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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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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.

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.[1-3] 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.[4,5] 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.[6]

Traditional imaging methods such as dual-echo, FLAIR, and Gd-enhanced sequences play an important role.[7] 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.[8] 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".[8,9]

Early in the course of MS, brain atrophy appears, which worsens as the disease progresses.[10] Gray matter atrophy progresses more quickly than white matter atrophy and is more common in the early stages of MS.[11] 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.

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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.[12] Cognitive impairment is aggravated by gray matter atrophy. Brain parenchymal and gray matter fractions have been used to estimate atrophy in patients with MS.[13] In clinical practice, fractional anisotropy (FA) values are indicators of the degree of MS brain atrophy exclusively in the corpus callosum.[14] 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 [15]. 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.[16] 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.[17] 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.[18] The protocol of this study was registered at the PROSPRO 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

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 ($I^2 = 0.0\%$). 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 ($I^2 = 0$) (Figure 6) and publication bias (Egger's test

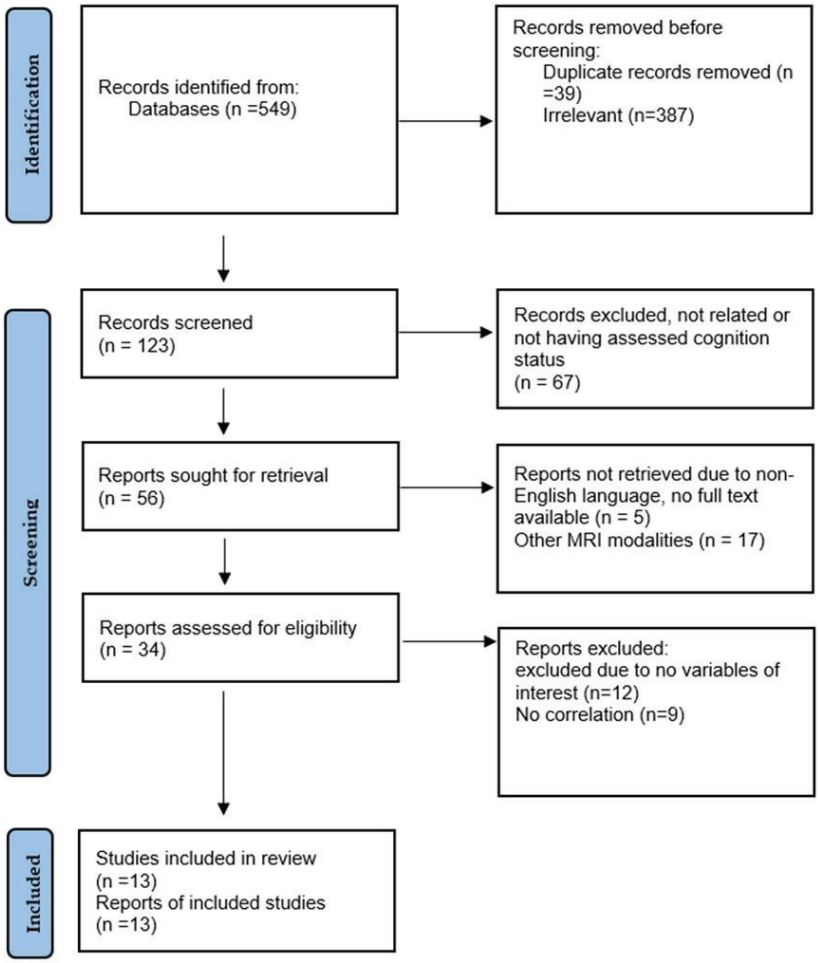

Figure 1. PRISMA flowchart of the study

Table 1. The main characteristics of the included studies

Study	Design	n-MS	n-Healthy controls	Mean age of MS patients	Female	Disease duration	RRMS	SPMS	PPMSPPMS	MRI modality	Cognition tests	NOS
Syc et al, 2013[21]	Case-control	101	16	44	75	11.5	64	24	13	DTI	MSFC (25FTW; 9-HPT; PASAT-3)	6
Rovaris et al, 2002[15]	Retrospective	34	0	34.8	21	6.5	34	0	0	DTI; T2, T1	EDSS	8
Koenig et al, 2015[22]	Case-control	**57**	**17**	44.6	39	11	44	13	0	DTI	BVMT; CVLT; PASAT; SDMT	7
Rovaris et al, 2008[23]	Case-control	98	19	45.4	37	(for benign 21.5; for sec-prog 15.0)	0	36	62*	Conventional; DTI	EDSS (composite cognitive score)	7
Lin et al, 2008[24]	Case-control	36	13	37.35	26	8.6	36	0	0	Conventional dual-echo; DTI; MTI	EDSS	7
Preziosa et al, 2016[20]	Case-control	61	61	39.7	40	8.2	61	0	0	T2; T1; dual- echo; 3D T1; DTI	EDSS; MNI	8
Meijer et al, 2016[25]	Case-control	30	32	53.45	20			30	0	Conventional; DTI	EDSS	7
Preziosa et al, 2017[26]	Case-control	149	40	41.6	83	13	83	41	25	DIR; DTI; dual-echo; 3D T;	EDSS; CII	8
Benedict et al, 2013[27]	Case-control	75	18	46.4	53	11.7	50	25	0	DTI	EDSS	7
Pokryszko-Dragan et al, 2018[9]	Case-control	50	27	36.4	37		50	0	0	DTI	SDMT; MSFC; EDSS; SDMT; FSS	7
Benedict et al, 2007[28]	Case-control	60		45.8	44.00	12.8	40	20	0	DWI	EDSS; CVLT-II; BVMT-R; PASAT; D-KEFS ST	8
Riccitelli et al, 2020[29]	Case-control	37	50	44.4	18	20	0	0	37*	Conventional; DTI	CII	7
Sbardella et al, 2013[30]	Case-control	36	25	34	26	7.4	36	0	0	Conventional; DTI	EDSS; MSFC	7

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.

