Cognitive Impairment in Multiple Sclerosis: Historical Aspects, Current Status, and Beyond

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ABSTRACT

Although the cognitive symptoms of multiple sclerosis (MS) were acknowledged in the 1800s, until the latter part of the 20th century, these symptoms were poorly recognized. Cognitive impairment associated with MS has a profound impact on many aspects of daily life, including employment, academic life, and social functioning. The cognitive reserve can be protected in MS patients to a certain limit, and prevention might

be linked to early treatment. The analyses of historical and contemporary data can help researchers gain a clear vision of the direction in which to proceed in the future for better insight into cognitive issues in MS.

Keywords: Cognitive symptoms, multiple sclerosis, impairment

INTRODUCTION

Multiple sclerosis (MS) is characterized not only by physical disability but also by gradual cognitive impairment (1). In his original description of MS, Jean Martin Charcot, the father of modern neurology (2), noted loss of memory and reduced understanding (1). In 1877, Charcot observed that people with MS might show “marked enfeeblement of the memory, conceptions are formed slowly, and intellectual and emotional faculties are blunted in their totality” (3).

Although the observation of cognitive dysfunction in MS patients can be traced back to Charcot, this wisdom was historically underappreciated, and another 100 years passed before researchers began to systematically investigate the frequency, nature, and correlates of these deficits (4). According to Langdon (1), cognitive impairment in MS was first scientifically investigated and understood in the early 1980s (1).

In a broad review of cognitive dysfunction in MS, Amato and Zipoli (5) underlined that cognitive dysfunction, as with other symptoms of MS, is highly variable based on estimations of its frequency ranging from 43% to 72% (5). Several authors who reported on the prevalence of cognitive dysfunction in MS gave similar numbers, suggesting that up to 70% of MS patients suffer from cognitive dysfunction during the course of their disease (1,4,6,7).

Cognitive dysfunction has been shown to have an adverse effect on the lives of people with MS and eventually leads to reduced employment, social function, physical independence, sexual dysfunction, limitation of everyday life activities, and lower quality of life (1); increasing attention has been devoted to this important topic, with a publication rate that has grown accordingly from a dozen articles in 1990 to over 200 papers currently (4). The present paper aims to provide an overview of our current understanding of cognitive dysfunction in MS. The methods of assessment for the early detection of cognitive issues during the course of the disease, available methods for the management of cognitive dysfunction in MS, and future prospects will be discussed.

“DEEP IMPACT” OF COGNITIVE IMPAIRMENT

The neuropsychological (NP) pattern of cognitive impairment in MS is depicted in Figure 1 (8). During the course of MS, cognitive function tends to decline over time, and impairments are unlikely to improve or resolve. Cognitive symptoms have not been conclusively linked to physical disability levels, but they may be indicative of disease progression despite stable physical symptoms (6). According to Langdon (1), the most commonly impaired domains of cognitive function are episodic memory, attention/concentration, processing speed, and verbal fluency (1). Furthermore, domains involving executive functions such as concept formation, abstract reasoning, planning, monitoring, and visual perception might often be compromised. Because cognitive dysfunction can have a dramatic impact on several aspects of the quality of life and is independent of the degree of physical disability (5), it significantly affects the ability to maintain employment; further, cognitively impaired patients require greater assistance with daily living activities and are less likely to socialize than cognitively intact MS patients.

The deep impact of cognitive impairment is often more frequent and more dramatic in children with MS than in adults; it can also severely impact the development of academic skills in this population, which may leave them disadvantaged in comparison to their healthy peers (6).

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The frequency of cognitive dysfunction in MS and its severity and impact on everyday functioning leads to an increasing consensus that neuropsychiatric assessment should accompany neurological examination and become a factor in therapeutic decision-making (5). Thus, the demand for an efficient, fast, reliable, and patient-friendly method of assessment is evident.

ASSESSMENT TOOLS OF COGNITIVE IMPAIRMENT IN MS

Multiple sclerosis patients often underestimate their deficits because of memory impairment or overestimate them due to depression. It is therefore difficult to evaluate the cognitive status of an MS patient without a formal NP assessment. Because it is impractical to refer all MS patients in clinical practice for comprehensive NP evaluation, clinicians should have a brief, cost-effective, and reliable NP screening test at their disposal (5).

The benchmark for the specific assessment of cognitive function in MS patients has been the comprehensive NP assessment battery. Unfortunately,

comprehensive NP testing can be expensive and rather lengthy. Thus, the main goal of MS cognitive assessment work over the last several years has been the development of shorter batteries for screening. These batteries focus on cognitive dysfunction associated with subcortical disease (7).

The batteries highlighted in Table 1 reflect three of the main schools of thought regarding the screening of MS patients for cognitive dysfunction: (1) short screening with traditional measures in a neurologist's office, (2) testing by a neuropsychologist with a minimal (but comprehensive) neurocognitive battery, and (3) testing with automated, computerized measures in a neurologist's office or as a part of a clinical trial (7).

