Conventional and Quantitative Magnetic Resonance Imaging and Cognitive Impairment in Multiple Sclerosis

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Abstract

An estimated 30–70% of patients with multiple sclerosis (MS) have some cognitive impairment. Cognitive function depends on a spectrum of faculties including information processing speed, sustained attention, recent memory and executive function. The broad definition of cognition has resulted in different assessments of function, and repeatable batteries of tests have been devised to gain an overall and repeatable view of cognition in MS. Many studies have attempted to find an association between cognitive function and MS pathology using magnetic resonance imaging (MRI). Conventional MRI has been used to show the relationship between cognitive impairment and MS lesion volume and/or brain volume (reflecting atrophy). Studies using quantitative MRI to estimate the degree of abnormality in tissue that is normal-appearing on conventional MRI have also found correlations with cognitive function. Longitudinally, cognitive decline has been found to correlate with changing MRI-detectable pathology in some studies. However, consistency between studies has been lacking, and the large number of cognitive tests available makes direct comparison of different studies difficult. Focus on specific cognitive domains may alleviate this issue in future studies.

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disease affecting the central nervous system (CNS) that is characterised by multiple areas of demyelination, focal and diffuse inflammation, axonal damage and loss and gliosis. The disease course falls into different broad clinical categories, including relapsing–remitting (RR), secondary progressive (SP) and primary progressive (PP) MS. Patients who do not have clinically definite MS according to the criteria[1,2] but do have an isolated event suggestive of MS are said to have clinically isolated syndrome (CIS).

Magnetic Resonance Imaging Measures in Multiple Sclerosis

MS lesions can be visualised with remarkable clarity using magnetic resonance imaging (MRI), which is used as a diagnostic tool and has also greatly improved our understanding of the mechanisms of MS by giving us the opportunity to study the pathology *in vivo*. There is vast literature on the use of MRI in the study of MS, the bulk of which has focused on conventional MRI.

Conventional T_2-weighted spin echo images reveal the lesions,[3] which appear hyperintense, most completely of the different contrasts. The T_2 MS lesion burden has probably been the most commonly used MRI outcome measure in large clinical trials, and is quantified by count, area or volume. Despite accurately depicting the distribution of MS lesions, correlation with clinical measures such as the expanded disability status scale (EDSS)[4] is poor. Explanations for this 'clinico-radiological paradox' include lack of pathological specificity, re-myelination and cortical plasticity. Another explanation is the lack of spatial information in the lesion burden measures, location of the lesion within the brain being paramount in determining effect.

Other conventional MRI measures have been used in an attempt to overcome some of the limitations of T_2-weighted imaging. T_1 relaxation time contrast is thought to reflect more specifically axonal loss, so the apparent lesion burden may correlate better with disability. Gadolinium-enhanced T_1-weighted images are reported to show lesions where the blood–brain barrier has been breached, and indicate new or active lesions and therefore active disease. Tissue loss, or atrophy, has also been estimated using high-resolution images. This loss has also been found to correlate with disability to varying degrees.

While conventional MRI has revealed much about the progression of the disease, its lack of pathological specificity has ultimately limited its impact on our understanding of MS. Recent work has shifted towards utilising new quantitative MRI measures. These allow the quantification of properties such as T_1 or T_2 relaxation time,

magnetisation transfer ratio (MTR), and diffusivity *in vivo*. Quantitative measures allow us to estimate change even within normal-appearing tissue that is known to be diseased in MS and may contribute to the patient's disability. Furthermore, these measures may be more specific for particular pathologies.

Cognitive Impairment in Multiple Sclerosis

An estimated 30–70%[5] of patients with MS have some cognitive impairment. Consequent impact on lifestyle includes unemployment[5,6] and revocation of licence to drive.[7] Cognitive function depends on a spectrum of faculties, including information processing speed, sustained attention, recent memory and executive function. The number of available neuropsychological tests and the broad definition of cognition has resulted in some studies investigating various assessments of cognitive function.

Recently, MS-specific batteries of tests have been developed, of which the Brief Repeatable Battery (BRB) of neuropsychological tests[8] is reported to be most widely used.[9] The Paced Auditory Serial Addition Test (PASAT)[10] is also used as a measure of cognitive function in MS and is part of the MS functional composite (MSFC)[11,12] score of disability. However, the PASAT is reported to be non-specific for MS cognitive dysfunction. Another commonly used measure of cognitive function is the cerebral (or mental) component of the EDSS; the common use of the EDSS may mean that this score is available in retrospective studies where neuropsychological tests were not performed. However, the reliability of the cognitive component of the EDSS has been considered doubtful by many investigators.