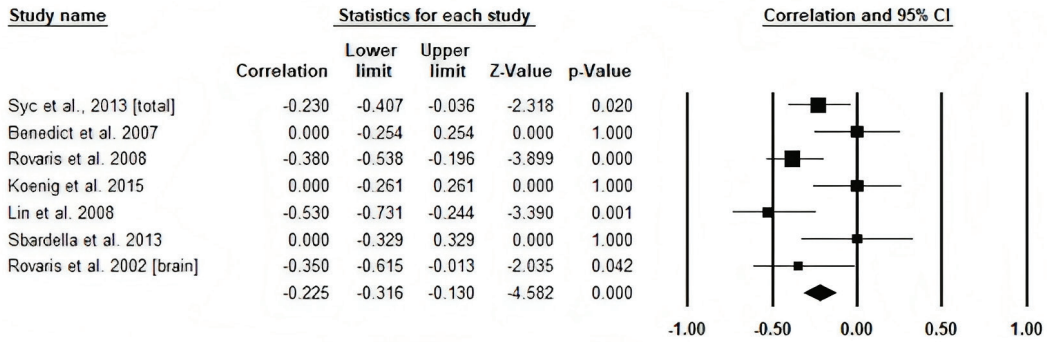

Figure 2. Forrest plot of the PASAT-3 correlation with mean diffusivity

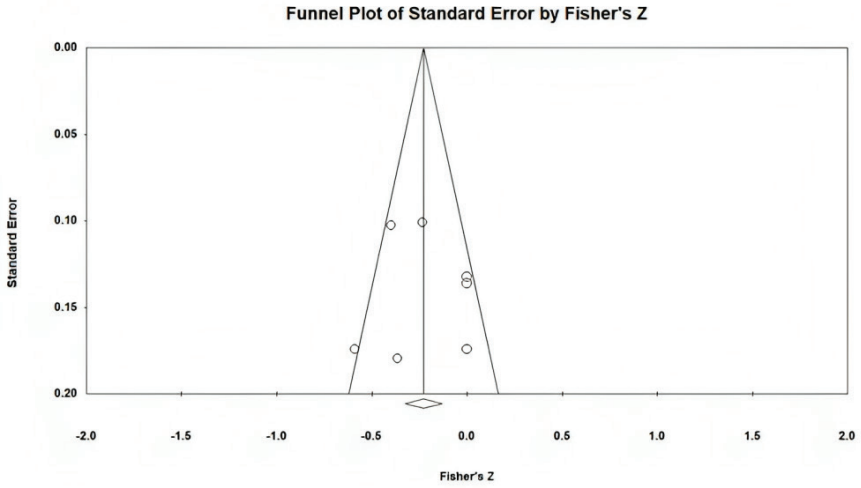

Figure 3. Funnel plot of the PASAT-3 correlation with mean diffusivity

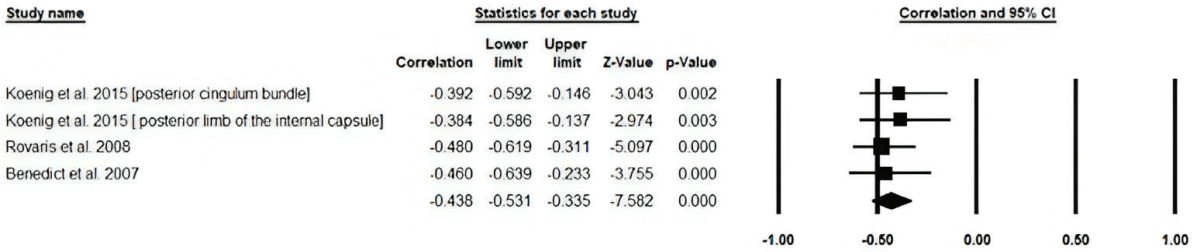

Figure 4. Forrest plot of the SDMT correlation with mean diffusivity

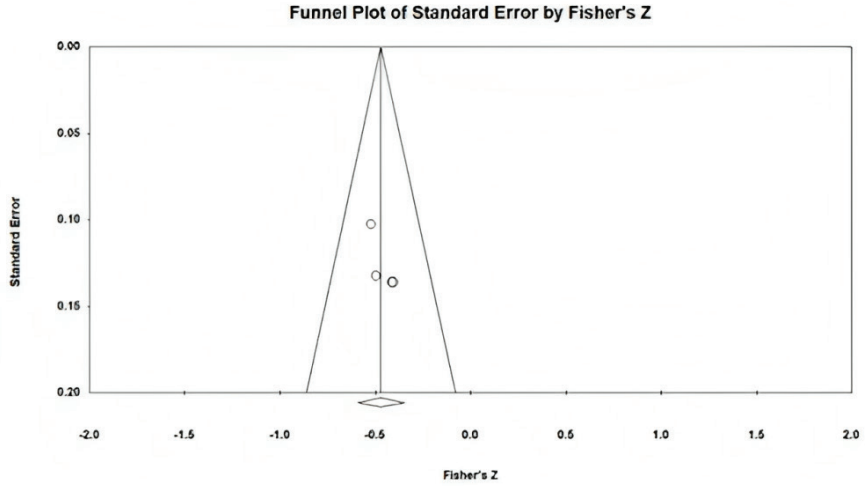

Figure 5. Funnel plot of the SDMT correlation with mean diffusivity

$P = 0.407$, Figure 7).

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 (Figure10).

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 ($I^2 = 0.0\%$). 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