The Brief Repeatable Battery of Neuropsychological Tests (BRB-N), proposed by Rao et al. (9), was designed for use by non-neurologists and can be administered and scored in a neurologist's office (7,9). Some researchers have added the Symbol Digit Modalities Test (SDMT) to the BRB-N, which originally included the Buschke Selective Reminding Test, 7/24 Spatial Recall Test, Paced Auditory Serial Addition Test (PASAT), and the Controlled Oral Word Association Test (7). Because PASAT is more demanding than SDMT for both the testee and tester (1) and the validity coefficients calculated using SDMT and PASAT are roughly equivalent, it has recently been proposed that PASAT be replaced with SDMT (10).

The Minimal Assessment of Cognitive Function in MS is a somewhat longer battery, which can be administered in approximately 90 min, and it covers major MS cognitive deficits, including processing speed, working memory, learning and memory, executive functioning, visuospatial processing, and word retrieval. The Automated Neuropsychological Assessment Metrics (ANAM) battery is used in the computerized screening battery (7). Because ANAM is automated, Wallin et al. (7) suggested that a patient can complete testing with only the assistance of a test administrator; the results, however, still require interpretation by a neuropsychologist (7).

Mendes et al. (11) reported on four cases of severe cognitive impairment in the early stages of MS, with results from NP tests and magnetic resonance imaging (MRI). The atypical presentation of MS in these cases led

Figure 1. Neuropsychological pattern, affected domains and percentage of impairment in cognitive dysfunction in multiple sclerosis (8)

Table 1. Major approaches of assessment for cognitive dysfunction screening in multiple sclerosis patients (7)

Screening battery	Component tests	Cognitive domain assessed
Brief Repeatable Battery of Neuropsychological Tests	Buschke Selective Reminding Test 7/24 Spatial Recall Test PASAT COWAT SDMT	Verbal learning and memory Visual learning and memory Working memory and resistance to interference Verbal fluency and word retrieval Processing speed and working memory
Minimal Assessment of Cognitive Function in Multiple Sclerosis	PASAT (1) SDMT California Verbal Learning Test-II Brief Visuospatial Memory Test-Revised Delis-Kaplan Executive Function System Judgment of Line Orientation COWAT	Working memory and resistance to interference Processing speed and working memory Verbal learning and memory Visual learning and memory Executive functioning and problem solving Visuospatial processing Verbal fluency and word retrieval
Automated Neuropsychological Assessment Metrics	Simple Reaction Time Procedural Reaction Time Code Substitution Code Substitution Delay Running Memory: Continuous Performance Test Math Processing Sternberg Memory Search Logical Relations Finger Tapping	Psychomotor speed Choice reaction time Processing speed and working memory Memory Processing speed and working memory Mental calculations Memory Problem solving and reasoning Motor speed

PASAT: Paced Auditory Serial Addition Test; COWAT: Controlled Oral Word Association Test; Symbol Digit Modalities Test

the investigators to proceed with extensive NP testing, which included the Mini-Mental State Examination, as well as cortical function tests for memory, praxia, speech, and gnosis (11). Based on a study of 47 benign MS patients, Amato et al. (12) underlined that cognitive assessment added to quantitative magnetic resonance metrics can help identify benign MS (12). Furthermore, in a study of 63 patients with benign MS, to assess whether NP tests and MRI measures could be used as predictors of short-term disease evolution, Portaccio et al. (13) found that cognitive assessment could predict short-term disease evolution in the studied patients (13).

In the recommendations for a Brief International Cognitive Assessment for MS (BICAMS), the requirements of an assessment method are summarised as not time-consuming (not more than 15 min) and demanding neither specific equipments nor specific assessor training (14). Based on the above criteria, BICAMS comprises the following tests: SDMT, the California Verbal Learning Test, and the Brief Visuospatial Memory Test (14). The cognitive assessment of MS patients remains an expensive and time-consuming investigation that requires expert input. According to Langdon et al. (14), an international validation protocol for BICAMS is under development; it is envisaged that over time, many nations will be able to utilize BICAMS as part of routine clinical MS practice, referring to appropriate national norms. Potential shorter assessment strategies for cognitive impairment in MS are outlined in Figure 2 (14).

COGNITIVE RESERVE: A NEW HOPE?

The idea of reserve against brain damage stems from the repeated observation that there does not appear to be a direct relationship between the degree of brain pathology or brain damage and the clinical manifestation of that damage (15). Thus, based on the conceptual suggestion by Stern (15), cognitive reserve (CR) can be defined as the degree of spare cognitive capacity available to protect against the effects of disease or trauma to the brain (15). According to Arnett (16), individuals with more CRs are theorized to be less likely to show cognitive changes associated with neurological change (16). Stern et al. (17) proposed a that higher neural reserve is implemented in the form of brain networks that are either more efficient or have greater capacity in the face of increased demand (17). Based on medical, neurological, psychiatric, and NP evaluations of 17 healthy older and 20 healthy younger adults, Stern et al. (17) hypothesized that individuals who possess more efficient or higher capacity brain networks are able to withstand a greater degree of age-related change while maintaining intact functioning (17).

