Cognitive Impairment in Multiple Sclerosis – Recent Advances and Future Prospects

Dawn Langdon

Clinical Neuropsychologist, and Reader in Neuropsychology, Royal Holloway, University of London

Abstract

Multiple sclerosis (MS) is characterised not only by physical disability but also by gradual cognitive impairment. A large proportion of patients exhibit signs of cognitive deficit that negatively affect their quality of life. Reduced processing speed is often seen with the disease and several tests have been developed to measure its severity, including the Paced Auditory Serial Addition Test (PASAT) and the Symbol Digit Modality Test (SDMT). Long-term memory function is also commonly impaired in MS and studies suggest problems in primary registration of information. Also affected are executive functions used in novel planning and problem-solving. To evaluate cognitive function, cognitive test batteries with varying effectiveness have been introduced. The correlation of cognitive performance with magnetic resonance imaging (MRI) results remains inconsistent as multiple pathologies lead to the observed impairments. Therefore, combinations of MRI data are most successful at predicting deficiencies. The efficacy of current MS treatments in terms of cognition is unclear, making their clinical evaluation a great unmet need; the same is true of universal, validated cognitive measures that can be easily administered to MS patients around the world.

Keywords

Multiple sclerosis, cognitive impairment, memory loss, executive functions, cognitive test batteries, rivastigmine

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Correspondence: Dawn Langdon, Department of Psychology, Royal Holloway, University of London, Egham, Surrey, TW20 0EX, UK. E: D.Langdon@rhul.ac.uk

The Extent of Cognitive Impairment in Multiple Sclerosis

In his original characterisation of multiple sclerosis (MS), Jean Martin Charcot noted a loss of memory and reduced understanding,[1] but this wisdom was overlooked for a century. It is only since the early 1980s that cognitive impairment in MS has begun to be scientifically investigated and understood.[2]

In part this may be because reduced functioning in the context of complex physical disability may seem reasonably attributable to physical impairments. In addition, the typical pattern of cognitive deficits in MS, with intact language masking inefficiencies in concentration, memory and reasoning, may escape casual (or even clinical) observation.

The prevalence of cognitive impairment in large heterogeneous groups of MS patients has been demonstrated by formal psychometric assessment to be 43–70%, with the higher prevalence rates from clinic samples.[3] Cognitive impairment has been reported at all stages and in all subtypes of the disease. In the comparative study by Potagas et al., the cognitive impairment prevalence rates were 27.3% in clinically isolated syndrome (CIS), 40.0% in relapsing–remitting MS (RRMS), 56.5% in primary progressive MS (PPMS) and 82.8% in secondary progressive MS (SPMS).[4] A cognitive impairment prevalence of 45% has been demonstrated in benign MS.[5] Cognitive impairment tends to progress over time, but rarely in the space of a few years.[6]

The Impact of Cognitive Impairment in Multiple Sclerosis

Cognitive impairment has been shown to have an adverse effect on the lives of people with MS, over and above that imposed by their physical impairments. Cognitive impairment leads to reduced employment, social function,[7] physical independence, sexual function,[8] progress in rehabilitation,[9] everyday life activities,[10] safety in driving[11] and adherence to medication.[12] Poorer self-reported scores on formal measures of quality of life have also been linked to cognitive status. Reduced information-processing speed has been associated with lower quality of life.[13]

However, in one study of patients with advanced disease, more intact autobiographical memory was associated with lower quality of life.[14] This suggests that once patients enter the stage of significant physical dependence, the clear comparison with previous independence afforded by intact memory and other cognitive function results in greater awareness of the deterioration of their condition, resulting in a more negative assessment of current quality of life.

Cognitive Impairment Profile

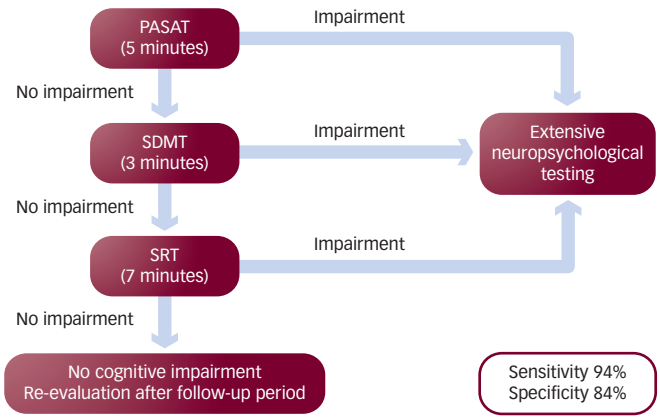
There is increasing (but not yet universal) agreement that reduced processing speed is the fundamental cognitive deficit in MS.[15] Processing speed affects the ability to maintain and manipulate information (working memory).[16,17] Processing speed and working memory are the cognitive processes most likely to be affected in MS.[18]

Table 1: Tests Used in the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS)

