Research Article

Quantification of Brain Atrophy in Early Multiple Sclerosis and Its Clinical Relevance

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Summary

Objective Background: In multiple sclerosis (MS), axonal loss and neurodegeneration occurs early in disease course and may lead to irreversible neurological impairment. We aimed to investigate brain volume loss as an accurate measure of axonal loss and its clinical relevance in early MS.

Methods: Twenty MS patients whose first symptoms beginning within the last 2 years were underwent a neurological examination included Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Functional Composite (MSFC). Cognitive status of patients was assessed with Paced Auditory Serial Addition Test (PASAT) and Rey Auditory Verbal Learning Test (RAVLT). For processing magnetic resonance imaging (MRI) data, region of interest technique (ROI) and JIM 4.0 software were established. Brain parenchymal fraction (BPF), cerebrospinal fluid (CSF) volume, gray and white matter volumes of brain was determined in MS patients and in control subjects. The relationship between MRI data and demographic, clinical variables was also evaluated.

Results: In MS patients, the mean BPF value was significantly lower than controls. BPF also negatively correlated with the duration of disease. 27.3% of the patients have impairment by verbal memory processes tests. We didn't find significant correlation between BPF scores and cognitive performance, and also MSFC/EDSS scores. There was only significant correlation between PASAT scores and white matter volume.

Conclusion: Measurement of BPF is a reliable method for brain atrophy that can be used in clinical practice and clinical trials. The atrophy beginning at the early phase of the disease might not cause clinical disability because of cortical reorganization and there might be individual threshold value of axon loss for clinical disability. In order to determine the clinical relevance of brain atrophy, longitudinal MRI studies with cognitive evaluation by comprehensive neurophysiological tests are needed.

Key words: Multiple sclerosis, brain atrophy, brain parenchymal fraction

Erken Evre Multipl Skleroz'da Beyin Atrofi Ölçümü ve Klinik Parametrelerle İlişkisi

Özet

Giriş: Multipl Skleroz (MS)'da aksonal kayıp ve nörodejenerasyon, hastalığın erken dönemlerinden itibaren oluşur ve kalsıcı özürülülüge yol açabilir. Bu çalışmada MS hastalarında beyin volum kaybı ve klinik parametrelerle ilişkisi araştırılmıştır.

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Metod: 20 erken evre MS hastasında fiziksel ve kognitif değerlendirme Expanded Disability Status Scale (EDSS) ve Multiple Sclerosis Functional Composite (MSFC), Rey Auditory and Verbal Learning Test (RAVLT) ile yapılmıştır. Manyetik rezonans görüntüleme (MRG) sonrası elde edilen veriler RIO (region of interest) tekniği ve JIM 4.0 software kullanarak işlenmiştir. BOS, gri, ve beyaz madde volümleri ve beyin parankimal fraksiyonu (BPF) hesaplanmıştır.

Bulgular: MS hastalarında ortalama BPF değerleri normal kontrollerden anlamılı olarak düşük bulunmuştur. BPF değerleri hastalık süresi ile negatif orantılıdır. MS hastalarının %27.3’ünde sözel ve işitsel bellek süreçleri testinde anormallik saptanmıştır. BPF değerleri ile kognitif performans, MSFC/EDSS skorlarında anlamılı bir ilişki saptanmıştır.


Anahtar Kelimeler: Multipl skleroz, beyin atrofisi, beyin parankimal fraksiyonu

INTRODUCTION

Multiple sclerosis (MS) is a chronic, autoimmune, inflammatory and demyelinating disease of the central nervous system and is the leading cause of non-traumatic neurological disability in young adults(10). Although MS is typically characterized by demyelination and inflammation, axonal loss and neurodegeneration occurs early in the disease course and may lead to irreversible neurological impairment(17). Recently, studies about the neurodegenerative aspect of the disease have been emerging. While the pathophysiological mechanisms behind brain atrophy are still unclear, significant brain volume loss is observed from the earliest stage of MS and proceeds throughout the disease course.

Axonal damage is thought to happen throughout the disease by multiple complex mechanisms. Repeated demyelination within previously remyelinated lesions, axonal degeneration due to the lack of trophic support from myelin and oligodendrocytes, chronic mitochondrial failure in the setting of increased energy demands, oxidative burst by activated microglia and alterations in the expression or activity of axonal ion channels are suggested mechanisms for axonal and neuronal loss(17,37).

