Effect of deep gray matter atrophy on information processing speed in early relapsing-remitting multiple sclerosis

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Abstract

Background. Cognitive dysfunction, including Information processing speed (IPS), is relatively common in multiple sclerosis (MS). IPS deficits have profound effects on several aspects of patients' life. Previous studies showed that deep gray matter atrophy is highly correlated with overall cognitive impairment in MS. However, the effect of deep gray matter atrophy on IPS deficits is not well understood. In this study, we evaluated the effects of deep gray matter volume changes on IPS in early relapse-remitting MS (RRMS) patients compared to healthy control.

Methods. In this case-control study, we enrolled 63 RRMS patients and 36 healthy controls. All patients were diagnosed within 6 years. IPS was evaluated using the Integrated Cognitive Assessment (ICA) test. We also performed a 1.5T MRI to evaluate deep gray matter structures.

Results. RRMS patients had lower accuracy in the ICA test (p = .01). However, the reaction time did not significantly differ between RRMS and control groups (p = .6). Thalamus volume was significantly lower in the RRMS group with impaired IPS compared to the RRMS with normal IPS and control groups (p < 10^{-4}). Other deep gray matter structures were not significantly different between the RRMS with impaired IPS group and the RRMS with normal IPS group.

Conclusion. MS patients are impaired in IPS even in the early stages of the disease. Thalamic atrophy affected IPS in these patients, however atrophy in other deep gray matter structures, including caudate, putamen, globus pallidus, hippocampus, amygdala, accumbens, and cerebellum, were not significantly correlated with IPS impairment in early RRMS.

Introduction

Cognitive dysfunction is relatively common in multiple sclerosis, impacting between 43% and 70% of patients (R. H. B. Benedict et al. 2020; McKay et al. 2019). Information processing speed (IPS) deficits represent the most prevalent cognitive dysfunction, and one of the most studied cognitive domains in patients with MS (Costa et al. 2017; Daugherty et al. 2020). Previous studies showed IPS deficits affect numerous aspects of cognition such as working memory (Genova et al. 2012; Leavitt et al. 2011), executive functions (Genova et al. 2013; Macniven et al. 2008), learning, and memory (Chiaravalloti et al. 2013). IPS deficits also predict several outcomes in patients with MS including employment, driving, and instrumental daily activities (such as medication management, quality of life, and fall frequency) (Costa et al. 2017). It is thus evident that deficits in IPS represent an important and prevalent consequence of MS. Given its importance and impact, an understanding of the underlying mechanisms of IPS deficits remains unclear.

Neuroimaging studies suggested that cognitive dysfunction may be related to demyelinating and neurodegenerative alterations of brain networks. Neurodegeneration is reflected by brain atrophy, which can be measured by volumetric measures in brain magnetic resonance imaging (MRI). Structural MRI studies showed that cognitive dysfunction is correlated with lesion load (Calabrese et al. 2009; Fulton et
al. 1999), white matter lesion location, microstructural injury, gray matter lesions, and cortical and subcortical gray matter atrophy (Sánchez et al. 2008; Zivadinov et al. 2001). Some gray matter regions, such as the deep gray matter (A Bisecco et al. 2015; Alvino Bisecco et al. 2021; Schoonheim et al. 2015), mesial temporal cortex (R. H. Benedict et al. 2009), and neocortex (Amato et al. 2004) are more correlated with cognitive impairment. Some studies also evaluated the effects of gray matter volume alterations on IPS deficits (Batista et al. 2012; A Bisecco et al. 2018; Moroso et al. 2017).

Deep gray matter structures including the thalamus are affected by volume loss more extensively than other regions (Eshaghi, Marinescu, et al. 2018; Eshaghi, Prados, et al. 2018). Deep gray matter atrophy is correlated with physical disability, cognitive impairment, and disease course in patients with MS (Eshaghi, Marinescu, et al. 2018; Eshaghi, Prados, et al. 2018). It is suggested that deep gray matter atrophy, especially the thalamus, is a potential neuroimaging marker for neurodegeneration in MS (Minagar et al. 2013). However, the effect of deep gray matter atrophy on IPS deficits is not yet well understood.