Neuropsychological Test	Cognitive Domain	Administration Time (minutes)
SDMT (Rao, 1981; Smith, 1982)	Processing speed and working memory	5
BVMT-R (Benedict, 1997)	Visual/spatial learning and memory	10
PASAT (Gronwall, 1977)	Processing speed and working memory	10
CVLT-II (Delis et al., 2000)	Auditory/verbal learning and memory	25
DKEFS – Sorting Test (Delis, 2001)	Executive function	25
JLOT (Benton, 1994)	Visual/spatial perception	10
COWAT (Benton, 1989)	Language and other domains, verbal fluency	5

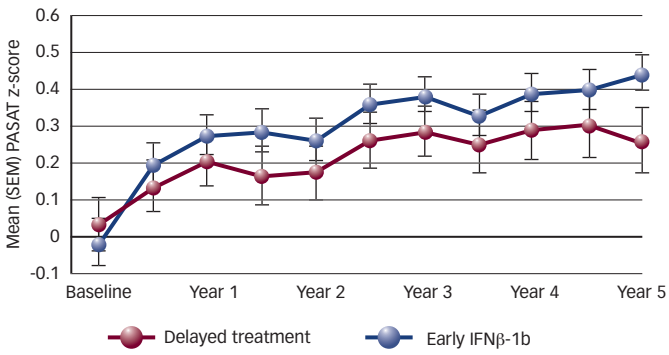
BVMT-R = Brief Visuospatial Memory Test (Revised); COWAT = Controlled Oral Word Association Test; CVLT-II = California Verbal Learning Test II; DKEFS = Delis-Kaplan Executive Function System; JLOT = Benton Judgement of Line Orientation Test; PASAT = Paced Auditory Serial Addition Test; SDMT = Symbol Digit Modalities Test.
Source: Benedict et al., 2002.[35]

Figure 1: Potential Shorter Assessment Strategies for Cognitive Impairment in Multiple Sclerosis



PASAT = Paced Auditory Serial Addition Test; SDMT = Symbol Digit Modalities Test; SRT = Selective Reminding Test.
Source: Portaccio et al., 2009.[37]

Figure 2: Early and Late Treatment with IFNβ-1b in the BENEFIT Study (Five-year Data) Showed Significant Differences in PASAT Z-scores of Cognitive Function*



**p=0.005 by non-parametric analysis of co-variance.*
Higher scores indicate better performance.
IFN = interferon; PASAT = Paced Auditory Serial Addition Test; SEM = standard error of mean.
Source: Kappos et al., 2009.[46]

There are two cognitive tests of complex attention that are time-dependent and are widely used in MS. The first is the Paced Auditory Serial Addition Test (PASAT), which requires the testee to listen to a string of pseudo-randomly ordered single digits presented aurally at the rate of one every three (or, in the harder version, two) seconds. The testee must add up the last two numbers heard and say the correct total before the next stimulus number is delivered. A sensitivity of 74% and specificity of 65% have been reported for the PASAT.[19] The second is the Symbol Digit Modality Test (SDMT), which presents the testee with nine simple abstract shapes as a 'key', each paired with a single digit. Below these shapes, the testee sees rows of the same nine abstract shapes in a random order. The testee must call out the correct number for each shape, looking along each row of shapes systematically, completing as many as possible within 90 seconds. A sensitivity of 82% and specificity of 60% have been reported for the SDMT.[20] The SDMT has been shown to be reliable when administered by nursing staff over several months.[21]

The PASAT is more demanding than the SDMT for both the testee and the tester. The two tests have been directly compared as part of the Multiple Sclerosis Functional Composite (MSFC), a brief assessment designed to 'sample' cognition (originally incorporating the PASAT), upper limb function and walking to produce an index of an MS patient's ability.[22] The results have been inconclusive.[23,24] There is some evidence that the SDMT may be less susceptible to practice effects than the PASAT.[21,25]

Long-term memory function is also commonly impaired in MS. Previous work pointed to a primary retrieval deficit rather than a problem with learning the information.[26] However, the primary registration of information has now been identified as the core deficit.[27] Verbal memory is normally assessed by a word list learning task. A frequently used verbal memory assessment is the California Verbal Learning Test-II (CVLT-II).[28] As far as individual-specific information is concerned, MS deficits in memory of episodic autobiographical incidents have been reported to be greater than deficits in memory of personal semantic information (the general facts, meanings and understanding we have about ourselves).[29]

Executive functions are complex cognitive processes that deal with novelty, are involved with planning and problem-solving and are crucial to goal-directed behaviour. Studies of people with MS have often shown them to be poor on tests of problem-solving, particularly when flexibility is required. A community sample of MS patients in New Zealand demonstrated a variable range of executive dysfunction, with most exhibiting impairment in some executive aspects.[30] The most frequently (and conveniently) tested aspect of executive function is verbal fluency. Phonemic and semantic fluency tests have been shown to be equally effective in MS.[31] Executive functions are clearly involved in complex decision-making, but decline over time in a standardised decision-making task occurred independently of other cognitive test scores.[32]

