Review Article

The correlation of conventional and advanced MRI findings with cognitive function in multiple sclerosis: A systematic review and meta-analysis

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Introduction

Multiple sclerosis (MS) is a chronic disease that most frequently affects young adults. It is pathologically characterized by inflammation and myelin loss in the brain and spinal cord. It can be an asymptomatic or progressive disease. However, most patients experience periods of relapse and recovery. Cognitive decline is a common finding in these patients that affects attention, learning, memory, information processing, verbal fluency, executive function, and visuospatial skills. Cognitive dysfunction may occur early in the course of the disease. It is one of the most problematic aspects of diseases. The diagnosis of MS and evaluation of disease progression are made based on the signs and symptoms of the disease along with brain magnetic resonance imaging (MRI). In the case of cognitive decline, MRI is a helpful diagnostic approach. Gray matter shrinkage is an early indicator of future cognitive decline, according to MRI studies. Besides, extensive alterations in brain networks lead to cognitive failure.

Traditional imaging methods such as dual-echo, FLAIR, and Gd-enhanced sequences play an important role. Functional MRI (FMRI) is more beneficial than other imaging modalities because it provides proof of MS. In comparison to healthy individuals, numerous investigations have found that MS patients had worse functional connectivity in transcallosal sensory networks. Another MRI based imaging is diffusion tensor imaging (DTI) that is being with the background assumption of “water diffusivity in MS lesions is higher than normal-appearing white matter, which is higher than water diffusivity in healthy individuals' white matter.”

Early in the course of MS, brain atrophy appears, which worsens as the disease progresses. Gray matter atrophy progresses more quickly than white matter atrophy and is more common in the early stages of MS. MRI technologies are commonly used to track the pathological progression of MS over time and determine the effects of therapy. To date, the quantity and amount of macroscopically apparent lesions have been investigated most often.

Abstract

There are limited data on the possible association between conventional and advanced magnetic resonance imaging (MRI) findings and cognitive function in patients with multiple sclerosis (MS). Therefore, this systematic review and meta-analysis aimed to explore the correlation between MRI-derived metrics and cognitive tests in patients with MS. An electronic literature search of the PubMed, Web of Sciences, Embase, and Scopus databases was performed to identify related studies. The correlation coefficients of the MRI indices and cognitive tests were pooled. Thirteen studies were selected for inclusion of 824 patients diagnosed with MS. Most evaluated patients (60.44%) had relapsing-remitting MS (RRMS). The Paced Auditory Serial Addition Test (PASAT-3), Brief Visuospatial Memory Test (BVMT), and Symbol Digit Modalities Test (SDMT) were inversely correlated with the mean diffusivity (MD) of the brain with pooled correlation coefficient of -0.225, -0.361, and -0.438, respectively ($p<0.0001$). The SDMT test positively correlated with fractional anisotropy (FA) with a correlation coefficient of 0.351 ($p<0.0001$) and inversely correlated with T2 lesion volume with a correlation coefficient of -0.367 ($p<0.0001$). In the case of other tests, there was low number of studies with significant correlations being reported. We found significant correlations between some neuropsychological tests and MRI findings in patients with MS. Brain atrophy might disrupt the process of correct registration between anatomical and MRI diffusion scans. However, we did not have enough studies with exactly matched anatomical areas to evaluate correlations and we recommend that histological validation of diffusion tensor imaging (DTI) findings for brain atrophy is needed as a basis for picture processing procedures and correlation with cognition status.
These MRI results showed clear therapeutic effects but no corresponding clinical benefits, implying that there are other components of MS pathogenesis that need to be examined. In this respect, quantifying brain atrophy as a more universal measure of the poor cognitive outcomes of MS pathology, whether it occurs in macroscopic lesions or normal-appearing tissues, has attracted attention. Cognitive impairment is aggravated by gray matter atrophy. Brain parenchymal and gray matter fractions have been used to estimate atrophy in patients with MS. In clinical practice, fractional anisotropy (FA) values are indicators of the degree of MS brain atrophy exclusively in the corpus callosum. Patients’ higher mean diffusivity (MD) values have been shown to be mostly restricted to the temporal and cingulate cortices. Compared with the normal-appearing cortex, the demyelinated cortex may have greater FA values. In addition, volumetric investigations have shown patterns of gray matter atrophy across the brain that appear to prevail in eloquent regions such as the thalamus, posterior cingulate cortex, and precuneus. In other studies, whole-brain volume, gray matter volume, and T2 lesion load were considered for brain atrophy assessment in relation to cognitive status in MS. Although various studies with different indicators of brain atrophy have used multiple MRI modalities for the assessment of cognitive disorders, the results are controversial. Therefore, the present systematic review and meta-analysis aimed to investigate the possible correlation between MRI findings and cognition tests in patients with MS with cognitive impairment and cognitively preserved patients or healthy patients.