In this case-control study, we evaluated the effects of deep gray matter volume changes on IPS in early relapsing-remitting MS (RRMS) patients compared to healthy control.

**Methods**

**Study design**

This case-control study enrolled 63 RRMS patients and 36 healthy control subjects. MS patients were admitted to the MS clinic, Kashani hospital, Isfahan, Iran, in 2021 and were diagnosed according to the 2017 revised McDonald criteria (Thompson et al. 2018), aged between 18–55, with disease duration between 0–6 years. They did not have any clinical relapse or corticosteroid use in the past one month. They did not have any history of brain surgeries, major neurologic disorders (stroke, epilepsy, brain tumor, or CNS infection), other neuroinflammatory disorders, psychiatric disorders (major depressive disorder, bipolar, or schizophrenia), or uncontrolled systemic disorders (diabetes, hypo- or hyperthyroidism, or B12 deficiency). Our participants had normal or corrected-to-normal vision, expanded disability status scale (EDSS) score between 0 and 5.5, and near-normal performance in the 9-hole peg test (9HPT < 45 sec). A clinical interview was performed for each participant, and demographic and clinical information were collected.

Integrated Cognitive Assessment (ICA) test:

To evaluate information processing speed, we performed the ICA test (Khaligh-Razavi et al. 2020). The ICA test is a rapid visual categorization task with backward masking. It was validated for IPS and cognitive assessment in patients with MS. Khaligh-Razavi et al. showed that ICA score was correlated with Symbol Digit Modalities Test (SDMT) and Brief International Cognitive Assessment in MS patients (Khaligh-Razavi et al. 2020).
ICA test was run on a personal tablet (Apple iPad 8th gen. 10.2). We selected 100 natural images (50 animals and 50 non-animal) with varying levels of difficulty. Each trial started with presenting an image stimulus (100 ms, size = ~ 7°). After that, there was an inter stimulus interval (ISI, 20 ms), followed by a dynamic noisy mask (250 ms). The subject had to categorize the stimulus to animal or non-animal groups (Fig. 1). The ICA test started with a 10 trials training block (5 animals, 5 non-animal) to familiarize participants with the task. These images were not presented in the main task. If participants performed above chance level (> 50%) on training, they were continued to the main task (90 trials).

Brain MRI acquisition:

MRI images were acquired with a 1.5T scanner (Siemens Avanto scanner system, Germany, Henkestr Erlangen). For imaging, we placed each participant on a bed in a supine position while the participant's head was placed in a twelve-channel coil. In addition to routine brain imaging sequences, a high-resolution 3D T1-weighted MPRAGE sequence (slice thickness: 1mm, EchoTime: 0.00273 s, RepetitionTime: 2.2 s, InversionTime: 0.9 s, FlipAngle: 8°, BaseResolution: 224 1/mm) was taken to examine the volume of the whole brain and the volume of subcortical structures.

MRI analysis and automated segmentation methods:

After receiving the imaging data, the initial quality control check was performed visually for the presence of artifacts such as motion artifacts. If the image quality was good, it was analyzed with a special image processing software. For this study, we used Volbrain for volume measurement. Volbrain is a publicly available online system for brain volume measurement (https://www.volbrain.upv.es/), and this software package was used before (Manjón and Coupé 2016). Volbrain first performed pre-processing on the image, including denoising (Manjón et al. 2010) and inhomogeneity correction (Tustison et al. 2010), and then automatically segmented the volume of the whole brain and other structures.

Manual volumetric analysis:

In the next step, the thalamus mask and other structures were checked in ITK snap image processing software (Yushkevich et al. 2006), and two experienced observers blinded to the patient's clinical information checked all images. If necessary, segmentation correction was done manually (Fig. 2). Then the edited mask was multiplied by the original T1 image in SPM12 software (Ashburner and Friston 2005).

