-shift artifacts on the relative amplitudes. A single NAA/Cr and Cho/Cr ratio is calculated from the entire spectroscopic volume of interest and used for further analyses.
Lesion volumes were determined by manual segmentation using locally developed software (Display. David MacDonald, Brain Imaging Center, Montreal Neurological Institute) that provides simultaneous access to proton density and to T2- and T1-weighted image sets. Lesion boundaries were primarily determined by the proton density images.

MEASURES

There were a total of 7 measures evaluated between the 2 groups: NAA/Cr, Cho/Cr, age, disease duration, lesion volume on T2-weighted images, and EDSS scores.

STATISTICAL ANALYSIS

A t test was used to compare the low- and the high-fatigue groups with respect to NAA/Cr, Cho/Cr, and age. A Mann-Whitney U test statistic was used to compare the 2 groups with respect to disease duration and T2 lesion volume because the assumption of normal distribution was not met and for EDSS, because it is an ordinal value. Bonferroni correction for multiple comparisons was performed.

An analysis of covariance was used to compare NAA/Cr between the low- and high-fatigue groups while controlling for the potential confounding effects of age and EDSS.

A Pearson correlation coefficient was determined to assess the linear association between NAA/Cr and age. A Spearman rank correlation coefficient was calculated to assess the association between variables that did not fulfill the criteria of normal distribution (ie, T2 lesion volume and disease duration) or consisted of an ordinal scale (FSS, EDSS). Bonferroni-corrected P values were reported because of the multiple tests done. A partial correlation coefficient was calculated for FSS and NAA/Cr while controlling for the effects of EDSS, T2 lesion volume, and disease duration. All statistical analyses were performed using SYSTAT 10.0 (Systat Software Inc, Richmond, Calif).

The demographics and clinical characteristics for the low- and the high-fatigue groups are presented in Table 1. The NAA/Cr ratio was significantly lower in the high-fatigue group (n = 34) than the low-fatigue group (n = 26) (mean ± SD, 2.69 ± 0.29 and 2.99 ± 0.33, respectively. P = .003) (Figure 2). The Cho/Cr ratio was not significantly different between the low- and high-fatigue groups (mean ± SD, 1.44 ± 0.15 and 1.48 ± 0.18, respectively. P > .99). As can be observed in Table 1, there was no significant difference between the 2 groups with respect to age, disease duration, the EDSS scores, or T2 lesion volumes after Bonferroni correction for multiple tests. There was, however, a trend toward a difference in EDSS between the 2 groups; the low-fatigue group had a lower EDSS of 2.69 ± 2.2 compared with the high-fatigue group’s EDSS of 3.81 ± 2.2 (P = .09). There was no significant difference in the FSS score between patients with relapsing-remitting and secondary progressive MS (4.66 ± 1.5 and 4.67 ± 1.8, respectively. P = .99).

Although only the NAA/Cr ratio was significantly different between the 2 groups, we wanted to eliminate the possibility that other variables were confounding the analysis. We ran an analysis of covariance on NAA/Cr

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while controlling for the effects of EDSS score and age. The EDSS score was chosen as a covariate because there was a trend toward a difference in the 2 groups. Age was chosen as a covariate because there was a disparity in the ranges between the 2 groups. The NAA/Cr ratio was still found to be significantly lower in the high-fatigue group as compared with the low-fatigue group ($P = .004$).

All subjects (N = 73) were included for evaluating the relationship between the various variables (Table 2). We found a statistically significant negative correlation between the FSS score and NAA/Cr ratio (Spearman rank $r = −0.361$, $P = .02$) (Figure 3). In addition, Table 2 reveals the correlation between the different variables used in this study. There is also a significant negative correlation between the NAA/Cr ratio and the EDSS score, disease duration, and T2 lesion volume. As expected, both EDSS score and age are positively correlated with disease duration, and EDSS score is positively correlated with age. In addition, disease duration is positively correlated with T2 lesion volume. The partial correlation between NAA/Cr ratio and FSS score, while controlling for the effects of EDSS score, disease duration, and T2 lesion volume, improved to $−0.474$.