Conventional Magnetic Resonance Imaging Studies of Cognitive Impairment in Multiple Sclerosis
Cross-sectional Studies

Conventional MRI measures have been found to correlate with clinical assessment of cognition, although the results are not consistent. Huber[13] used a battery of neuropsychological tests (BNT) including assessment of language, memory, cognition, visuospatial skills and depression to classify patients into cognitively impaired and intact groups. MRI was used to measure the number and distribution of lesions, as well as the presence of cerebral atrophy and atrophy of specific anatomical structures. The only significant difference between the groups was greater atrophy of the corpus callosum (CC) in the impaired group. Franklin[14] also used a BNT on 60 patients with chronic or progressive MS, and developed a lesion rating measure that was found to correlate moderately with degree of cognitive function.

Rao[6] attributed the moderate relationship between MRI and cognitive function to several factors: subjective measures of lesion size, incomplete testing of cognitive function and lack of control for age and education level. Consequently, 53 patients were recruited and a large BNT – 34 in total – was used to classify patients as impaired or intact. The effects of age and education were accounted for in the analysis. Demographic variables, EDSS and disease duration/course did not differ between the groups. By contrast, MRI measures of total lesion area (TLA), relative ventrical size and CC size were different; in particular, high TLA was the best predictor of impairment. With the exception of relative ventricular size, MRI measures were also correlated with neuropsychological test scores. Swirsky-Sacchetti et al.[15] report a similar study, but with the extended aim of investigating the impact on cognition of lesions in the frontal, temporal and parieto-occipital regions of each hemisphere. Impaired and intact groups were defined on the basis of neuropsychological testing. TLA, relative ventrical size and CC size were also measured on MRI. TLA was higher in the impaired group, in agreement with Rao; the other MRI measures were not different between groups. TLA also correlated with almost all cognitive measures. Frontal region lesions were the most significant predictors in almost half of the cognitive tests, despite accounting for only 26% of the TLA.

Another study investigating the impact of regional pathology on cognition was reported by Edwards et al.[16] Forty-one MS patients and 12 controls underwent a BNT interrogating multiple cognitive domains from which a global cognitive score was derived. Using MRI, the volume of supratentorial structures and the area of the CC were estimated using stereology. The cognitive score was significantly different in patients compared with controls, and correlated with white-matter volumes and CC area but not with grey-matter volumes.

Miki et al.[17] hypothesised that isolated U-fibre involvement in MS may have a role in cognitive dysfunction. Conventional MRI was used to identify lesions isolated to the U-fibres. Patients were subsequently divided into two groups: those with more than one isolated U-fibre lesion and those with one or none. While the groups did not differ in their physical disability, they differed on three (out of 11) neuropsychological tests – the three tests reflecting performance in executive control and memory. Moriarty[18] used fluid-attenuated inversion recovery (FLAIR) images to improve detection of small juxtacortical lesions relative to conventional T_2-weighted spin echo images. The number of these lesions correlated with impairment on cognitive tests and tests of delayed memory. A similar study by Lazeron[19] also found that juxtacortical lesions identified by FLAIR MRI correlated with cognitive impairment assessed using the BRB of neuropsychological tests.

Charil et al.[20] studied a large cohort (n=452) of RR MS patients, and hypothesised that, with such a large group of patients, it may be possible to relate dysfunction to the presence of lesions in particular brain regions. Conventional MRI was used to create lesion masks automatically for every patient. Statistical mapping was used to identify areas where lesion probability correlated with specific function. No neuopsychological testing was performed, but the mental score from the EDSS was available, although it was recognised that this score is probably a relatively poor indicator of cognitive function. Areas of significant correlation between mental score and lesion probability were identified in tracts linking associative areas, and were largely at the grey–white-matter junction, in agreement with other studies.[17–19] In contrast to other studies, no correlation was found between total lesion load and cognitive function. It was therefore suggested that for low EDSS scores (4.5 or less in this study), lesion location may be a more important predictor of cognitive function than total lesion load.

Recently, Houtchens et al.[21] tested the hypothesis that atrophy of the thalamus would correlate with cognitive impairment in MS. Seventy-nine patients were studied: 62 RR, 16 SP and one PP. A host of MRI measures were estimated, including the thalamic volume. A BNT was also performed. In all models predicting neuropsychological test performance, the thalamic volume explained the most variance of all predictors.