Cognitive Test Batteries

There are a range of cognitive test batteries used for assessing cognition in MS, mainly in research studies. The Brief Repeatable Battery of Neuropsychological Tests (BRB-N)[33] is a set of tests of short duration (30 minutes) with a sensitivity of 71% and specificity of 94%. The battery comprises the SDMT, the PASAT, the Selective

Reminding Test (SRT), the 10/36 Spatial Recall Test and the Controlled Oral Word Association Test (COWAT). Reliability for the individual tests has been reported as adequate to good over 18-month intervals, with moderate practice effects for most tests (using versions A and B alternately).[34] The Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) test battery was developed by a consensus committee in 2001 and contains 36 measures of the five key cognition domains.[35] It is reasonably short (90 minutes) and easily conducted, and it has good test–re-test reliability. The tests included in MACFIMS are given in *Table 1*. A study tested the validity of MACFIMS in 291 patients and 56 control patients; the parameters SDMT and Brief Visuospatial Memory Test—Revised (BVMT-R) were the most effective for discriminating between MS patients and controls and for identifying cognitively impaired MS patients.[18]

The BRB-N and MACFIMS have many tests in common and, unsurprisingly, were found to have comparable sensitivity when directly compared.[36] However, the BVMT-R (a component of MACFIMS) appeared more sensitive than the corresponding 10/36 Spatial Recall Test (a component of BRB-N). A short version of the BRB-N has been proposed, utilising only the PASAT, SDMT and SRT; an initial study reported a sensitivity of 94% and specificity of 84% (see *Figure 1*).[37] Cognitive assessment remains an expensive and time-consuming investigation that requires expert input.

Relation of Cognition to Magnetic Resonance Imaging Variables

Cognitive performance on psychometric tests is only moderately correlated with T_2 lesion load and cortical atrophy.[38] This may be because plaques in the white matter are only part of the cerebral pathology that disrupts cognition. Axons are damaged and lost, affecting nerve conduction. In grey matter, MS pathology results in loss of synapses and cell bodies, which also affects cognition. Axonal loss is recognised as an increasingly early aspect of pathology.[39] These multiple pathologies, not all evident on conventional magnetic resonance imaging (MRI), may explain why combinations of MRI variables have proved the most successful at predicting cognitive impairment.

Cortical lesion volume and neocortical grey matter volume have been reported as independent predictors of cognitive impairment.[40] Neocortical grey matter loss over time has also been linked to cognitive deterioration.[41] Intriguingly, PASAT performance has been directly linked to gadolinium enhancement, seeming to confirm that the PASAT is especially sensitive to inflammation.[42] There is also growing evidence for a gene–cognition link in MS, which may explain the mechanisms of how the pathology relates to cognitive performance.[43]

Treatment

The efficacy of conventional disease-modifying treatment on cognition remains largely unclear.[44] There is some evidence for a treatment effect of interferon-beta 1a (IFNβ-1a) on cognition, but the randomised controlled trial was stopped early, making secure interpretation of results difficult.[45]

Cognitive assessments were made in the BENEFIT trial, comparing early versus late start of IFNβ-1b in 468 initially CIS patients.[46] PASAT z-scores were significantly better at three and five years (p=0.005) for the earlier treatment group (see *Figure 2*). Unfortunately, the early promise of some symptomatic treatments does not seem to have held up in large multicentre studies.[47] Rivastigmine has been shown to change functional MRI (fMRI) activation, which is thought to represent improved cognitive processing, but no improvement in cognitive performance was demonstrated in this small study.[48] Rivastigmine has also been shown to improve short-latency afferent inhibition, a cortical phenomenon assessed by transcranial magnetic stimulation.[49] However, a single-centre randomised controlled trial failed to show a treatment effect of rivastigmine on cognition in RRMS.[50] The evidence base for cognitive rehabilitation resulting from treatment in MS remains at an early stage.[51]

Future Prospects

There is a need for validated cognitive measures that can be used in different cultures and countries to facilitate clinical assessment of cognition and to provide advice, treatment where appropriate and management for all people with MS. There is also a need for a standardised, validated and feasible MS cognitive screen that can be used in primary settings, where access to neuropsychological expertise may be lacking and available time may be short. There also needs to be scientific evaluation of the efficacy of some of the newer treatment agents on MS cognition. ■

Dawn Langdon is a Clinical Neuropsychologist and a Reader in Neuropsychology at Royal Holloway, University of London. She is neuropsychology lead on a number of multinational trials. Her research work centres on psychological aspects of multiple sclerosis (MS), and current projects include the efficacy of medication in protecting cognition, cognitive rehabilitation, cognitive profiles in clinically isolated syndrome (CIS) and early MS and cognition in the later stages of MS, including its relation to early disease status. Dr Langdon is a frequent contributor to international scientific meetings and committees and is a Trustee of the UK MS Trust, with whom she has authored the MS cognition website (www.stayingsmart.org.uk). Dr Langdon completed her training as a clinical psychologist at Oxford University and the Institute of Psychiatry, London. She worked as a clinical neuropsychologist at the National Hospital, Queen Square, London for 16 years, obtaining a PhD on reasoning in organic brain syndromes, and is registered as both a neuropsychologist and a health psychologist.

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