In a recent study of 62 patients (30 women) with definite MS, Sumowski et al. (18) provided evidence of brain reserve (BR) in MS and showed that CR independently protects against disease-related cognitive decline over and above BR (18). After testing the BR hypothesis in MS by examining whether larger maximal lifetime brain volume (MLBV) protects against disease-related cognitive impairment and then investigating whether CR gained through life experience protects against cognitive decline independently of MLBV (BR), Sumowski et al. (18) concluded that a larger MLBV moderated/attenuated the negative impact of disease burden on the cognitive status, thereby supporting the BR hypothesis in MS. As emphasized by Sumowski et al. (18), early-life intellectual enrichment (CR) protects patients from disease-related cognitive impairment independently of MLBV (BR), thereby supporting the independent role of enriching experiences in protecting against cognitive decline (Figure 3) (18). Enhancing CR could thus be implemented at an early stage of the disease, when the impact of the disease on the brain is typically lower and when such interventions would likely be most effective (16).

COGNITIVE DYSFUNCTION AND POTENTIAL BENEFITS OF EXERCISE IN MS

In a 6-month study of 59 elderly (60–79 years) and 20 younger (18–30 years) neurologically intact adults, Colcombe et al. (19) found significant increases in brain volume in both the gray and white matter regions as a function of fitness training for older adults who participated in aerobic fitness

training. They suggested that cardiovascular fitness is associated with the sparing of brain tissue in aging humans and hypothesized a strong biological basis for the role of aerobic fitness in maintaining and enhancing central nervous system health and cognitive functioning in older adults (19).

Based on gerontology literature, which suggests that exercise training in older adults with or without dementia leads to cognitive improvement relative to a control condition (4,19), potential cognitive benefits of exercise can also be assumed for MS patients. The body of research on exercise, cognition, and brain MRI in gerontology is sufficiently strong to encourage the systematic examination of exercise training and cognition in MS (20). It is reasonable to suggest that better aerobic fitness is associated with cognitive capacity and brain structure and function in MS; however, further studies are needed to maximize the likelihood of association between exercise training and cognition that can ultimately have a demonstrable impact on the lives of MS patients, as suggested by Motl et al. (20).

COGIMUS STUDY: BEFORE AND BEYOND

The decline in physical ability in MS is not reversible, meaning that what is lost is not regained. Thus, an effective treatment for MS-related cognitive impairment needs to improve or maintain not only cognitive test performance but also psychosocial functioning (6). To increase our knowledge, screening tests for cognitive assessments should be incorporated into future clinical studies to determine the cognitive effects of therapy. According to Patti (6), data from studies of disease modifying drugs (DMDs), symptomatic therapies, and cognitive rehabilitation provide evidence to support that most DMDs can protect against cognitive decline in MS patients (6). In a recent observational study of 550 patients (18–50 years) with relapsing-remitting MS, Bastianello et al. (21) found that subcutaneous IFN β -1a significantly decreased MRI measures of the disease, with a significant benefit shown for the 44- μ g dose over the 22- μ g dose. Furthermore, Bastianello et al. (21) provided evidence suggesting that higher-dose treatment also predicted better cognitive outcomes over three years (21). Cognitive impairment associated with MS has a profound impact on many aspects of daily life, including employment, education (particularly for children), and social functioning (6). Based on available evidence (16,18), we suppose that CR can be protected in MS patients to a certain limit and that prevention is found to be linked to early treatment. Although we cannot change BR, we can change CR. Because most studies with drug-modifying therapies suggest at least some positive effects, it is reasonable to suggest that early treatment is more effective for preserving intact cognitive functioning. A few studies show positive effects of rehabilitation on the cognitive functioning of MS patients. Cognitive rehabilitation is an option in clinical practice; however, more rigorous proof-of-concept studies are needed to develop standards and guidelines. Science once made the mistake of not remembering what the pioneers of MS first learned about cognitive deficits, much to the disadvan-

Figure 3. a, b. Independent protection afforded by the cognitive reserve over and the above brain reserve. Graphical depiction of (a) the positive correlation between early-life cognitive leisure (cognitive reserve) and overall cognitive status and (b) the interaction between early-life cognitive leisure and T2 lesion load, whereby greater engagement in cognitive leisure moderates the negative impact of T2 lesion load on cognitive status. These results demonstrate the independent protection afforded by cognitive reserve over and above the brain reserve (intracranial volume) (18)

tage of MS patients (22). The analyses of historical and contemporary data can help researchers gain a clear vision of the direction in which to proceed in the future for better insight into cognitive issues in MS.

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