MRI is a sensitive tool allowing users to visualize brain lesions, monitoring disease progression and treatment. Diffuse damage can be detected using non-conventional MRI techniques such as magnetization transfer imaging and diffusion tensor imaging or estimated by means of brain volume quantification. Brain parenchymal fraction (BPF) is one of the most popular measurements of brain volume in MS studies(4,19,39).

Cognitive impairment affects a large proportion of patients with MS, with a prevalence rate ranging from 40% to 70 %. Some studies have shown that these deficits may be detectable even in the earliest stages of the disease(1,29). The process of axonal loss, known to occur early in the disease process, might be associated with the abnormal cognitive findings. The presence of pathological abnormality within the cortex was demonstrated by both pathological studies and by the extensive application of modern MRI-based techniques. Cortical demyelination probably contributes to advanced brain and cortical atrophy with slowly progressive axonal injury in the normal appearing white mater and it is
associated with disease progression and cognitive impairment\(^9\).

A number of recent studies have concern on the clinical relevance of brain volume change as a measure of neurological and neuropsychological disability\(^5,13\). The objective of this study was to evaluate brain atrophy in early phase of RRMS patients and determine the relationship between brain atrophy and clinical status, cognitive dysfunction.

**MATERIAL AND METHODS**

**Subjects and Study Design**

MS Patients and controls: Twenty consecutive unselected patients aged between 18 and 50 with definite diagnosis of relapsing remitting MS who have onset of their symptoms within the last 2 years were recruited from our multiple sclerosis outpatient department. They underwent a neurological examination that included a complete history and determination of current disability using the Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Functional Composite (MSFC) score which consists of three separate components; the 25 foot walk (TW), 9 Hole Peg Test (9HPT) and Paced Auditory Serial Addition Test-3 (PASAT-3). The composite z score of these three tests was calculated. All participants gave informed consent to participate in this study, which was approved by the Ethics Committee of the Hospital. All patients fulfilled the 2005 McDonald's diagnostic criteria. None of the MS patients had suffered from an acute relapse in ≤4 weeks before MRI, and none had been treated with corticosteroids or immunosuppressants in the months prior to scanning. MS patients with other neurological disease, drug or alcohol abuse, major psychiatric illness, learning disability, and severe physical disability interfering tests, were excluded from the study. Exclusion criteria included patients taking any medications used to treat cognition or other drugs that may act as temporary stimulants or depressants of the central nervous system. Ten sex and age-matched healthy volunteers (HVs) were also investigated for normal database. All of the subjects were normal in a neurological examination and none had any history of neurological and psychiatric disease or of other medical condition.

We assessed the cognitive status of patients with neuropsychological tests which have reliability and validity studies for Turkish patients. Hamilton Depression Status Scale was used to quantify the severity of depression. Participants with moderate and severe depression (who have scores over 16) were excluded from the study. The neuropsychological tests were considered to have failed when the results were outside the normal range (means ±2 SDs obtained by the healthy control group). Neuropsychological tests included the following:

**Paced Auditory Serial Addition Test (PASAT):** PASAT is a neuropsychological test used to assess auditory information processing speed, sustained attention and calculation ability. The PASAT is presented on compact disk (CD) to control the rate of stimulus presentation. Single digits are presented either every 3 seconds (trial 1) or every 2 seconds (trial 2), and the patient must add each new digit to the one immediately prior to it. The test score is the total number of correct sums given (out of 60 possible) in each trial.

**Rey Auditory and Verbal Learning Test I and II (RAVLT modified by Öktem Ö.)\(^6\):** RAVLT is used to interpret short term auditory verbal memory, learning, and retrieval. Participants are given a list of 15 unrelated words repeated over ten different trials and are asked to repeat. A 15-noun list is read to the patient by presentation rate of one word per second. The patient is asked to recall the words. After the first trial, the list is read to the patient nine more times, every time the patient is asked to recall. Total number of words remembered gives the total learning score.
After 40 minutes delay the participants are asked to recall the original list of 15 words. The number of words gives the remembering score. If there is an unrecognized word, the word is read to the patient with two similar words. If he can remember the word this time, the number of words gives the recognizing score. Total learning score under 90, remembering score under 13 and recognizing score under 15 is accepted as abnormal. The patients were also evaluated by visual learning test which is not standardized to Turkish population. The scores were not used for statistical analysis.