Methods
This study was conducted according to the guidance provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The protocol of this study was registered at the PROSPERO registry (CRD42022300985).

Search strategy
We implemented our systematic search in online databases such as PubMed, Embase, Web of Sciences (WOS), and Scopus to identify the studies reporting cognitive impairment in patients with MS along with various MRI modality findings. Following terms were used (“MRI” [All Fields] OR “functional MRI” [All Fields] OR “diffusion tensor MRI” [All Fields] OR “conventional MRI” [All Fields] OR “DTI MRI” [All Fields] OR “Magnetic Resonance Imaging” [All Fields]) AND (“Cognition” [All Fields] OR “cognitive decline” [All Fields] OR “cognitive assessment” [All Fields]) AND (“MS” [All Fields] OR “multiple sclerosis” [All Fields] OR “BRB-N” [All Fields] OR “PASAT” [All Fields] OR “MSFC” [All Fields]).

Eligibility criteria
The inclusion criteria were studies applying any MRI assessment along with cognition assessment in patients with MS with case-control retrospective designs, prospective cohort studies, or case series. Pairwise comparison of groups of eligible studies should report the correlation coefficients of MRI findings with cognition tests in patients with MS. Furthermore, exclusion criteria were studies with no data of interest available, non-English language, study designs of the descriptive cross-sectional, randomized trials, studies with confounding variables affecting cognition, and studies focusing on diseases along with MS that significantly affect cognition, head trauma, and dementia. Preprint studies and grey literature were not included in this study.

Outcome measure
Cognitive tests included a 3 seconds-interstimulus interval Paced Auditory Serial Addition Test (PASAT-3), Symbol Digit Modalities Test (SDMT), and Brief Visuospatial Memory Test (BVMT). Final scores of these cognition tests were considered in analyses. All MRI findings for individual brain regions or whole brain that were used for correlation coefficient tests were recorded.

Screening and data extraction
Two independent reviewers assessed studies for eligibility, and a third skilled author judged inclusion in case of disagreement between the two reviewers. The reference lists of the final included papers were manually searched for potentially relevant studies. A checklist of data extraction was used to extract the results of the cognition tests for MS along with the MRI findings. Age, sex, MS disease duration, severity and type of MS, count of relapsing-remitting MS (RRMS)/secondary-progressive MS (SPMS), and primary-progressive MS (PPMS) were recorded. The correlation coefficient and the number of observations were recorded as the main outcomes. Two independent authors completed the checklist. Significant differences in the extracted data were considered.

Risk-of-bias and publication bias assessment
The Newcastle-Ottawa Scale (NOS) was used for each eligible study and was judged by two independent reviewers and ranked as low-risk, moderate-risk, or high-risk. A third reviewer judged the in case of a disagreement. The NOS has four scores for selection, two scores for comparability, three for exposure and a final score of 9. Studies with NOS scores ≥ 6 were included.

Statistical Analysis
When data were presented in different groups of patients with MS based on the severity of disease, subgrouping was performed. Disease duration was considered for meta-regression in cases with high heterogeneity levels. The correlation coefficients and the corresponding 95% CI as a pooled effect size (ES) of MRI findings with cognition tests in cognitively impaired patients with MS were pooled.
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using the CMA version 3 software. Fixed or random effects models were used to pool data.19

Results
A total of 549 articles were identified in the primary search of which 123 relevant and non-duplicate articles were selected. Based on the abstracts, 54 potentially relevant records were collected for full-text review. Finally, 13 articles were included in the present meta-analysis of qualitative analysis (Figure 1).

A total number of 824 patients with MS were elated in selected studies. MRI modalities were conventional and DTI processed MRI. Neuropsychological tests were variable in studies but tests had overlap. One single study had used Montreal Neurological Institute (MNI) tests that were not included in quantitative analyses as there was no other study using MNI scoring. 20 Multiple Sclerosis Functional Composite (MSFC) was used in three studies. Expanded Disability Status Scale (EDSS) was the most applied test for neuropsychological profiling. Cognitive impairment index was used in two studies. Brief Visuospatial Memory Test-Revised was used in two studies. The mean age of MS participants was about 42 years old. Disease duration was ranging from about six years to 21.5 years (Table 1). In the case of disease type, most evaluated patients (60.44%) were RRMS, following SPMS (22.94%), benign MS (15.05%), and PPMS (1.58%). Notably, studies with low quality (NOS score less than 6) were excluded from the study. Therefore, we reduced the possible sources of bias as much as possible.