Depression was not formally assessed, as this was a retrospective study. Because depression is associated with fatigue, we wanted to ensure this factor was not responsible for our results. We undertook a medical record review of the 73 patients and excluded all those who were taking antidepressants, anxiolytics, or fatigue-modulating drugs, such as amantadine, at the time of the scan and those who had received a diagnosis of depression by the treating physician. This analysis included 49 patients, and, similar to our previous analysis, only the NAA/Cr ratio was significantly different between the 2 fatigue groups. The analysis of covariance performed with EDSS and age as covariates again revealed a significantly lower NAA/Cr ratio in the high-fatigue group as compared with the low-fatigue group ($P = .02$). There was no difference between the 2 groups with respect to disease duration or T2 lesion volume. Again, we found a statistically significant linear correlation between FSS score and NAA/Cr ratio, while controlling for the effects of EDSS score and age.

### Table 1. Demographics and Clinical Characteristics for the Low- and the High-Fatigue Groups

<table>
<thead>
<tr>
<th>Fatigue Group</th>
<th>Low (FSS Score ≤4) (n = 26)</th>
<th>High (FSS Score ≥5) (n = 34)</th>
<th>Bonferroni-Corrected P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS type, No. (%) of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>20 (77)</td>
<td>26 (76)</td>
<td>. . .</td>
</tr>
<tr>
<td>SP</td>
<td>6 (23)</td>
<td>8 (24)</td>
<td>. . .</td>
</tr>
<tr>
<td>NAA/Cr ratio, mean ± SD (range)*</td>
<td>2.99 ± 0.33 (2.44-3.72)</td>
<td>2.69 ± 0.29 (1.98-3.32)</td>
<td>.003</td>
</tr>
<tr>
<td>EDSS score, mean ± SD (range)†</td>
<td>2.69 ± 2.2 (0-9)</td>
<td>3.81 ± 2.2 (0-9)</td>
<td>.09</td>
</tr>
<tr>
<td>Age, y, mean ± SD (range)*</td>
<td>38.09 ± 10.2 (24.0-62.2)</td>
<td>42.12 ± 6.9 (29.6-57.8)</td>
<td>.46</td>
</tr>
<tr>
<td>Disease duration, y, mean ± SD (range)†</td>
<td>10.35 ± 9.5 (0.321-39.1)</td>
<td>10.59 ± 7.3 (0.54-30.8)</td>
<td>.99</td>
</tr>
<tr>
<td>T2 lesion volume, cm³, mean ± SD (range)†</td>
<td>11.24 ± 13.2 (0.29-42.1)</td>
<td>13.44 ± 13.4 (1.02-54.0)</td>
<td>.82</td>
</tr>
</tbody>
</table>

Abbreviations: EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; MS, multiple sclerosis; NAA/Cr, N-acetylaspartate–creatine ratio; RR, relapsing-remitting; SP, secondary progressive. *t Test. †Mann-Whitney U test.
and NAA/Cr ratio (Spearman rank \( r = -0.376 \), [Bonferroni corrected]; \( P = .04; n=58 \)).

**COMMENT**

The results of this study suggest that diffuse periventricular axonal injury is associated with increased fatigue in patients with MS. Independent of EDSS score, T2 lesion volume, age, and disease duration, the NAA/Cr ratio was significantly lower in the high-fatigue group as compared with the low-fatigue group. Moreover, a significant correlation was present between fatigue and the NAA/Cr ratio.

Although the mechanisms responsible for fatigue in patients with MS are still not known, there is increasing evidence that fatigue has a central origin and that the problem lies rostral to the corticospinal tracts.\(^{39}\) The frontal lobes have attracted particular attention in the search for mechanisms responsible for fatigue. Abnormal latencies and amplitudes from the frontal lobes have been reported when recording event-related evoked potentials during memory tasks in patients with MS and fatigue.\(^{12}\) The authors hypothesized that change in the synchrony of activity or speed of conduction between brain sites could account for the delayed reaction times in MS patients with fatigue. A positron emission tomography study revealed reduced energy metabolism in the prefrontal area, including the adjacent white matter.\(^{17}\) Lesions in the dorsolateral prefrontal cortex are characterized by deficits in motor programming and executive function.

Our spectroscopic volume of interest is located over the corpus callosum and includes the corticospinal tracts, as well as frontal, parietal, and occipital lobe white matter. Decreases in NAA in this area are highly correlated with a reduction of NAA throughout the brain of patients with MS.\(^{40}\) The results from our study suggest that fatigue is likely a consequence of diffuse axonal dysfunction.