Thalamus volume measurements and normalization:

Normalized volumes were calculated by dividing the volume of each structure by the intracranial volume (Total Intracranial Volume; the sum of all voxels classified as grey, white matter or as cerebrospinal fluid) multiplied by 1000) (Tavares et al. 2020). The final image obtained from the thalamus was divided into medial and lateral parts based on histogram and its volume was calculated in ITK snap software.

**Statistical analysis**
Accuracy was defined as the number of correct responses divided by the total number of trials, multiplied by 100. We also calculate mean reaction times for correct trials for each subject. We performed an independent samples t-test or Mann-Whitney U test to compare ICA accuracy and reaction time between RRMS and control groups.

We used a multinomial logistic regression classifier, a supervised regression-based learning algorithm, to calculate probability of IPS impairments in patients as described before in details [30]. The classifier trained based on a set of features extracted from the ICA test output for each participant. These features included the ICA accuracy and reaction time. The classifier also took subject's age, gender and education in order to match subjects with similar demographics. ICA score was defined as the probability of normal IPS performance. We divided patients to two groups, impaired IPS (ICA score < 50%) and preserved IPS (ICA score > 50%). To compare demographic variables between impaired IPS, preserved IPS, and control groups, we performed one-way ANOVA or Kruskal–Wallis test for numeric variables and a Chi-squared test for categorical variables. If we found a significant difference, then we performed post-hoc analysis with the Tukey HSD test. The Shapiro-Wilk test was used to evaluate whether variables were normally distributed. We also performed a sub-group linear regression to evaluate the effects of demographic variables on ICA accuracy in RRMS and control groups, separately. Statistical analysis was performed with Python 3.8.5. A significant p-value was defined as less than .05.

**Result**

We enrolled 63 RRMS patients and 36 healthy control subjects, all of them passed the training session in the ICA test. Patients' ages were 33.06 ± 6.00 (mean ± sd) years old, and 80% of them were female. They had studied for 14.20 ± 2.80 years. They were diagnosed with MS 3.87 ± 1.41 years ago and their EDSS score was 1.26 ± 1.15. Healthy subjects' ages were 33.14 ± 5.93, and 55% of them were female. They studied for 16.54 ± 2.59 years. The main demographic and clinical characteristics are summarized in Table 1. ‘Education’ and ‘gender’ were different between RRMS and control groups (p = .0001 and p = .0143, respectively). However, in subgroup regression analysis ICA accuracy was not correlated with Education in RRMS or control groups (p = .5 and p = .28, respectively).
Table 1
Demographic and clinical characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Impaired IPS (N = 5)</th>
<th>Preserved IPS (N = 55)</th>
<th>Healthy (N = 36)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean ± SD)</td>
<td>35.40 ± 4.03</td>
<td>32.70 ± 6.15</td>
<td>33.14 ± 5.93</td>
<td>0.6236</td>
</tr>
<tr>
<td>Education (Mean ± SD)</td>
<td>18 ± 3.46</td>
<td>14.11 ± 2.55</td>
<td>16.54 ± 2.80</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Gender (%Female)</td>
<td>100</td>
<td>80</td>
<td>55</td>
<td>0.0143*</td>
</tr>
<tr>
<td>Disease duration (Mean ± SD)</td>
<td>3 ± 1.22</td>
<td>3.90 ± 1.40</td>
<td>-</td>
<td>0.1668</td>
</tr>
<tr>
<td>EDSS (Mean ± SD)</td>
<td>1.4 ± 1.51</td>
<td>1.24 ± 1.15</td>
<td>-</td>
<td>0.7813</td>
</tr>
</tbody>
</table>

* Denotes a significant difference (p-value < 0.05)

The RRMS group had lower accuracy in ICA task compared to the control group (Mann–Whitney U test, p = .0178, Fig. 3A), however the reaction time did not significantly differ between groups (Mann–Whitney U test, p = .6012, Fig. 3B). Thalamus and all thalamic sub-regions volumes were decreased in RRMS patients compared to healthy subjects (Mann–Whitney U test, p < 10^{-4}). Also, volumes of putamen (t-test, p = .0029) and accumbens (t-test, p = .0032) were smaller in RRMS compared to the healthy controls. Volumes of cerebellum (t-test, p = .4423), caudate (Mann–Whitney, p = .5872), globus pallidus (t-test, p = .1334), hippocampus (t-test, p = .2623), or amygdala (t-test, p = .1444) had no significant difference between RRMS and control groups.