In the pooled analysis of the correlation of the PASAT-3 test with MD of MRI findings in the brain, seven studies were included in the random-effect model ($I^2 = 65.2\%$). The pooled correlation coefficient was statistically significant ($r = -0.225$, 95% CI $= -0.316$ to $-0.130$, $P < 0.0001$) (Figure 2). Egger’s test showed a 1-tailed $P = 0.440$, supporting the absence of publication bias, as well as gross symmetry in the funnel plot (Figure 3).

In the pooled analysis of the correlation of the SDMT test with MD of MRI findings in the brain, three studies (four sub-studies) were included in the fixed-effect model ($I^2 = 0\%$). The pooled correlation coefficient was statistically significant ($r = -0.438$, 95% CI $= -0.531$ to $-0.335$, $P < 0.0001$) (Figure 4). Egger’s test did not show publication bias and symmetry in the funnel plot ($P = 0.089$) (Figure 5).

The SDMT test was positively correlated with FA in two studies (three sub-studies) ($r = 0.351$, 95% CI $= 0.212$ to $0.476$, $P < 0.0001$), with a low possibility of heterogeneity ($I^2 = 0\%$) and publication bias (Egger’s test

Figure 1. PRISMA flowchart of the study
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>n-MS</th>
<th>n-Healthy controls</th>
<th>Mean age of MS patients</th>
<th>Female</th>
<th>Disease duration</th>
<th>RRMS</th>
<th>SPMS</th>
<th>PPMSPMS</th>
<th>MRI modality</th>
<th>Cognition tests</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syc et al, 2013⁴¹</td>
<td>Case-control</td>
<td>101</td>
<td>16</td>
<td>44</td>
<td>75</td>
<td>11.5</td>
<td>64</td>
<td>24</td>
<td>13</td>
<td>DTI</td>
<td>MSFC (25FTW; 9-HPT; PASAT-3)</td>
<td>6</td>
</tr>
<tr>
<td>Rovaris et al, 2002⁴⁵</td>
<td>Retrospective</td>
<td>34</td>
<td>0</td>
<td>34.8</td>
<td>21</td>
<td>6.5</td>
<td>34</td>
<td>0</td>
<td>0</td>
<td>DTI; T2, T1</td>
<td>EDSS</td>
<td>8</td>
</tr>
<tr>
<td>Koenig et al, 2015⁴⁵</td>
<td>Case-control</td>
<td>57</td>
<td>17</td>
<td>44.6</td>
<td>39</td>
<td>11</td>
<td>44</td>
<td>13</td>
<td>0</td>
<td>DTI</td>
<td>BVMT; CVLT; PASAT; SDMT</td>
<td>7</td>
</tr>
<tr>
<td>Rovaris et al, 2008⁴⁵</td>
<td>Case-control</td>
<td>98</td>
<td>19</td>
<td>45.4</td>
<td>37</td>
<td>(for benign 21.5; for sec-prog 15.0)</td>
<td>0</td>
<td>36</td>
<td>62*</td>
<td>Conventional; DTI</td>
<td>EDSS (composite cognitive score)</td>
<td>7</td>
</tr>
<tr>
<td>Lin et al, 2008⁴⁴</td>
<td>Case-control</td>
<td>36</td>
<td>13</td>
<td>37.35</td>
<td>26</td>
<td>8.6</td>
<td>36</td>
<td>0</td>
<td>0</td>
<td>Conventional dual-echo; DTI; MTI</td>
<td>EDSS</td>
<td>7</td>
</tr>
<tr>
<td>Preziosa et al, 2016⁴⁰</td>
<td>Case-control</td>
<td>61</td>
<td>61</td>
<td>39.7</td>
<td>40</td>
<td>8.2</td>
<td>61</td>
<td>0</td>
<td>0</td>
<td>T2; T1; dual-echo; 3D T1; DTI</td>
<td>EDSS; MNI</td>
<td>8</td>
</tr>
<tr>
<td>Meijer et al, 2016⁴³</td>
<td>Case-control</td>
<td>30</td>
<td>32</td>
<td>53.45</td>
<td>20</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Conventional; DTI</td>
<td>EDSS</td>
<td>7</td>
</tr>
<tr>
<td>Preziosa et al, 2017⁴⁶</td>
<td>Case-control</td>
<td>149</td>
<td>40</td>
<td>41.6</td>
<td>83</td>
<td>13</td>
<td>83</td>
<td>41</td>
<td>25</td>
<td>DIR; DTI; dual-echo; 3D T1</td>
<td>EDSS; CII</td>
<td>8</td>
</tr>
<tr>
<td>Benedict et al, 2013⁴⁷</td>
<td>Case-control</td>
<td>75</td>
<td>18</td>
<td>46.4</td>
<td>53</td>
<td>11.7</td>
<td>50</td>
<td>25</td>
<td>0</td>
<td>DTI</td>
<td>EDSS</td>
<td>7</td>
</tr>
<tr>
<td>Pokrzywka-Drożan et al, 2018⁴⁸</td>
<td>Case-control</td>
<td>50</td>
<td>27</td>
<td>36.4</td>
<td>37</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>DTI</td>
<td>SDMT; MSFC; EDSS; SDMT; FSS</td>
<td>7</td>
</tr>
<tr>
<td>Benedict et al, 2007⁴⁹</td>
<td>Case-control</td>
<td>60</td>
<td></td>
<td>45.8</td>
<td>44.00</td>
<td>12.8</td>
<td>40</td>
<td>20</td>
<td>0</td>
<td>DWI</td>
<td>EDSS; CVLT-II; BVMT-R; PASAT; D-KEFS ST</td>
<td>8</td>
</tr>
<tr>
<td>Riccitelli et al, 2020⁵⁰</td>
<td>Case-control</td>
<td>37</td>
<td>50</td>
<td>44.4</td>
<td>18</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>37*</td>
<td>Conventional; DTI</td>
<td>CII</td>
<td>7</td>
</tr>
<tr>
<td>Shardella et al, 2013⁵¹</td>
<td>Case-control</td>
<td>36</td>
<td>25</td>
<td>34</td>
<td>26</td>
<td>7.4</td>
<td>36</td>
<td>0</td>
<td>0</td>
<td>Conventional; DTI</td>
<td>EDSS; MSFC</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviations: MS, multiple sclerosis; DIR, Double inversion recovery; DWI, Diffusion-weighted imaging; 3D, three-dimensional; MNI, Montreal Neurological Institute; SDMT, Symbol Digit Modalities Test; MSFC, Multiple Sclerosis Functional Composite; EDSS, Expanded Disability Status Scale; DTI, diffusion tensor imaging; PASAT, Paced Auditory Serial Addition Test; BVMT-R, Brief Visuospatial Memory Test-Revised; CII, Cognitive Impairment Index; D-KEFS ST, Delis-Kaplan Executive Function System Sorting Test; 25FTW, Timed 25-Foot Walk; 9-HPT, 9-Hole Peg Test; FSS, Fatigue Severity Scale; CVLT, California Verbal Learning Test.