MRI acquisition: All scans were performed on a 1.5 T clinical MRI scanner with a standard quadrature headcoil (Siemens, Erlangen, Germany). Pre-contrast and post-contrast multiplanar magnetisation transfer TSE T1 weighted images (repetition time/echo time (TR/TE): 650/10ms, section thickness: 5 mm, nex: 1) and sagittal FLAIR images (TR/TE:8690/128, section thickness:5 mm, nex:1) obtained by routine MRI protocol which is applied for MS patients. For BPF analysis, thin section high resolution volume-rendering data sets of the whole head were acquired using axial T1-weighted sequence consisting of 160–180 sagittal partitions (TR/TE:650/14, section thickness:3 mm, nex:2).

MRI data processing and BPF calculation: The sequence images obtained for the analysis of BPF transferred to a windows-based personal computer in which JIM 4.0 software was established, in DICOM-3 format sections. BPF measurements were done fully automatically (threshold: 0.2). In the sections obtained by this method, whole brain is automatically separated from the other structures by region of interest (ROI) technique. Then, MRI data were fully automatically segmented into fractions by chosen threshold value, containing grey matter (GM), white matter (WM), cerebrospinal fluid (CSF), and extra-cranial tissue. For every patient pixel depth, height and width, CSF volume, gray matter volume, white matter volume, brain + CSF volume, CSF/brain ratio and BPF were calculated. BPF was determined by dividing the sum of corrected GM and WM fractions by the total intracranial fraction. (BPF: Brain tissue volume / volume of brain within surface contours). The results were compared with the control group.

Statistical analyses:

Results are expressed as arithmetic median (min-max) or mean ± SD. We applied the Mann–Whitney U-test to assess group differences between the two groups (multiple sclerosis patients versus healthy controls) in age, BPF, gray and white-matter volume, and other MRI parameters. Correlations between age, EDSS, MSFC, the number of relapses and duration of disease on the one hand and MRI parameters on the other were calculated by Spearman's correlation coefficient. The Fisher exact test was used to test for differences regarding gender distribution between the multiple sclerosis and the control group. Differences were considered statistically significant at p< 0.05

RESULTS

Eighteen out of 20 patients were included in the study. Two of the patients were excluded because they could not complete of the tests. 14 patients were women (71.5%), 4 patients were men (28.5%), the mean age of the patient group was 29.06±9.0 years (range 18–50). In normal control group, 8 patients were women (%80.8), 2 patients were men (%22.3) with the mean age of 31.50±5.0 (range 25-41) (Table-1)

We didn't find statistically significant difference between MS patients and normal controls in terms of gender and age (p=0.211). The mean score of disease severity which was assessed by EDSS was 1.37 (range 1-3). The mean disease duration (since the first symptom) was 20±76 months (range 12–24). The mean
number of well-documented MS relapses was 2.00 (range 1–3).

MS patients had significantly lower BPF (0.8399±0.0206, mean± SD) when compared with control subjects (0.8555 ± 0.0104 mean± SD) (p=0.029) Table-2. By the means of ROC curve analysis, the cutoff value of BPF with the highest sum of sensitivity and specificity was determined as 0.8494. (Area under the curve (AUC):0.753, p=0.029) (Graphic 1).

The gray matter volume (617.83±81.264 ml, mean± SD ), white matter volume (501.39±88.639 ml, mean± SD ), brain+CSF volume (1322.0±117.645 ml, mean± SD ) and brain volume (1109.67±95.144 ml, mean± SD ) of MS patients were lower than the normal control group (635.40±49.771 ml, 540.70±67.236 ml, 1351.10±99.994 ml, 1154±81.939 ml, respectively). However the differences were not statistically different. There was not any difference between controls and subjects in terms of white matter intensity and gray matter intensity.

Negative correlation between BPF values and disease duration in MS patients was found (p=0.022, correlation coefficient: – 0.538). When BPF decreased, the disease duration increased. In patient group, a negative correlation was also observed between BPF values and age of patients ( p=0.046, correlation coefficient: -0.476). In contrast, the number of relapses and EDSS were not significantly correlated either with BPF values or with other MRI parameters.

