Cognitive Dysfunction in Multiple Sclerosis New Frontiers in Assessment and Treatment

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Guest Editors

This issue of the IJMSC is dedicated to an important and too often overlooked aspect of clinical disability in multiple sclerosis (MS). Cognitive dysfunction is one of several impairments faced by people with MS, but it is the most significant domain affecting work capacity,¹ and it has marked impacts on success in treatment,² future neurologic status,³ and caregiver distress.⁴ Some noteworthy developments led to a burgeoning of interest in the topic over the past 10 to 15 years. First, consensus has developed regarding the best methods for measuring cognitive function in MS.⁵⁻⁸ Second, the rapid expansion of sensitive brain magnetic resonance imaging (MRI) metrics has led to a greater understanding of how defects detected by these neuropsychological tests are related to different forms of cerebral pathology in MS.⁹ Finally, with some promising behavioral and pharmacologic treatment studies,¹⁰⁻¹⁵ we are slowly emerging from the state of the literature characterized by the oft-uttered question, “Why evaluate cognition in MS patients, since there is nothing to do about it anyway?”

This issue highlights some innovative, if preliminary, approaches to the assessment and management of cognitive dysfunction in MS. The need for innovation is clear, as nicely summarized by Dr. Foley and colleagues in their report of a consensus conference on screening, assessment, and treatment for cognitive dysfunction in MS that was sponsored by the Consortium of Multiple Sclerosis Centers. The conference participants noted that cognitive dysfunction is common and often missed by neurologist clinicians, necessitating development of

screening strategies. The Symbol Digit Modalities Test (SDMT)¹⁶ shows some promise, but it does not evaluate memory, and more research is needed before we can confidently use it for screening with sufficient sensitivity and specificity. Dr. Foley et al. commented on the poor correspondence between self-reported cognitive problems and actual performance on neuropsychological tests. This theme is echoed by Dr. Becker and colleagues, who examined tests from the Patient-Reported Outcomes Measurement Information System (PROMIS)¹⁷ initiative. While these scales are very brief and have good reliability, the degree of correlation with “gold standard” neuropsychological tests is quite modest, ranging from 0.01 to 0.34.

Dr. Becker et al. reported better correlations between neuropsychological tests and a series of tasks involving the performance of activities of daily living. The use of more face-valid, ecologically relevant tasks is an avenue of new research in MS¹⁸ as we continue to search for optimal, clinically relevant outcome measures. Likewise, in the study by Dr. Akinwuntan and colleagues, neuropsychological testing was correlated with an on-road driving test evaluation. The cognitive tests were innovative in that they emphasized visuospatial processing (visual cancellation task) and item content directly related to driving (eg, Road Sign Recognition test). A discriminant function analysis using these tests correctly classified more than 80% of passing versus failing patients on the on-road driving test.

Dr. Walker and colleagues remind us that neuropsychological tests vary in their acceptability to patients, with some tests actually creating stress for them. The Paced Auditory Serial Addition Test (PASAT)¹⁹ is a sensitive and valid test but has a reputation for being unpleasant for the patient and examiner alike. Indeed, a recent position paper²⁰ commented on the idea that it may be time to replace the PASAT with another test

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of processing speed, the SDMT.²¹ In the Walker study, the PASAT was rated as more unpleasant for patients than both the SDMT and a computer-administered test of processing speed called the Computerized Test of Information Processing (CTIP).²² Ms. Wojtowicz and colleagues also present new data on the CTIP collected from 18 MS patients and 18 healthy controls. Rather than focus on mean accuracy measures, as is common in the literature, the authors compared the groups on the degree of variability in performance. As predicted, MS patients showed greater intra-individual variability than controls as indicated by standard deviations and the coefficient of variation.