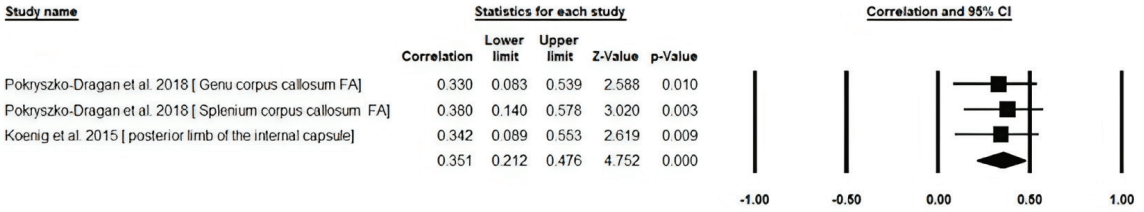

Figure 6. Forrest plot of the SDMT correlation with fractional anisotropy

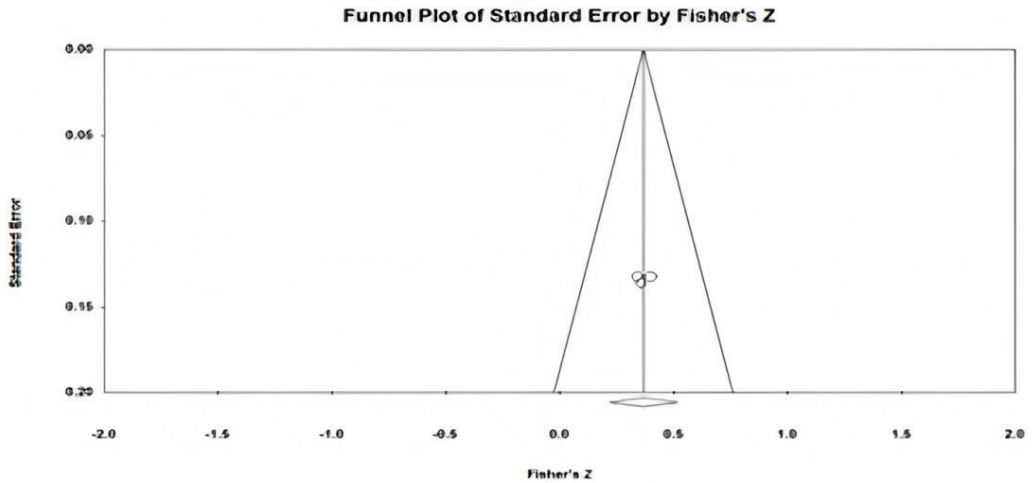

Figure 7. Funnel plot of the SDMT correlation with fractional anisotropy

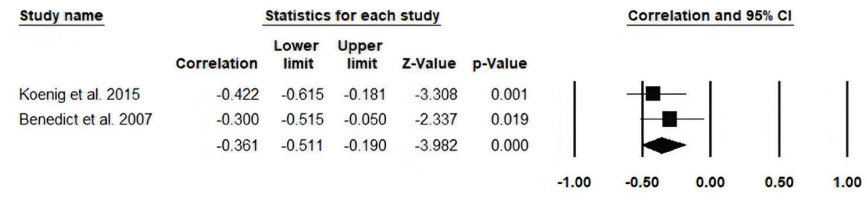

Figure 8. Funnel plot of the BVMT correlation with mean diffusivity

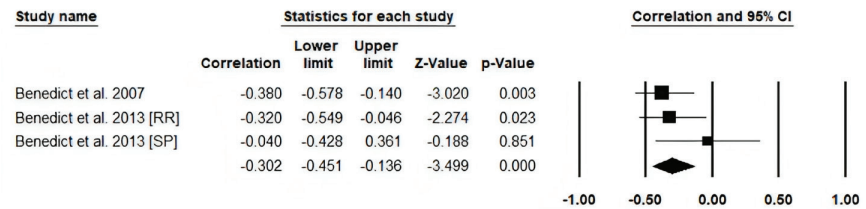

Figure 9. Funnel plot of the BVMT correlation with T2 lesions volume

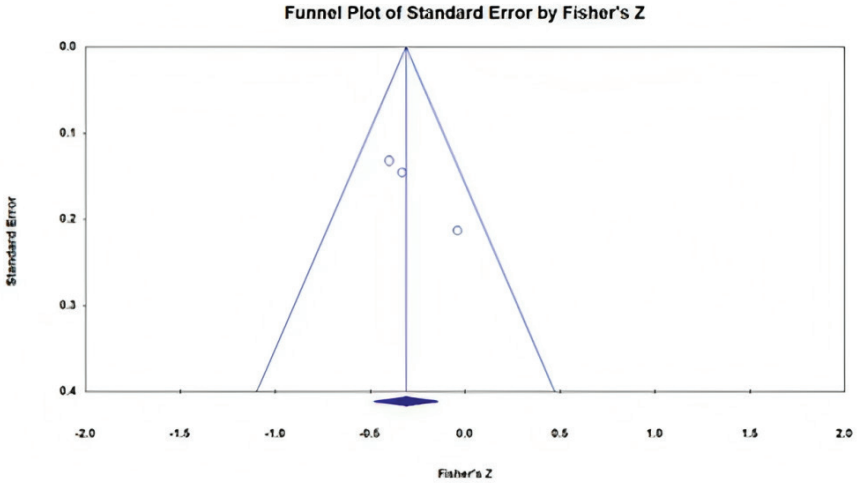

Figure 10. Funnel plot of the BVMT correlation with T2 lesions volume

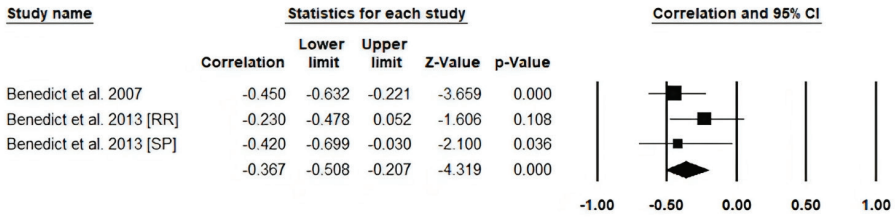

Figure 11. Funnel plot of the SDMT test with T2 lesions

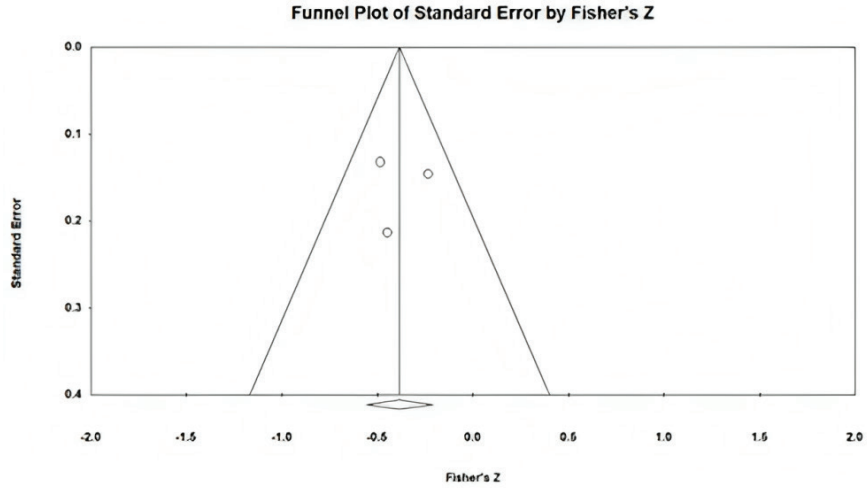

Figure 12. Funnel plot of the SDMT test with T2 lesions

MS. Using lesion-symptom mapping, researchers have discovered numerous areas linked to lower PASAT scores. Matias-Guiu and colleagues' study[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[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.[33]

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

In another systematic review and meta-analysis,[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

methodologies for both cognitive tests and brain imaging, as well as the conclusion of our study.

The neurodegenerative process underlying brain atrophy causes irreversible damage and is linked to physical and mental impairments.[12] Strong evidence supports the association between lesions in different anatomical areas of the brain and clinical disability in patients with MS.