The relationship between PASAT, 9-HPT, TW and MRI parameters was also evaluated. The mean PASAT score of the patients was 30.64 ± 9.07 (range, 14-54 for 2sec) and 40.65±7.05 (range,20-62 for 3 sec). There was no significant difference between MS patients and normal controls (32.55±9.88 for 2 sec, 41.69± 1.06 for 3sec) with respect to PASAT scores. The correlation between BPF values and PASAT scores in MS patients was not significant. We found positive correlation between PASAT score and white matter volume (p= 0.010, correlation coefficient: 0.608). We also found positive correlation between PASAT score and brain volume (p=0.000, correlation coefficient: 0.767) and brain+CSF volume (p= 0.002, correlation coefficient:0.684). The patients who had lower PASAT scores had lower white matter, brain and brain+CSF volume.

The patients' average TW score was 6.5(6-8) seconds. We didn't find statistically significant correlation between MRI parameters and TW scores. The patients' average completion time for the 9-Hole Peg Test (9-HPT) was 22.4 seconds (range, 21-30) for right hand and 21.8 seconds (17-26) for left hand. There was no statistically significant correlation between MRI parameters and 9-HPT scores (p>0.05).

The patients' average learning score was 113 (80-142), remembering score was 13 (9-15), recognizing score was 14.3 (12-15). 13 (72.7 %) of the patients had normal learning, remembering and recognizing points. 5 (27.3%) of the patients had abnormal scores comparing with the normal subjects. We didn't find statistically significant correlation between neuropsychological test scores and MRI parameters including BPF values (p>0.05).

Post-hoc power analysis ( two- sample T-test power analysis) is conducted after the study has been completed, and used the obtained sample size and effect size to determine what the power was in the study, assuming the effect size in the sample is equal to the effect size in the population.

For analysis of BPF, our group sample size of 18 patients and 10 normal controls achieve 70% power to detect a difference with a significance level (alpha) of 0.05 using two sided Mann-Whitney test, assuming that the actual distribution is normal. We determined that for achieving
80% power for BPF with a significance level (alpha) of 0.05, 21 patients and 12 normal controls were required. The post hoc power was found to be very low for other MRI parameters (0.23 for white matter- volume and 0.1 for gray-matter volume analysis, etc.). For detect a significant difference for other MRI parameters more than 100 patients and controls were required in a study that was larger than anticipated.

**Table 1.** Demographic and clinical data of MS patients

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender female/male</td>
<td>14 (%71.5)/ 4 (%28.5)</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>29.06±9.0 (18-50)</td>
</tr>
<tr>
<td>Mean disease duration (mos)</td>
<td>20±76 (12-24)</td>
</tr>
<tr>
<td>Mean EDSS</td>
<td>1,37 (1-3)</td>
</tr>
<tr>
<td>Mean number of relapses</td>
<td>2 (1-3)</td>
</tr>
</tbody>
</table>

**Table 2.** MRI parameters of MS patients and control subjects

<table>
<thead>
<tr>
<th>MRI parameters</th>
<th>MS patients</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n:18</td>
<td>n:10</td>
</tr>
<tr>
<td></td>
<td>Mean± SD</td>
<td>Mean± SD</td>
</tr>
<tr>
<td>BPF value</td>
<td>0.8399±0.0206</td>
<td>0.8555±0.0104</td>
</tr>
<tr>
<td>p:0.029</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gray matter volume (ml)</td>
<td>617.83±81.264</td>
<td>635.40±49.771</td>
</tr>
<tr>
<td>p&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White matter volume (ml)</td>
<td>501.39±88.639</td>
<td>540.70±67.236</td>
</tr>
<tr>
<td>p&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain+CSF volume (ml)</td>
<td>1322.0±117.645</td>
<td>1351.10±99.994</td>
</tr>
<tr>
<td>p&gt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain volume (ml)</td>
<td>1109.67±95.144</td>
<td>1154±81.939</td>
</tr>
<tr>
<td>p&gt;0.05</td>
<td></td>
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</tr>
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</table>
DISCUSSION

Axonal loss and neurodegeneration occurs early in the disease course and may lead to irreversible neurological impairment in MS\(^{17,37}\). Conventional MRI techniques are very useful for evaluating inflammation and demyelination but they show weak correlation with neuronal damage and its clinical relevance disability progression\(^{13}\). NAA which is an amino acid found in the mature neurons, had also decreased in the normal - appearing gray and white matter when MS patients evaluated by Hydrogen Magnetic Resonance Spectroscopy (H-MRS)\(^{4,19,20}\). Measuring metabolites for neuroaxonal damage by H-MRS might cause problems in following up patients because of the difficulty of reproducibility and sampling.