Ninety-two newly diagnosed MS and CIS patients were studied by Glanz et al.[22] The BRB of neuropsychological tests was performed, and conventional T_2-weighted images acquired. Lesion volumes and tissue volumes were computed. Patients were classified as cognitively intact or impaired by comparison with cognitive scores achieved by 27 healthy volunteers. There was no statistical difference between the intact and impaired groups in any MRI measure, suggesting that cognitive impairment may pre-date the appearance of gross structural abnormalities on MRI.

Longitudinal Studies

Several longitudinal studies investigating cognitive decline using MRI have now been performed, with follow-up from three months to 8.5 years. Mariani et al.[23] investigated 19 moderately impaired RR (initially) MS patients over an average of two years. Neuropsychological tests indicated a very mild overall impairment, which did not decline over the study period. There was also no evidence of change on MRI. Mattioli et al.[24] investigated nine mildly disabled RR MS patients over three months using gadolinium-enhanced MRI and neuropsychological evaluation. Again, there was no overall decline in cognitive performance, and in patients whose scores reduced in absolute terms there was no correlation with the changes on MRI.

Hohol et al.[25] studied 44 MS patients with various disease courses over a period of one year. Frequent scanning with conventional MRI was performed and two MRI measures, total lesion volume (LV) and brain-to-intracranial cavity volume ratio were estimated automatically. Significant correlations were found between neuropsychological test scores and the MRI measures at both baseline and follow-up. However, cognitive performance did not worsen on average over the study period. Nevertheless, change in information processing speed and attention was found to correlate with change in total LV.

Zivadinov et al.[26] studied a homogeneous group of 53 early-phase RR MS patients with a two-year follow-up period to investigate whether cognitive decline depends on progression in lesion burden or on the loss of brain tissue. A BNT was used, and MRI measures were T_1 and T_2 lesion volumes and brain parenchymal volume (BPV). Patients were categorised as cognitively improved, stable or worsened at follow-up. At baseline, cognitive function did not correlate with any MRI measure. However, BPV reduced significantly more in patients who were cognitively worsened at follow-up. Furthermore, decline in cognitive function over the two-year study period correlated with reduction in BPV but not LV.

Sperling et al.[27] studied 28 patients over a period of four years with assessment at baseline, one year and four years. Initially, 15 patients were RR and 13 chronic progressive. The BRB tests were performed. Lesion volumes were automatically estimated in four regions in the brain. Lesion volumes correlated significantly with cognitive performance at baseline and at each follow-up. No cognitive decline or change on MRI was detected over the study period.

Piras et al.[28] studied 12 RR MS patients at baseline and at 8.5 years. Patients underwent neuropsychological testing and MRI. LV and cortical and subcortical atrophy were estimated. There was mild cognitive impairment at baseline, and significant worsening at follow-up. There were also apparent changes on MRI; however, these did not correlate with the cognitive decline.

Camp et al.[29] studied a group of 99 PP MS patients over two years. Patients were assessed at 12-month intervals using the BRB of neuropsychological tests. Also, at each assessment the T_1 and T_2 lesion volumes and partial brain volume were estimated. At baseline, there was moderate correlation between T_1 and T_2 lesion volumes and cognitive function. Overall cognitive function did not change over the study period, although results on individual tests showed some decline. There was no correlation between the changes seen on MRI and cognitive function.

Quantitative Magnetic Resonance Imaging Studies of Cognitive Impairment in Multiple Sclerosis

Most conventional MRI studies have used LV as a measure of disease burden, but excluded contribution from MRI-normal-appearing brain tissue (NABT). Studies that estimate tissue loss include NABT, but not exclusively. Quantitative MRI modalities such as magnetisation transfer imaging have been shown to be sensitive to changes even within the NABT, and can therefore be used to assess its contribution directly.

Filippi[30] assessed NABT change using MTR in 19 patients with MS. Neuropsychological testing was performed and patients classified as impaired (n=12) or intact (n=7). Lesions were identified and brain volume estimated. MTR summary statistics were computed within lesions and in the whole NABT by excluding the lesions. In the impaired group the LV was higher, brain volume smaller, lesion MTR lower and NABT MTR lower. A multivariate regression model revealed that MTR of the NABT was the only significant predictor of cognitive function in the impaired group. A similar study methodology was followed by Zivadinov,[31] but focusing on early RR MS. The study involved 63 MS patients and 30 healthy controls. An extensive BNT was administered and 15 patients were found to be impaired. NABT MTR was significantly lower in the patient group, and was lowest in the impaired group. However, lesion volumes did not differ between impaired and intact patients, although there was a trend for reduced MTR in the lesions of the impaired group. Brain volume was also smaller in the impaired group than the intact group. Overall cognitive impairment correlated with both brain volume and NABT MTR, even though these predictors did not correlate with each other.