[36] However, in the case of cognition disorders, although many studies have been conducted, most studies used new methods and different capabilities of brain MRI imaging, which has caused great variability in the methodology of the studies. The lack of a uniform protocol between studies and the lack of(repetition) uniform definitions for brain atrophy makes data pooling very difficult. As Koenig et al pointed out,[22] cerebral atrophy itself disrupts the processing of diffusion data and warns of 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.[37] 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.[38]

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.[39] 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.
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Formal analysis: Elnaz Asadollahzadeh, Zahra Ebadi, Abdorreza Naser Moghadasi.
Funding acquisition: Elnaz Asadollahzadeh, Fereshteh Ghadiri, Zahra Ebadi, Abdorreza Naser Moghadasi.
Investigation: Elnaz Asadollahzadeh, Fereshteh Ghadiri, Zahra Ebadi, Abdorreza Naser Moghadasi.
Methodology: Elnaz Asadollahzadeh, Abdorreza Naser Moghadasi.
Project administration: Elnaz Asadollahzadeh, Abdorreza Naser Moghadasi.
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Supervision: Elnaz Asadollahzadeh, Abdorreza Naser Moghadasi.
Validation: Elnaz Asadollahzadeh, Fereshteh Ghadiri, Zahra Ebadi, 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

Competing Interests

The authors declared that they had no conflict of interest.