Brain volume loss, observed from the earliest stage of MS and proceeding throughout the disease course, may be an accurate measure of neurodegeneration and axonal loss. Brain atrophy measurements are thought to be more sensitive for demonstrating diffuse neuroaxonal loss and can also correlate disease progression better than lesion measurements on conventional MRI\(^{7,8,13,21,22}\). There are a number of magnetic resonance imaging-based methods for determining global or regional brain volume, including cross-sectional (e.g. brain parenchymal fraction) and longitudinal techniques [e.g. SIENA (Structural Image Evaluation using Normalization of Atrophy)]. Quantitative 2 and 3 dimension measures are more sensitive, more easily-reproducible than other methods. They are usually based on tissue segmentation in a semi-automated or automated way and allow the measurement of either global (e.g. BPF) or regional (e.g.FreeSurfer) brain volume\(^{16,23}\).

By these methods, intra-parenchymal structures are segmented as parenchymal and non-parenchymal and whole brain volume, regional brain volume or white matter and gray matter volumes can be also calculated quantitatively. BPF and SIENA are the most frequently used methods to

![Graphic 1: ROC curve analysis for BPF value](image-url)
measure brain volume in clinical practice and in MS trials. BPF shows the proportion of brain tissue volume to the total brain volume of the brain surface contours. Although these methods are sensitive and reproducible, the influence of various confounding factors needs to be taken into consideration when interpreting brain volume data. Quality of image acquisition, MS-related factors (e.g., inflammation, gliosis, remyelination, demyelination) and MS unrelated factors (e.g., age, life habits, dehydration, genetic load and other comorbidities) can alter brain volume.

Anti-inflammatory drugs have been demonstrated to significantly decrease brain volume within the first 6 months to 1 year of treatment, reflecting the resolution of ongoing edema and inflammation. This phenomenon is termed ‘pseudo-atrophy. Due to these reasons, MS patients with an acute relapse within ≤4 weeks before MRI and patients treated with corticosteroids or immunosuppressant in the months prior to scanning were excluded from the study. However 6 of them were under the first year of disease modifying therapy.

By this study we aimed to investigate brain atrophy in early MS patients and its clinical relevance as a measure of neurological and neuropsychological disability. When studies about early phase RRMS patients are revised, it's been thought that neuro-axonal damage starts at the early phase. In our MS patients, the mean BPF value was significantly lower than normal controls as reported in the recent literature. BPF also negatively correlated with the duration of disease. Although white and grey matter volumes were lower in MS patients than normal controls, BPF was the only significant measure among these MRI measures. Caution was exercised for confounding factors (age, comorbidities and MS related factors) in exclusion criteria in our subjects. Some technical factors (the image acquisition and analysis techniques) may contribute these negative results. The post-hoc analysis showed that our sample size is enough to detect a difference for BPF value with a significance level between patients and normal controls. The non-significant results related to the differences between groups with respect to MRI parameters other than BPF are probably due to a Type II error because of the small sample size. Considering the sample size needed to provide adequate statistical power in MR imaging studies of brain volume, BPF analysis is more practical for cross-sectional and longitudinal studies.

Our study showed that BPF values were decreased in MS group and normal control group with increasing age. Importance of choosing age-matched control groups while planning a brain atrophy study was emphasized once again.