Deep gray matter structures were compared between impaired IPS (n = 5), preserved IPS (n = 58), and control (n = 36) groups and were summarized in Table 2. Thalamic volume was significantly decreased in Impaired IPS group compared to preserved IPS and control groups (one-way ANOVA, p < 10^{-4}). Volume of putamen, amygdala, and accumbens were significantly different between groups (mentioned above), but in post-hoc analysis there was no significant difference between impaired IPS and preserved IPS groups (p = .62, p = .09, and p = .11, respectively). Cerebellum, caudate, globus pallidus, hippocampus, and amygdala were not significantly different between impaired IPS, preserved IPS, and control groups. We also compared thalamic sub-regions volumes between these three groups and summarized them in Table 3. Both right and left thalami volumes were decreased in impaired IPS group compared to other groups (Table 3). In post-hoc analysis, right lateral thalamus, left lateral thalamus, and left medial thalamus volumes were decreased in impaired IPS group compared to preserved IPS group (p = .0045, p = .0459, and p = .0467, respectively). However, right medial thalamus was not significantly different between impaired IPS group compared to preserved IPS group (p = .2131).
Table 2

Compare deep gray matter volumes between impaired IPS, preserved IPS, and control groups.

<table>
<thead>
<tr>
<th>Deep gray matter</th>
<th>Impaired IPS</th>
<th>Preserved IPS</th>
<th>Healthy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalamus</td>
<td>6.46 ± 1.29</td>
<td>7.35 ± 0.83</td>
<td>8.46 ± 0.55</td>
<td>&lt; 10^{-4}*</td>
</tr>
<tr>
<td>Caudate</td>
<td>5.04 ± 0.92</td>
<td>5.24 ± 0.57</td>
<td>5.28 ± 0.48</td>
<td>0.5776</td>
</tr>
<tr>
<td>Putamen</td>
<td>5.7 ± 0.82</td>
<td>5.89 ± 0.56</td>
<td>6.22 ± 0.48</td>
<td>0.0078</td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>1.64 ± 0.22</td>
<td>1.69 ± 0.14</td>
<td>1.73 ± 0.11</td>
<td>0.1951</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>5.42 ± 0.57</td>
<td>5.34 ± 0.36</td>
<td>5.44 ± 0.39</td>
<td>0.4622</td>
</tr>
<tr>
<td>Amygdala</td>
<td>1.07 ± 0.14</td>
<td>1.17 ± 0.13</td>
<td>1.11 ± 0.11</td>
<td>0.0418</td>
</tr>
<tr>
<td>Accumbens</td>
<td>0.39 ± 0.1</td>
<td>0.45 ± 0.08</td>
<td>0.5 ± 0.07</td>
<td>0.0019</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>90.47 ± 10.08</td>
<td>92.9 ± 6.51</td>
<td>93.69 ± 6.3</td>
<td>0.4759</td>
</tr>
</tbody>
</table>

* Denotes a significant difference between impaired and preserved IPS groups in post-hoc analysis (p-value < 0.05)

Table 3

Compare thalamus sub-regions between impaired IPS, preserved IPS, and control groups.