Data Availability Statement

Data will be made available on request.

Ethical Approval

Not applicable.

References

1. Eshaghi A, Young AL, Wijeratne PA, Prados F, Arnold DL, Narayanan S, et al. Identifying multiple sclerosis subtypes using unsupervised machine learning and MRI data. Nat Commun. 2021;12(1):2078. doi: 10.1038/s41467-021-22265-2.
2. Sarihi S, Niknam M, Mahjour S, Hosseini-Bensenjan M, Moazzen F, Soltanabadi S, et al. Toxic heavy metal concentrations in multiple sclerosis patients: a systematic review and meta-analysis. EXCLI J. 2021;20:1571-84. doi: 10.17179/excli2021-3484.
3. Rostami A, Abbasi Y, Jamalnia S, Asadian A, Enani H, Jafarinia M. Mesenchymal stem cells as a new approach for the treatment of multiple sclerosis: a literature review. Galen Med J. 2022;11:e2529. doi: 10.31661/gmj.v11i.2529.
4. Giedraitiene N, Drukteiniene E, Kizlaitiene R, Cimbalas A, Asoklis R, Kaubrys G. Cognitive decline in multiple sclerosis

is related to the progression of retinal atrophy and presence of oligoclonal bands: a 5-year follow-up study. Front Neurol. 2021;12:678735. doi: 10.3389/fneur.2021.678735.
5. Petracca M, Pontillo G, Moccia M, Carotenuto A, Cocozza S, Lanzillo R, et al. Neuroimaging correlates of cognitive dysfunction in adults with multiple sclerosis. Brain Sci. 2021;11(3):346. doi: 10.3390/brainsci11030346.
6. Fox RJ, Beall E, Bhattacharyya P, Chen JT, Sakaie K. Advanced MRI in multiple sclerosis: current status and future challenges. Neurol Clin. 2011;29(2):357-80. doi: 10.1016/j.ncl.2010.12.011.
7. Filippi M, Rocca MA, De Stefano N, Enzinger C, Fisher E, Horsfield MA, et al. Magnetic resonance techniques in multiple sclerosis: the present and the future. Arch Neurol. 2011;68(12):1514-20. doi: 10.1001/archneurol.2011.914.
8. Genova HM, Hillary FG, Wylie G, Rypma B, Deluca J. Examination of processing speed deficits in multiple sclerosis using functional magnetic resonance imaging. J Int Neuropsychol Soc. 2009;15(3):383-93. doi: 10.1017/s1355617709090535.
9. Pokryszko-Dragan A, Banaszek A, Nowakowska-Kotas M, Jeżowska-Jurczyk K, Dziadkowiak E, Gruszka E, et al. Diffusion tensor imaging findings in the multiple sclerosis patients and their relationships to various aspects of disability. J Neurol Sci. 2018;391:127-33. doi: 10.1016/j.jns.2018.06.007.
10. Fujimori J, Uryu K, Fujihara K, Wattjes MP, Suzuki C, Nakashima I. Measurements of the corpus callosum index and fractional anisotropy of the corpus callosum and their cutoff values are useful to assess global brain volume loss in multiple sclerosis. Mult Scler Relat Disord. 2020;45:102388. doi: 10.1016/j.msard.2020.102388.
