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Cognitive Dysfunction in Multiple Sclerosis

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Neuropsychological studies have provided evidence of disease-based cognitive loss in a substantial number of patients with MS. Among volunteer patients from the general community or patients with recently diagnosed or mild MS, the frequency of cognitive impairment is 30–40%[1–3]. Among patients attending an MS clinic the frequency is roughly 60%[4]. These cognitive deficits are often not appreciated or addressed by the treating physician, and sometimes go unrecognized even by the patients themselves[5,6]. However, they can have a significant impact on the lives of the patients and their family members[7–11]. Cognitive changes are a primary cause of early departure from the workforce. In addition, cognitive changes can impact a person's self-esteem and self-confidence, and interfere with communication and interpersonal relationships.

COGNITIVE FUNCTIONS AFFECTED BY MS

MS is a disease that impacts the brain in many different ways, including the hallmark demyelinating lesions in the central nervous system (CNS), less visible but equally important types of injury to myelin and axonal fibers, ventricular enlargement, and atrophy of whole brain as well as specific tissue compartments such as the mesial temporal lobe, thalamus, and deep gray matter structures [12–16]. As a result, there is wide variation in degree and type of cognitive impairment among MS patients[17–19]. Some people are not affected at all while others are severely impaired. Some have primarily memory impairment, and others have marked slowness of mental processing speed. In large sample studies examining the profile of cognitive impairment in MS[2–4], slowed processing speed and memory are the most commonly affected functions, followed closely by impairment in executive function and visual/spatial processing. Below are some examples of what these deficits imply in a functional sense:

- **Memory impairment:** difficulty learning new information, remembering recent conversations or tasks to be done, following book or movie plots, keeping appointments.
- **Slowed information processing speed:** difficulty keeping up with conversations and processing incoming information, particularly when it is coming from multiple sources at the same time; difficulty with multi-tasking; thinking feels slowed.

- **Impaired executive function:** difficulty with organization, planning and prioritizing, sequencing, and abstract reasoning.
- **Visual/spatial processing:** difficulty with right-left orientation, reading maps and diagrams, navigating in familiar or unfamiliar places.

Cognitive impairment is difficult to predict on the basis of clinical indicators[17]. In general, relapse rate and neurologic disability as measured by the Expanded Disability Status Scale (EDSS) are poor predictors of the degree of cognitive dysfunction. Patients may be mildly affected physically but present with significant cognitive dysfunction. The converse is also true—some patients are severely physically disabled and yet neuropsychologically intact. Research has shown, however, that patients with a secondary-progressive course are more likely to be cognitively impaired, and there is also some evidence suggesting that male MS patients and those with less education or lower baseline intelligence are at higher risk for cognitive decline.

COGNITIVE FUNCTION AND BRAIN MRI IN MS

Association between cognitive impairment and white matter lesion burden is well established[19,20]. Better correlation is achieved, however, when neuropsychological tests are measured against amount of volume decrease (atrophy) of the whole brain[22] or of specific brain regions such as the deep gray matter[13] , corpus callosum[23], cerebral cortex[24–25], mesial temporal lobe[26,27], and even specific sub-regions of the cortex[28]. These measures of brain atrophy are thought to be markers of the most destructive aspects of MS pathology[29]. In general, brain volume correlates better with cognitive performance than lesion volume, both in cross-sectional[20] and longitudinal[30] studies.

In addition to studies of brain volume, recent studies using double inversion recovery and phase-sensitive inversion recovery sequences have shown an increase of cortical lesions over time that correlates with impairment on neuropsychological testing[31,32]. Abnormalities in the normal-appearing white matter are known to contribute to cognitive impairment in MS patients. These kinds of subtle abnormalities can be observed with quantitative MRI techniques such as magnetization transfer imaging, diffusion tensor imaging, and proton MR spectroscopy[33]. These techniques reveal pathology that is also correlated with impairment on cognitive testing in MS[34–41]. Thus, different aspects of MS-related brain pathology as seen on brain MRI influence mental abilities in MS. Damage to white matter tracts impairs cognitive functions that rely on rapid transfer of information, while degeneration of neurons in the gray matter affects a wide range of cognitive functions ranging from mental speed to memory and executive function.

ASSESSMENT OF COGNITIVE IMPAIRMENT IN MS

Given the heterogeneity of cerebral pathology in MS, it is of no surprise to learn that there is no single, brief test that is sufficiently sensitive to screen for cognitive impairment in this disease[42,43]. Fortunately, research has identified two relatively brief neuropsychological batteries that are useful in monitoring cognitive function in MS. Both are validated and have reached a threshold of wide acceptance and replicability: the Rao Brief Repeatable Neuropsychological Battery (BRNB) [44] and

TABLE 1
Neuropsychological Tests Included in the BRNB and MACFIMS

Rao BRNB	Cognitive Domain	MACFIMS
PASAT	Auditory Processing Speed and Working Memory	PASAT
SDMT	Visual Processing Speed and Working Memory	SDMT
SRT	Auditory/Verbal Episodic Memory	CVLT2
10/36	Visual/Spatial Episodic Memory	BVMTR
COWAT	Expressive Language	COWAT
	Spatial Processing	JLO
	Executive Function	DKEFS Sorting

SDMT = Symbol Digit Modalities Test; PASAT = Paced Auditory Serial Addition Test; SRT = Selective Reminding Test; CVLT2 = California Verbal Learning Test, second edition; 10/36 = 10/36 Spatial Recall Test; BVMTR = Brief Visuospatial Memory Test—Revised; COWAT = Controlled Oral Word Association Test; JLO = Judgment of Line Orientation; DKEFS = Delis-Kaplan Executive Function System.

the Minimal Assessment of Cognitive Function in MS (MACFIMS)[4,45]. The tests from each battery are listed in Table 1.