<table>
<thead>
<tr>
<th>Deep gray matter</th>
<th>Impaired IPS</th>
<th>Preserved IPS</th>
<th>Healthy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right thalamus</td>
<td>3.19 ± 0.66</td>
<td>3.65 ± 0.41</td>
<td>4.22 ± 0.28</td>
<td>&lt; 10^{-4}*</td>
</tr>
<tr>
<td>Right medial thalamus</td>
<td>0.83 ± 0.24</td>
<td>0.94 ± 0.18</td>
<td>1.17 ± 0.13</td>
<td>&lt; 10^{-4}</td>
</tr>
<tr>
<td>Right lateral thalamus</td>
<td>2.26 ± 0.44</td>
<td>2.61 ± 0.29</td>
<td>2.94 ± 0.2</td>
<td>&lt; 10^{-4}*</td>
</tr>
<tr>
<td>Left thalamus</td>
<td>3.26 ± 0.64</td>
<td>3.7 ± 0.44</td>
<td>4.24 ± 0.27</td>
<td>&lt; 10^{-4}*</td>
</tr>
<tr>
<td>Left medial thalamus</td>
<td>0.82 ± 0.27</td>
<td>0.98 ± 0.19</td>
<td>1.19 ± 0.09</td>
<td>&lt; 10^{-4}*</td>
</tr>
<tr>
<td>Left lateral thalamus</td>
<td>2.32 ± 0.41</td>
<td>2.6 ± 0.33</td>
<td>2.95 ± 0.22</td>
<td>&lt; 10^{-4}*</td>
</tr>
</tbody>
</table>

* Denotes a significant difference between impaired and preserved IPS groups in post-hoc analysis (p-value < 0.05)

Discussion

We assessed the relationship between IPS and deep gray matter volumes in RRMS patients with mild disability. In comparison to healthy subjects, RRMS patients showed lower accuracy in ICA tasks and higher amounts of thalamic atrophy. Among patients with MS, the highest amount of thalamic atrophy was in patients with impaired IPS. The significantly lower accuracy in ICA tasks among RRMS patients could not be explained by speed-accuracy trade off.
IPS deficit was reported in different neurological disorders such as Alzheimer(Daugherty et al. 2020), Parkinson(Sawamoto et al. 2002), and Epilepsy(Dow et al. 2004). It represents the most common form of cognitive deficit of MS. IPS impairments affect different cognitive processes, i.e. working memory(Genova et al. 2012; Leavitt et al. 2011), executive functions(Drew et al. 2009; Genova et al. 2013; Macniven et al. 2008), learning, and memory(Chiaravalloti et al. 2013). Previous studies showed that IPS deficits have been associated with poorer quality of life and functions in MS (including employment, driving, and daily activities)(Costa et al. 2017).

Our study showed that gray matter atrophy and related IPS impairment is present even in patients with mild disability at early stages of RRMS. This finding was in line with previous studies that showed cognitive deficits, including IPS impairment, occur in early stages of MS and clinically isolated syndrome(Anhoque et al. 2010; Hynčicová et al. 2017; Johnen et al. 2017). Similar profiles of cognitive deficits have been also observed at the preclinical stage, in patients with radiologically isolated syndromes(Amato et al. 2012).

Another aspect of IPS impairment can be its value in predicting future disease progression. Some studies showed the occurrence of isolated cognitive relapses in MS patients without subjective cognitive deficits or depression(Oset et al. 2020; Pardini et al. 2014). Hence, it is plausible that IPS impairment may be a precursor to other cognitive deficits and disability progression. Impairment in IPS can be easily measured by SDMT and Paced Auditory Serial Addition Test(PASAT)(Oset et al. 2020). However, the ICA test assesses the combination of speed and accuracy of visual processing in a rapid visual categorization task to evaluate IPS with a high reliability. It has several advantages over pen-and-paper tests such as efficient administration, automatic scoring, and easier integration with electronic medical records or research databases. The ICA test is independent of education, language, and culture(Khaligh-Razavi et al. 2019).