A number of cross-sectional studies demonstrated that both global brain volume loss and selective measures of brain volume loss correlate with disability progression in MS. Recent studies provided evidence that brain atrophy might be useful prognostic marker for early development of multiple sclerosis and disability progression. Global brain and gray matter volume loss were found to be greater in patients with CIS who developed MS than those who did not and in patients with established MS who showed sustained progression of disability than those who were stable in the follow-up period. Several longitudinal studies demonstrated that loss of brain volume early in the disease course predicts disability progression over the longer term. Patients with sustained disease progression at 5 years had significantly cortical and thalamus atrophy at diagnosis compared with patients who had stable disease. In our early MS patients, we didn't find significant relationship between MRI measures and EDSS scores. EDSS has some limitations for clinical assessment of MS patients. MSFC provides a more comprehensive
assessment allowing independent clinical data together; upper extremity, lower extremity and cognitive functions. MSFC scores have been found to be correlated with MRI lesion load, better than EDSS scores. MSFC's subcomponent PASAT also correlated better with MRI lesion load\(^{(40)}\). However BPF values were not found to be correlated with any MSFC scores in our study. The relevance between brain atrophy and physical disability was not clearly demonstrated in some studies especially in the early phase of MS\(^{(11,12,27)}\) as in our study. The weak relationship between lesion based MRI measures and disability may be an example of classic clinical-imaging paradox. An explanation for our result may be offered that the atrophy beginning at the early phase of the disease might not cause clinical disability because of cortical reorganization and there might be individual threshold value of axon loss for clinical disability. However in the later stage the correlation between brain atrophy and disability appeared clearly. In a study where RR, SP and PPMS were compared; in patients who had higher EDSS scores, had significant brain volume loss\(^{(28)}\). We also demonstrated that neither relapses nor type of symptoms related with brain atrophy as shown in other studies\(^{(25)}\).

Cognitive impairment (CI) is one of the major reasons of neurological disability and significant source of patient morbidity. The frequency of disturbance of cognitive functions in MS patients show significant inter patient variability and depend on the methods used and on the type of the patients examined. Cognitive impairment in MS can be detectable even in the earliest stages of the disease. Memory, attention, information processing speed, mental flexibility, intelligence and executive functions are affected most whereas semantic verbal fluency and visuospatial functions seemed to be spared. In our study 27.3% of the patients have impairment either on RAVLT-1 which interpret learning or on RAVLT-2 which interpret long term memory. Deficits of working memory and information processing speed are usually interpreted by tests like PASAT, FST, and symbol digit modalities test (SDMT)\(^{(6,19,40)}\). We only performed PASAT among these tests. There was no significant difference between MS patients and normal controls with respect to PASAT scores in our study. PASAT tends to be associated with significant patient anxiety and on the contrary of other reports, PASAT seemed not to be appropriate to screen cognitive impairment in our patient groups as in our other study\(^{(6)}\).

A number of studies have demonstrated a correlation between brain volume loss and cognitive impairment\(^{(2,9,14,36)}\). Several longitudinal studies reported that early loss of brain volume may be predictive of longer-term cognitive changes in RRMS\(^{(2,3,14)}\). In the early phase of MS, regional or cortical atrophy measures might better explain cognitive dysfunction rather than whole brain atrophy parameters. GM volume, including thalamic volume or hippocampal volume, is strongly associated with CI. A reduction in regional GM volume is associated with future cognitive impairment. In one study, a correlation between reduced thalamic volumes and cognitive impairment mostly affecting executive functions, auditory memory, lexical verbal fluency, attention and psychomotor speed were found in CIS and RRMS patients\(^{(13)}\).

In our study, we didn't find significant correlation between BPF scores and cognitive performance evaluated by verbal memory processes tests and PASAT. However we found positive correlation between patients' PASAT scores and other regional brain volumes. The patients who had lower white matter volume, brain+CSF volume had significantly lower PASAT scores. There was no correlation between cognitive performance and gray matter volume in our study. Loss of gray matter volume was shown to be better predictive
of cognitive decline\(^{(13,38)}\). However, the importance of WM volume should not be ignored. A functional disconnection between GM structures, secondary to damage located in specific WM areas of frontal and subcortical circuits has been reported as one of the most important mechanisms leading to cognitive impairment in MS\(^{(14,15,24,30,32)}\).

In conclusion, early phase MS patients might have brain atrophy and cognitive impairment even if neurological physical disability is mild. Brain atrophy can be detected by quantitative MRI measures instead of conventional MRI measures. Many confounding factors can contribute while interpreting the brain volume data. BPF is a reliable method that can be used in clinical practice and clinical trials. Changes in brain volume may provide an accurate measure of cognitive impairment and disability progression over the long term. In order to determine the clinical relevance of brain atrophy and its prognostic value, longitudinal MRI studies with cognitive evaluation by comprehensive neurophysiological tests are needed.

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