As can be seen, there is considerable overlap between these batteries. Yet there are some subtle advantages to each approach. The BRNB requires less time and has been translated into multiple European languages. The MACFIMS has a stronger psychometric foundation and includes assessment of spatial processing and higher executive function abilities. The batteries were recently compared psychometrically by Strober, Rao and Benedict[46].

Both the BRNB and the MACFIMS include the Symbol Digit Modalities Test (SDMT)[47] which measures visual processing speed. This is a traditional, person-administered test that requires only five minutes and can be combined with motor tests to form a reliable version of the Multiple Sclerosis Functional Composite (MSFC)[48]. The SDMT is also among the more reliable and sensitive[42] tests in the MS literature and despite its brevity is probably the most robust correlate of abnormal brain MRI in MS studies[6,13,25,49–53].

TREATMENT AND MANAGEMENT OF COGNITIVE LOSS IN MS

Data are limited regarding the effects of immunomodulating agents on cognitive dysfunction as studies have not employed neuropsychological tests as primary outcomes. However, clinical trials have suggested that such disease modifying therapies do improve some aspects of cognition, as would be expected[54,55].

TABLE 2
Summary of Symptomatic Medication Studies

	Drug	No. of Treated Pts.	Findings	Comment
Giesler 1996[59]	Amantadine Pemoline	16	––	Trend observed favoring amantadine showing positive effects on SDMT
Wilken 2008[60]	Modafinil	23	++	No placebo control Unclear analysis No control for multiple comparison s
Harel 2009[55]	Methylphenidate	14	++	Single dose Trt Grp↑ at baseline
Benedict 2008[57]	l-Amphetamine	19	++	Treated n = 19 Single dose
Morrow 2009[58]	l-Amphetamine	108	––	Positive effects seen on tests of episodic memory, which were secondary outcomes
Krupp 2004[61]	Donepezil	35	++	Groups differ on disease course
Shaygannejad 2008[62]	Rivastigmine	30	––	Poor design Insensitive outcome measure Differences on baseline NP testing Differences in education level
Krupp 2011[63]	Donepezil	61	––	Groups differ on disease course

Another avenue for treating cognitive disorders in MS patients are the emerging medications for clinical symptoms. Some of this research is summarized in Table 2. Psycho-stimulants present an opportunity for adjunctive symptomatic therapy for MS-associated inattention or slowed information processing. Two studies, examining the effects of methylphenidate [56] and l-amphetamine[57], showed positive effects on cognitive testing when the tests were administered shortly after drug administration. However, the effects of the latter on processing speed tests were not replicated in a large sample study of daily 30 mg dose (of note: there were positive effects on tests of episodic memory but as these tests were secondary outcomes, the significance of this observation is unclear)[58].

Two, well designed, placebo-controlled studies of acetyl-cholinesterase inhibitors have been conducted with MS patients. Krupp and colleagues[61] examined the effects of donepezil over 24 weeks. While there were a few methodological shortcomings (e.g., small sample, treatment groups not matched on disease course) positive effects favoring the active arm of the study were seen on an adapted version of the Selective Reminding Test and a clinician impression of change. However,

these findings were not replicated in a study examining the effects of a similar medication, rivastigmine[62], or in a follow-up study with donepezil[63].

Cognitive rehabilitation has rarely been examined in MS patients. As noted in recent reviews of this emerging literature[64,65], the findings are mixed on the efficacy of cognitive rehabilitation in MS. O'Brien et al. critically reviewed the literature and found very few studies that used methodology that would yield reliable conclusions. A large proportion of these studies have been poorly controlled. On exception may be a study by Chiaravalloti et al. examining the effects of an internal, compensatory strategy for verbal learning[66]. This work is based on the idea that impaired verbal learning in MS[67] is primarily related to impairment of efficient encoding of new information.

Overall, the best management approach at this point appears to be to recognize and diagnose cognitive loss early, and to provide appropriate support and consultation for patients and families in order to minimize the psychological, social and vocational impact. If the problem is ignored, the result can be calamitous. That being said, there is no definitive treatment for cognitive loss in MS. Therefore, while a number of interventions can be tried, the needs and specifications for each patient are likely to be unique. The family plays an important role, both in diagnosis and management. The steady support of family members is key in assisting the patient's process of acceptance and in facing any social or vocational role changes that occur. Referrals to neuropsychologists for comprehensive assessment can be helpful in many cases, particularly if the individual is experiencing challenges at work or is applying for Society Security Disability (cognitive changes being one of the four recognized criteria for disability in MS). Some occupational therapists and speech/language pathologists also provide assessment and treatment of cognitive dysfunction in people with MS, focusing on compensatory strategies to deal with any changes or losses that have occurred.

TIPS FOR CLINICIANS

- A person's cognitive impairment can be significant enough to interfere with everyday activities without being apparent to you during a brief office visit; it is important not to base your assessment of the person's cognitive status on her or his physical status.
- Patients may or may not mention their cognitive challenges; it is helpful and appropriate to ask if they are experiencing any, as that will help guide your work with them.
- Patients with MS may have difficulty remembering their appointments or arriving on time for them; reminders are extremely helpful.
- Providing instructions in written form as well as orally can help to improve treatment adherence.
- Patients may ask to bring a tape recorder to their appointment so that they can review their conversation with you, or bring a relative or friend to help them remember the important information.

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RECOMMENDED READING

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