An important advantage of computer-administered tests is the precise measurement of response latency that can be automatically calculated for every response during the task. Dr. Omside and colleagues present some interesting work with the computer-administered Attention Networks Test–Interactions (ANT-I). In their preliminary study of 12 MS patients and 12 healthy controls, the ANT-I discriminated the groups on the basis of response latency, which was not possible with the comparison task, the PASAT. In addition, the ANT-I showed a more robust relationship with brain MRI metrics than did the PASAT.

Turning from assessment to treatment, we are fortunate to have a contribution from Dr. Edwards and colleagues, who examined the effects of natalizumab in 40 MS patients known to have cognitive impairment based on a comprehensive neuropsychological evaluation. While we must judge the results with some caution, as the study did not include a control group, the marked improvement on cognitive testing after treatment is indeed impressive ($P = .0002$). These data suggest that natalizumab is exerting some positive influence on cognitive function in the short term, not just preventing future decline over several years. The observation echoes findings of similar gains on the SDMT.²³

The contributions to this issue demonstrate that we have moved well beyond studies that demonstrate the frequency with which cognitive impairment is found in MS and the most common patterns of deficits to a focus on specific aspects of cognitive dysfunction, ways to better assess these, and applications to activities of daily living. Studies such as these represent a move to a more interdisciplinary approach to MS care. Recognition of and interest in cognitive functioning in MS has spread to other (ie, non-neuropsychological) health-care providers and researchers to the extent that at nearly

every interdisciplinary conference, we are asked about how to more easily assess cognitive functioning in MS. In particular, there is growing interest in computerized test batteries. In addition to single-cognitive-domain computer-based tests such as those discussed in this issue, comprehensive (ie, multidomain) computerized test batteries have been recently developed. As outlined in a joint position paper by the American Academy of Clinical Neuropsychology and the National Academy of Neuropsychology,²⁴ there are several advantages to this type of assessment, including potentially reduced cost, greater accessibility, increased precision in measuring abilities such as reaction time, and availability of interpretive algorithms for determining impairment or statistically reliable change. However, full interpretation of the results of these tests requires consideration of an individual's medical history and psychosocial context. Providing guidance to the individual on how to manage any identified deficits should be the ultimate goal.

Moreover, computerized cognitive test batteries do not yet have the ability to assess free recall (versus recognition memory), expressive language, visuoconstructional skills, and executive functioning—all domains pointed out by Rao et al.⁵ as commonly affected in MS. Thus, the results from an automated test battery may miss important aspects of cognitive functioning that affect a person's ability to work, perform social roles, and maintain a sense of competency. It would be exciting to see the user–computer program interface develop to the extent that these cognitive domains could be reliably assessed in MS. Clearly, although computer-assisted testing has many limitations, advances are being made and there is much promise for the future. As for treatment of cognitive dysfunction in people with MS using computer-based cognitive training programs, these are worth evaluating, especially within the context of a comprehensive rehabilitation effort. This is another area in which collaborative efforts between computer program developers, neuropsychologists, speech therapists, and occupational therapists could yield valuable tools for individuals with MS.

So, in answer to the question “Why evaluate cognition in MS patients, since there is nothing to do about it anyway?” we can respond, “Why not try to better understand a core feature of MS and how it affects individuals as a means of helping those who live with this disease achieve an improved quality of life?” □

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The *International Journal of MS Care* (IJMSC) (ISSN 1537-2073) is the official peer-reviewed publication of the Consortium of Multiple Sclerosis Centers (CMSC). It has also been adopted as the official publication of the International Organization of Multiple Sclerosis Nurses (IOMSN), the International Organization of Multiple Sclerosis Rehabilitation Therapists (IOMSRT), and Rehabilitation in Multiple Sclerosis (RIMS). It is published quarterly in Spring, Summer, Fall, and Winter by the Delaware Media Group, 66 S. Maple Ave., Ridgewood, NJ 07450. It contains peer-reviewed articles in areas of interest to multiple sclerosis health-care professionals.

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PRINTING INFORMATION

Printed in the United States of America at Quad/Graphics, 1700 James Savage Rd., Midland, MI 48642.