* Benign MS.
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Figure 2. Forrest plot of the PASAT-3 correlation with mean diffusivity

Figure 3. Funnel plot of the PASAT-3 correlation with mean diffusivity

Figure 4. Forrest plot of the SDMT correlation with mean diffusivity

Figure 5. Funnel plot of the SDMT correlation with mean diffusivity
Regarding the pooled analysis of the correlation of the BVMT test with the MD of MRI findings in the brain, two studies were included in the fixed-effect model ($I^2 = 0\%$). The pooled correlation coefficient was statistically significant ($r = -0.361$, 95% CI = -0.511 to -0.190, $P < 0.0001$) (Figure 8). Egger’s test was not conducted due to a low number of studies.

In the pooled analysis of correlation of the BVMT test with the T2 lesions volume of MRI findings, two studies (three sub-studies) were included in the fixed-effect model ($I^2 = 4.1\%$). The pooled correlation coefficient was statistically significant ($r = -0.302$, 95% CI = -0.451 to -0.136, $P < 0.0001$) (Figure 9). Egger’s test was significant ($P = 0.010$) as well as non-asymmetric funnel plot (Figure 10).

The pooled results obtained based on the two included articles (three sub-studies) using the fixed-effects model revealed that the SDMT test with T2 lesion volume of MRI findings in the brain was negatively correlated ($r = -0.367$, 95% CI = -0.508 to -0.207, $P < 0.0001$) (Figure 11). There was no evidence of significant heterogeneity across the included articles ($I^2 = 0\%$). Moreover, Egger’s test results were not statistically significant ($P = 0.487$) (Figure 12).

Discussion

In this study, we found an inverse correlation between PASAT-3, SDMT, and MD of the brain in patients with...
MS. Using lesion-symptom mapping, researchers have discovered numerous areas linked to lower PASAT scores. Matias-Guiu and colleagues’ study\textsuperscript{31} showed white matter lesions in the left cingulum, corpus callosum, corticospinal tract, and arcuate fasciculus were associated with worse performance in the PASAT test, while diffusion tensor MRI was not used.