11. Andravizou A, Dardiotis E, Artemiadis A, Sokratous M, Siokas V, Tsouris Z, et al. Brain atrophy in multiple sclerosis: mechanisms, clinical relevance and treatment options. Auto Immun Highlights. 2019;10(1):7. doi: 10.1186/s13317-019-0117-5.
12. Rojas JI, Patrucco L, Miguez J, Cristiano E. Brain atrophy in multiple sclerosis: therapeutic, cognitive and clinical impact. Arq Neuropsiquiatr. 2016;74(3):235-43. doi: 10.1590/0004-282x20160015.
13. Miller DH, Barkhof F, Frank JA, Parker GJ, Thompson AJ. Measurement of atrophy in multiple sclerosis: pathological basis, methodological aspects and clinical relevance. Brain. 2002;125(Pt 8):1676-95. doi: 10.1093/brain/awf177.
14. Solana E, Martinez-Heras E, Montal V, Vilaplana E, Lopez-Soley E, Radua J, et al. Regional grey matter microstructural changes and volume loss according to disease duration in multiple sclerosis patients. Sci Rep. 2021;11(1):16805. doi: 10.1038/s41598-021-96132-x.
15. Rovaris M, Iannucci G, Falautano M, Possa F, Martinelli V, Comi G, et al. Cognitive dysfunction in patients with mildly disabling relapsing-remitting multiple sclerosis: an exploratory study with diffusion tensor MR imaging. J Neurol Sci. 2002;195(2):103-9. doi: 10.1016/s0022-510x(01)00690-6.
16. Eshaghi A, Marinescu RV, Young AL, Firth NC, Prados F, Jorge Cardoso M, et al. Progression of regional grey matter atrophy in multiple sclerosis. Brain. 2018;141(6):1665-77. doi: 10.1093/brain/awy088.
17. Casanova Peño LI, de Silanes de Miguel CL, de Torres L, Eimil-Ortiz M, Gil-Moreno MJ, Oyanguren Rodeño B, et al. Brain atrophy and physical and cognitive disability in multiple sclerosis. Basic Clin Neurosci. 2023;14(2):311-6. doi: 10.32598/bcn.2021.1893.1.
18. Tugwell P, Tovey D. PRISMA 2020. J Clin Epidemiol. 2021;134:A5-A6. doi: 10.1016/j.jclinepi.2021.04.008.
19. Zheng M, Jin H, Shi N, Duan C, Wang D, Yu X, et al. The relationship between health literacy and quality of life: a systematic review and meta-analysis. Health Qual Life Outcomes. 2018;16(1):201. doi: 10.1186/s12955-018-1031-7.
20. Preziosa P, Rocca MA, Pagani E, Stromillo ML, Enzinger C, Gallo A, et al. Structural MRI correlates of cognitive impairment in patients with multiple sclerosis: a multicenter study. Hum Brain Mapp. 2016;37(4):1627-44. doi: 10.1002/hbm.23125.
21. Syc SB, Harrison DM, Saidha S, Seigo M, Calabresi PA, Reich DS. Quantitative MRI demonstrates abnormality of the fornix and cingulum in multiple sclerosis. Mult Scler Int. 2013;2013:838719. doi: 10.1155/2013/838719.
22. Koenig KA, Sakaie KE, Lowe MJ, Lin J, Stone L, Bermel RA, et al. The relationship between cognitive function and high-resolution diffusion tensor MRI of the cingulum bundle in multiple sclerosis. Mult Scler. 2015;21(14):1794-801. doi: 10.1177/1352458515576983.