Neuroimaging studies have markedly improved the understanding of mechanisms of cognitive deficits in MS(R. H. B. Benedict et al. 2020; Štecková et al. 2014; Sumowski et al. 2018). Regional brain atrophy, especially in deep gray matter, was correlated with cognitive impairment in MS (for review see(R. H. B. Benedict et al. 2020)). Thalamus, deep and cortical gray matter, hippocampus, and cerebellum volumes can predict IPS deficit in patients with MS(Batista et al. 2012; Marzi et al. n.d.; Moroso et al. 2017). We showed that Thalamus, putamen and accumbens were atrophic in early RRMS patients compared to healthy control subjects. Among these measures, thalamic atrophy in patients with impaired IPS was markedly greater compared to those with preserved IPS. Other deep gray matter structures, including caudate, putamen, globus pallidus, hippocampus, amygdala, accumbens, and cerebellum, were not significantly different between impaired IPS and preserved IPS groups. Similar to our results, Eshaghi et al.(Eshaghi, Marinescu, et al. 2018; Eshaghi, Prados, et al. 2018) showed that deep gray matter atrophy, especially in thalamus, may be present in the early stages of the disease and it is strongly correlated with the disease course and disability accumulation over time.
Specific limitations in the use of structural MRI in localizing pathologic changes associated with performing a cognitive function remain unchanged. Based on functional connectivity studies, thalamic volume, skeleton diffusivity, and resting-state connectivity are independent predictors of cognitive impairment in patients with MS (Schoonheim et al. 2015). PASAT task performance is correlated with the activation of basal ganglia, thalamus, inferior and middle frontal gyrus, inferior parietal cortex and superior and middle temporal gyrus (Mainero et al. 2004). But, more functional studies are required to find the underlying neural correlates of IPS deficits in MS (Rocca et al. 2014; Sumowski et al. 2018).

Our study has some limitations. We had few patients in impaired IPS group and education and gender were not balanced between groups. However, in subgroup regression, education was not correlated with ICA performance and as mentioned above previous studies showed that ICA test is intrinsically independent of education. We also considered demographic variables in calculating ICA score and found that they had no effect on our data. We did not enroll patients with progressive phenotype of MS and did not follow the correlation between thalamic atrophy and IPS performance over time. We suggest that future cohort studies can evaluate IPS deficit and thalamic atrophy as a marker for predicting clinical outcomes such as treatment response and disability progression.

**Conclusion**

MS patients are impaired in IPS even in the early stages of the disease. Thalamic atrophy affected IPS in these patients, however atrophy in other deep gray matter structures, including caudate, putamen, globus pallidus, hippocampus, amygdala, accumbens, and cerebellum, were not significantly correlated with IPS impairment in early RRMS.

**Abbreviations**

CNS
Central Nervous System
EDSS
Expanded Disability Status Scale
IPS
Information Processing Speed
ICA
Integrated Cognitive Assessment
MS
Multiple Sclerosis
MRI
Magnetic Resonance Imaging
RRMS
Relapsing Remitting Multiple Sclerosis
SDMT
Symbol Digit Modalities Test
PASAT
Paced Auditory Serial Addition Test
9HPT
9-Hole Peg Test

**Declarations**

**Acknowledgment**

None

**Funding**

NO Funding.

**Competing interests**

The authors declare no conflict of interest.

**Ethical Approval**

The Ethics Committee of the School of Medicine, Isfahan University of Medical Sciences, approved this study (approval number: IR.ARI.MUI.REC.1400.118). This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

**Consent to participate**

Written informed consent was obtained from all participants before the start of the study.

**Availability of data and material**

Data and analysis can be made available upon request through contacting the Corresponding Author.

**Authors' contributions**

Conception and study design (I.A and M.S and F.A), data collection or acquisition (S.N and F.D and N.R and Z.K), software (S.K), statistical analysis (A.P and I.A and M.S), interpretation of results (I.A and M.S and F.A), drafting the manuscript work or revising it critically for important intellectual content (S.N and I.A and M.S and V.S) and approval of final version to be published and agreement to be accountable for the integrity and accuracy of all aspects of the work (All authors).
References


Figures

**Figure 1**

Experimental design in ICA task. A few sample images are shown for demonstration purposes on the right.

**Figure 2**
Deep gray matter segmentation.

(A) Accuracy

(B) Reaction time

* p = 0.01

p = 0.6

Figure 3

Accuracy and reaction time between RRMS and control groups. RRMS patients had lower accuracy in the ICA test. However, the reaction time did not significantly differ between RRMS and control groups.