We attribute the lower NAA/Cr ratio observed in the high-fatigue group to a lower NAA and not a higher Cr level. This is highly probable in view of the known sensitivity of NAA levels to demyelinating injury and the relative stability of the Cr level under these circumstances.\(^{41,42}\) Furthermore, the Cho/Cr ratio was not significantly different between the 2 fatigue groups. Absolute quantitation of metabolites with in vivo magnetic resonance spectroscopy studies requires assumptions about coil radiofrequency homogeneity, coil coupling, metabolite relaxation times, tissue composition of the voxel, point spread function, slice selection profile, and standards that may not be justified in abnormal tissue. Studies attempting absolute quantitation in vivo have reported discrepant results pertaining to Cr in MS.\(^{35-47}\) An in vitro study revealed a decrease of Cr only in MS plaques, while Cr in the normal-appearing white matter remained unchanged.\(^{44}\) The total lesion volume is small relative to the whole brain, and therefore it is unlikely that changes of Cr in lesions have affected our overall NAA/Cr measures.

The NAA/Cr ratio has been used as a surrogate marker of neuronal integrity and has been reported as a good indicator of disease extent in patients with MS.\(^{30,22,23,26,38,30,38}\) The results of this study, with the NAA/Cr ratio positively correlating with EDSS score, disease duration, and T2 lesion volume, support previous results.\(^{46,49}\) As expected, EDSS was correlated with disease duration and T2 lesion volume.\(^{50,51}\) Also disease duration was correlated with T2 lesion volume.\(^{52}\) The significant correlations between the various variables are not unexpected since many of them interact. The fact that FSS score correlates significantly with the NAA/Cr ratio and not with other parameters of the disease, such as T2 lesion volume and disease duration, serves to strengthen the point that there may be some diffuse process occurring in the brain of patients with MS not directly related to the lesion.

There is growing evidence that compensatory reorganization takes place in patients with MS.\(^{33-58}\) Functional magnetic resonance imaging studies have demonstrated a larger area of activation of the brain for the same task in patients with MS compared with controls.\(^{33-58}\) Increased activation of the ipsilateral sensorimotor cortex with simple hand movements was demonstrated in patients with mild or no physical impairment compared with normal controls, and the extent of the increase was strongly correlated with a decrease in brain NAA levels.\(^{56-58}\) The increased activation was attributed to adaptive plasticity and “unmasking” of latent motor pathways. Fatigue may be the price to pay for this plasticity. A recent functional magnetic resonance imaging study has demonstrated altered brain-activation patterns in fatigued vs nonfatigued patients with MS.\(^{39}\) Increased electroencephalographic activity recorded in the frontal lobes in fatigued patients might be explained by supplementary motor-area overactivity to voluntary movement as a compensatory mechanism to subclinical motor impairment.\(^{19}\) The modest correlation between T2 lesion volume and disability in patients with MS\(^{40,61}\) may be partly due to compensatory mechanisms becoming operational. Compensation has been hypothesized in recovery from stroke, as well as MS attacks.\(^{53,56,62-64}\) It may be hypothesized that diffuse white matter disease translates into an increase in the central nervous system effort required by a patient with MS to perform the same activity as compared with a disease-free subject, with resultant fatigue.

The magnetic resonance imaging lesion volume data has not yielded consistent results when assessing the relationship between lesion burden and fatigue. A recent

<table>
<thead>
<tr>
<th>Item</th>
<th>NAA/Cr Ratio</th>
<th>EDSS Score</th>
<th>FSS Score</th>
<th>Age</th>
<th>Disease Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDSS score</td>
<td>( r = -0.498 )</td>
<td>( P = .001 )</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>FSS score</td>
<td>( r = -0.361 )</td>
<td>( p = 0.258 )</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Age</td>
<td>( r = -0.300 )</td>
<td>( p = 0.453 )</td>
<td>( r = 0.197 )</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Disease volume</td>
<td>( r = -0.385 )</td>
<td>( p = 0.440 )</td>
<td>( r = -0.006 )</td>
<td>( p = 0.540 )</td>
<td>...</td>
</tr>
<tr>
<td>T2 lesion volume</td>
<td>( r = -0.704 )</td>
<td>( p = 0.548 )</td>
<td>( p = 0.047 )</td>
<td>( r = 0.262 )</td>
<td>( p = 0.407 )</td>
</tr>
</tbody>
</table>

**Table 2. Correlation Between the Different Variables Used in This Study**

Abbreviations: EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; NAA/Cr, \(^{1}H\)-acetylaspartate–creatine ratio.
magnetic resonance imaging study showed that nondisabled patients with fatigue, as compared with those without fatigue, had a higher MS lesion burden in the areas of the parietal lobe, the periventricular trigone, and the internal capsule. Previous studies that included disabled patients found no correlation between fatigue severity and a regional or global magnetic resonance image plaque load or atrophy. Our study, which included nondisabled and very disabled patients (EDSS score range, 0-9), also revealed no correlation between FSS score and T2 lesion volume.