23. Rovaris M, Riccitelli G, Judica E, Possa F, Caputo D, Ghezzi A, et al. Cognitive impairment and structural brain damage in benign multiple sclerosis. Neurology. 2008;71(19):1521-6. doi: 10.1212/01.wnl.0000319694.14251.95.
24. Lin X, Tench CR, Morgan PS, Constantinescu CS. Use of combined conventional and quantitative MRI to quantify pathology related to cognitive impairment in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2008;79(4):437-41. doi: 10.1136/jnnp.2006.112177.
25. Meijer KA, Muhlert N, Cercignani M, Sethi V, Ron MA, Thompson AJ, et al. White matter tract abnormalities are associated with cognitive dysfunction in secondary progressive multiple sclerosis. Mult Scler. 2016;22(11):1429-37. doi: 10.1177/1352458515622694.
26. Preziosa P, Pagani E, Morelli ME, Copetti M, Martinelli V, Pirro F, et al. DT MRI microstructural cortical lesion damage does not explain cognitive impairment in MS. Mult Scler. 2017;23(14):1918-28. doi: 10.1177/1352458516689147.
27. Benedict RH, Hulst HE, Bergsland N, Schoonheim MM, Dwyer MG, Weinstock-Guttman B, et al. Clinical significance of atrophy and white matter mean diffusivity within the thalamus of multiple sclerosis patients. Mult Scler. 2013;19(11):1478-84. doi: 10.1177/1352458513478675.
28. Benedict RH, Bruce J, Dwyer MG, Weinstock-Guttman B, Tjoa C, Tavazzi E, et al. Diffusion-weighted imaging predicts cognitive impairment in multiple sclerosis. Mult Scler. 2007;13(6):722-30. doi: 10.1177/1352458507075592.
29. Riccitelli GC, Pagani E, Meani A, Valsasina P, Preziosa P, Filippi M, et al. Cognitive impairment in benign multiple sclerosis: a multiparametric structural and functional MRI study. J Neurol. 2020;267(12):3508-17. doi: 10.1007/s00415-020-10025-z.
30. Sbardella E, Petsas N, Tona F, Prosperini L, Raz E, Pace G, et al. Assessing the correlation between grey and white matter damage with motor and cognitive impairment in multiple sclerosis patients. PLoS One. 2013;8(5):e63250. doi: 10.1371/journal.pone.0063250.
31. Matias-Guiu JA, Cortés-Martínez A, Montero P, Pytel V, Moreno-Ramos T, Jorquera M, et al. Structural MRI correlates of PASAT performance in multiple sclerosis. BMC Neurol. 2018;18(1):214. doi: 10.1186/s12883-018-1223-0.
32. Yu HJ, Christodoulou C, Bhise V, Greenblatt D, Patel Y, Serafin D, et al. Multiple white matter tract abnormalities underlie cognitive impairment in RRMS. Neuroimage. 2012;59(4):3713-22. doi: 10.1016/j.neuroimage.2011.10.053.
33. Mollison D, Sellar R, Bastin M, Mollison D, Chandran S, Wardlaw J, et al. The clinico-radiological paradox of cognitive function and MRI burden of white matter lesions in people with multiple sclerosis: a systematic review and meta-analysis. PLoS One. 2017;12(5):e0177727. doi: 10.1371/journal.pone.0177727.
34. Jandric D, Doshi A, Scott R, Paling D, Rog D, Chataway J,