White matter impairment, in contrast to gray matter atrophy has been reported to have a secondary role in PASAT performance decline\textsuperscript{32}; however, we were forced to analyze whole-brain data due to the limited reported data in the included studies.

In a similar study to our meta-analysis, Mollison et al focused on only T2 hyperintense lesion volume and found that SDMT had a summary effect size of $r = -0.37$ and PASAT had a summary impact size of $r = -0.28$ that in case of SDMT. These findings were in line with our results, but we found a further correlation between DTI MRI findings (MD and FA) that has not been reported in any previous meta-analysis.\textsuperscript{33}

Another recent meta-analysis by Jandric et al evaluated fMRI connectivity changes in comparison to cognition,\textsuperscript{34} which does not include any cognition tests.

In another systematic review and meta-analysis,\textsuperscript{35} it was suggested that to resolve the continuing clinical-radiological contradiction, various components of the complicated disease will most likely need to be evaluated simultaneously utilizing the best assessment

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure10.png}
\caption{Funnel plot of the BVMT correlation with T2 lesions volume}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure11.png}
\caption{Funnel plot of the SDMT test with T2 lesions}
\end{figure}
methodologies for both cognitive tests and brain imaging, as well as the processing of diffusion data and the need for multiple steps to ensure the comparison of identical brain regions.

Because of these issues, the results of our study might have been highly biased by comparing data of heterogeneous regions from the brain. This limits these findings to the clinical setting; therefore, we aimed to unify definitions based on postmortem studies as the most trustworthy data available. As for histological validation of DTI with post-mortem data, DTI-based assessments can be very sensitive to white and gray matter microstructures. Schmierer et al discovered a substantial association between two conventional diffusion measurements (MD and FA), myelin content, and to a lesser extent, axonal count in a postmortem analysis of progressive MS cases.

The present meta-analysis had some limitations that should be considered when interpreting the findings. One main limitation of our study was the lack of meta-regression and subgroup analysis due to the small number of studies; while we know that as an advantage of DTI imaging in MS patients, it helps display differences in the type of MS disease. This limitation deterred the authors from elucidating the possible confounders and the characteristics of the included studies such as MS types, RRMS, PPMS, SPMS, and disease duration. Patients with SPMS showed significant changes in the amount of MD and FA compared to RRMS patients but we were not able to adjust for this. Another limitation of the study was that meta-regression of disease duration and study variables was not possible due to the small number of studies; while we know that based on previous reports brain atrophy and DTI-derived metrics are substantially linked to the duration of MS. Moreover, even though some studies compared the MRI findings between cognitive impairment and non-cognitive impairment groups, we could not include them in the analyses, which could be considered a limitation. However, further studies are recommended to explore such possible relationship between these groups. On the other hand, our study's key strength is that there might be independent associations between numerous MRI parameters and cognitive impairment in MS patients.

Nonetheless, the various quantitative MRI indicators used in studies have made it difficult to perform pooled analyses of results.

Conclusion
Our study showed that the PASAT-3, BVMT, and SDMT tests exhibited a negative correlation with brain MD, and the SDMT test positively correlated with FA and inversely correlated with T2 lesion volume. In the case of other tests, there were just a few research that revealed significant relationships.

Authors’ Contribution
Conceptualization: Elnaz Asadollahzadeh, Abdorreza Naser Moghadasi.
Data curation: Elnaz Asadollahzadeh, Fereshteh Ghadiri, Abdorreza Naser Moghadasi.
Formal analysis: Elnaz Asadollahzadeh, Zahra Ebadi, Abdorreza Naser Moghadasi.
Funding acquisition: Elnaz Asadollahzadeh, Fereshteh Ghadiri, Zahra Ebadi, Abdorreza Naser Moghadasi.
Methodology: Elnaz Asadollahzadeh, Abdorreza Naser Moghadasi.
Project administration: Elnaz Asadollahzadeh, Abdorreza Naser Moghadasi.
Resources: Elnaz Asadollahzadeh, Zahra Ebadi, Abdorreza Naser Moghadasi.
Supervision: Elnaz Asadollahzadeh, Abdorreza Naser Moghadasi.
Visualization: Elnaz Asadollahzadeh, Fereshteh Ghadiri, Abdorreza Naser Moghadasi.
Writing—original draft: Elnaz Asadollahzadeh, Zahra Ebadi, Abdorreza Naser Moghadasi.
Writing—review & editing: Elnaz Asadollahzadeh, Fereshteh Ghadiri, Zahra Ebadi, Abdorreza Naser Moghadasi.