Recently, diffusion-weighted MRI (DWI) has become a popular research tool in MS. Using an appropriate protocol, diffusion tensor imaging (DTI) can be performed and quantitative metrics that detail the diffusivity *in vivo* computed; these metrics are thought to reflect demyelination. Several studies have now employed this to measure changes in the NABT. Rovaris et al.[32] studied 34 RR MS patients using DTI metrics as well as conventional MRI measures. Patients also underwent an extensive BNT. No significant difference on MRI was detected between cognitively intact and impaired patient groups. However, mean diffusivity of brain tissue and NABT moderately correlated with some cognitive test scores. Benedict et al.[33] performed a similar study on 40 RR MS and 20 SP MS patients. Again, there were moderate correlations between cognitive function and MRI measures. Intact and impaired patients differed in conventional MRI measures, but not in metrics derived from diffusion data.

Sophisticated analysis techniques have been developed that use DWI to estimate orientation of the white-matter fibres. Tractography can then produce stream lines that approximate the path of the fibres through the brain.[34] This scheme has been developed into a method

of mapping voxels belonging to specific tracts.[35] It has recently been suggested by Lin et al.[36] that relating pathology in specific tracts to relevant measures of function may improve correlations; this approach was named importance sampling. In that study the voxels within the CC were identified in 29 RR MS patients. Within the CC diffusion metrics and lesion volumes were measured and related to cognitive function assessed using the PASAT. It was found that while lesion volumes did not correlate with cognitive function, the mean diffusivity did. The same group performed a similar study on 36 RR MS patients, this time measuring the MTR within the CC as well as mean diffusivity; CC area measured on a mid-sagittal slice and LV within the CC were also estimated. Both MTR and mean diffusivity within the CC and the area of the CC correlated with PASAT scores, but again the within-CC LV did not.

Another analysis method specific to DTI is Tract-Based Spatial Statistics (TBSS).[37] This uses the quantitative anisotropy measure derived from the DTI to identify a skeleton image of the white-matter tracts. Using such images, tract-specific group comparisons and correlation between tract-specific measures and clinical measures are possible. Recently, Dineen et al.[38] utilised this method to investigate disconnection as a mechanism for cognitive dysfunction in 37 MS patients with mild impairment. Regional reduction in anisotropy was significantly associated with tests of sustained attention, working memory and processing speed, visual working memory and verbal learning and recall. Statistically significant localisations were found in tracts interconnecting cortical regions thought to be involved in processing in these cognitive domains, or involved possible compensatory processing pathways.

Summary

Conventional MRI has been used to study the relationship between cognitive impairment and LV and/or brain volume (reflecting atrophy). In general, MS-related cognitive dysfunction is shown to relate to lesion burden and tissue loss. Furthermore, it has been demonstrated in longitudinal studies that cognitive decline might be related to changes on MRI. However, results have not always been consistent, and there are several possible explanations for this. First, the cohort of patients varies in terms of disease course between studies. The heterogeneous cohort in some studies might promote correlation compared with those using homogeneous cohorts, due to known differences in MRI measures and in impairment between the different disease courses.

Second, the tests of cognitive function vary considerably between studies. Some studies use an extensive battery of tests, usually with a score summarising the results. Often the summary score does not correlate with dysfunction, yet some of the many individual test scores do; in these cases there is danger of type 1 statistical error, so results need to be repeated to confirm the correlation. In some studies only a single score of cognitive function is available, such as the PASAT or the mental score from the EDSS. While this reduces the risk associated with multiple statistical tests, a single test will probably not encompass the whole domain of cognitive function.

Another major limitation of the conventional MRI studies is the unknown contribution of the NABT to dysfunction, although it is probably included to some extent within studies of brain volume. Quantitative MRI is now feasible on clinical scanners, and can be used to measure changes due to pathology, even within the NABT. Several studies have now shown that changes within the NABT do correlate with cognitive dysfunction; indeed, some studies indicate that these changes are more important than the lesion burden. Inclusion of quantitative imaging therefore seems necessary in future studies. However, even with the inclusion of quantitative imaging, the resulting picture may still be incomplete. Recent evidence from functional MRI studies suggests that cognitive function can be maintained by cortical plasticity.[39,40] This may complicate the relationship between cognitive function and pathology assessed by MRI and, ultimately, limit the correlations. ■

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