et al. A systematic review of resting-state functional MRI connectivity changes and cognitive impairment in multiple sclerosis. Brain Connect. 2022;12(2):112-33. doi: 10.1089/brain.2021.0104.
35. Tóth E, Faragó P, Király A, Szabó N, Veréb D, Kocsis K, et al. The contribution of various MRI parameters to clinical and cognitive disability in multiple sclerosis. Front Neurol. 2018;9:1172. doi: 10.3389/fneur.2018.01172.
36. Cordani C, Hidalgo de la Cruz M, Meani A, Valsasina P, Esposito F, Pagani E, et al. MRI correlates of clinical disability and hand-motor performance in multiple sclerosis phenotypes. Mult Scler. 2021;27(8):1205-21. doi: 10.1177/1352458520958356.
37. Seehaus A, Roebroeck A, Bastiani M, Fonseca L, Bratzke H, Lori N, et al. Histological validation of high-resolution DTI in human post mortem tissue. Front Neuroanat. 2015;9:98. doi: 10.3389/fnana.2015.00098.
38. Schmierer K, Wheeler-Kingshott CA, Boulby PA, Scaravilli F, Altmann DR, Barker GJ, et al. Diffusion tensor imaging of post mortem multiple sclerosis brain. Neuroimage. 2007;35(2):467-77. doi: 10.1016/j.neuroimage.2006.12.010.
39. Fink F, Klein J, Lanz M, Mitrovics T, Lentschig M, Hahn HK, et al. Comparison of diffusion tensor-based tractography and quantified brain atrophy for analyzing demyelination and axonal loss in MS. J Neuroimaging. 2010;20(4):334-44. doi: 10.1111/j.1552-6569.2009.00377.x.