We did not find a significant correlation between FSS and EDSS scores after correcting for multiple comparisons, but when assessed alone, there was a significant correlation (Spearman rank \( r = 0.258, P = .03 \)) between fatigue and EDSS scores as in the work of Kinkel. In addition, there was a significant correlation between depression severity and fatigue. Although we did not formally evaluate the impact of depression on fatigue in this study, we attempted to control for its effect by reanalyzing the data without patients who were clinically depressed or taking mood-altering or fatigue-modulating medications. Our results remained significant.

There was no significant difference in FSS scores between patients with relapsing-remitting and secondary progressive MS. Although this may seem surprising, the FSS stresses general fatigue, which may be dependent on the level of disability. In other words, questions in the FSS such as “my fatigue prevents sustained physical functioning” may be less applicable to a severely physically disabled person. Furthermore, patients who retain a high level of physical functioning, as is more likely in the relapsing-remitting group, will expect more of themselves and are more likely to still be involved in activities that will be affected by fatigue. Since we had an equal proportion of secondary progressive patients in the low- and high-fatigue groups, we do not believe that the inclusion of secondary progressive patients in this study had a significant effect on our between-group results.

Our observations, combined with those of others, suggest that widespread axonal dysfunction is associated with fatigue in MS. Increased recruitment of cortical areas and pathways in response to brain injury may be responsible for the patient’s sense that the effort required to perform actions is disproportionately high. It is conceivable that functional magnetic resonance imaging experiments of a fatiguing task, be it mental or physical, may be able to provide further insight into the pathophysiology of fatigue. Another avenue worthy of investigation in the search for a substrate for fatigue is the cortical gray matter. There is growing evidence that there are gray matter abnormalities in MS.

Fatigue has a tremendous effect on the activities of daily life for patients with MS; it interferes with work, family life, and social activities. The results of this study imply that neuroprotective agents that would serve to halt or delay axonal injury may be beneficial in postponing the development of fatigue.

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Author contributions: Study concept and design (Drs Tartaglia, Narayanan, De Stefano, and Arnold); acquisition of data (Drs Tartaglia, Narayanan, Santos, De Stefano, and LaPierre and Mr Francis); analysis and interpretation of data (Drs Tartaglia and Santos); drafting of the manuscript (Dr Tartaglia); critical revision of the manuscript for important intellectual content (Drs Tartaglia, Narayanan, Santos, De Stefano, LaPierre, and Arnold and Mr Francis); statistical expertise (Dr Tartaglia); obtained funding (Drs Tartaglia and Arnold); study supervision (Drs De Stefano and Arnold).

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REFERENCES

31. Simmons ML, Frondoza CG, Coyle JT. Immunocytochemical localization of N-
29. Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mork S, Bo L. Axonal transec-
28. Miller DH, Grossman RI, Reingold SC, McFarland HF. The role of magnetic reso-
27. Matthews PM, Francis G, Antel J, Bo L. Proton magnetic resonance spectroscopy of demyelinat-
26. Arnold DL, Matthews PM, Francis G, O’Connor J, Antel JP. Proton magnetic resonance spectroscopy for metabolic characterization of demyelinat-
25. Simmons ML, Frondoza CG, Coyle J. Immunochemical localization of N-
17. Vercoulen JH, Swanink CM, Zitman FG, et al. Randomised, double-blind, placebo-
12. Arnold DL, Matthews PM, Francis G, O’Connor J, Antel JP. Proton magnetic resonance spectroscopy for metabolic characterization of demyelinat-
6. Ng AV, Miller RG, Kent-Braun JA. Central motor drive is increased during vol-
tum muscle contractions in multiple sclerosis. Muscle Nerve. 1997;20:1213-
5. Ng AV, Miller RG, Kent-Braun JA. Central motor drive is increased during vol-
tum muscle contractions in multiple sclerosis. Muscle Nerve. 1997;20:1213-