

# Neuropsychology of Multiple Sclerosis: Looking Back and Moving Forward



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## Abstract

The neuropsychological aspects of multiple sclerosis (MS) have evolved over the past three decades. What was once thought to be a rare occurrence, cognitive dysfunction is now viewed as one of the most disabling symptoms of the disease, with devastating effects on patients' quality of life. This selective review will highlight major innovations and scientific discoveries in the areas of neuropathology, neuroimaging, diagnosis, and treatment that pertain to our understanding of the neuropsychological aspects of MS. Specifically, we focus on the recent discovery that MS produces pathological lesions of gray matter (GM) that have consequences for cognitive functions. Methods for imaging these GM lesions in MS are discussed along with multimodal imaging studies that integrate structural and functional imaging methods to provide a better understanding of the relationship between cognitive test performance and functional reserve. Innovations in the screening and comprehensive assessment of cognitive disorders are presented along with recent research that examines cognitive dysfunction in pediatric MS. Results of innovative outcome studies in cognitive rehabilitation are discussed. Finally, we highlight trends for potential future innovations over the next decade. (*JINS*, 2017, 23, 832–842)

**Keywords:** Multiple sclerosis, Neuropsychology, Cognition, Neuropathology, MRI, Gray matter, Rehabilitation

## INTRODUCTION

Our understanding of the neuropsychological aspects of MS was quite different 30 years ago than it is today. Most medical textbooks in the 1980s viewed “intellectual” changes to be a rare occurrence in MS patients. The most common estimate was 5%, with the understanding that such changes only occurred in patients with extensive physical disability and with a long disease duration (>30 years). These opinions were fairly universally accepted throughout the 20th century, despite the astute clinical observations in 1877 by the French neurologist, Jean Charcot, that most patients with MS had a “marked enfeeblement of the memory” and “conceptions that are formed slowly” (Charcot, 1877).

Two major scientific events occurred during the decade between 1985 and 1995 that changed how the disease is viewed from a neuropsychological perspective. The first was the publication of large-scale, controlled studies using batteries of standardized neuropsychological measures that demonstrated the prevalence of cognitive dysfunction in MS to be in the 40–65% range (for a review, see Rao, 1995). Furthermore, these studies showed that cognitive dysfunction is weakly correlated with physical disability (e.g., ambulation) and disease duration (Rao, Leo, Bernardin, & Unverzagt, 1991); is most commonly observed on measures of information processing speed (Rao, St Aubin-Faubert, & Leo, 1989) and episodic memory (Rao, Leo, et al., 1989); and can have a meaningful and specific impact on activities of daily living (Rao, Leo, Ellington, et al., 1991).

The second event was the introduction of magnetic resonance imaging (MRI). Because of its unique sensitivity to changes in water content in tissue, MS-related white matter

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(WM) lesions could be readily observed as WM hyperintensities (WMH) on T2-weighted scans. Moderate correlations between severity of cerebral WMH load and degree of cognitive dysfunction were observed (Rao, Leo, Haughton, St Aubin-Faubert, & Bernardin, 1989), clearly indicating that cognitive dysfunction could be related to underlying MS-related brain pathology rather than non-specific disease-related factors, such as fatigue, depression, or anxiety.

Since these early studies, the neuropsychology of MS has continued to evolve. This review is not designed to be an exhaustive appraisal of this large body of scientific literature. Rather, the intent is to highlight major innovations and scientific discoveries in the areas of neuropathology, neuroimaging, diagnosis, and treatment that pertain to our understanding of the neuropsychological aspects of MS. Finally, we highlight trends for potential future innovations over the next decade.

## NEUROPATHOLOGY

Traditionally, MS has been thought to be a disease of WM. This view was supported by early pathological studies that used standard histochemical myelin stains, such as luxol fast-blue (LFB). However, LFB works well in WM where there is an abundance of myelin, but is considerably less sensitive to detecting scarce amounts of myelin as contained in gray matter (GM). Only recently have investigators begun to appreciate that GM demyelination is a common pathological feature of MS. This newly found appreciation was made possible with the development of more advanced immunohistochemistry techniques based on myelin basic protein and proteolipid protein. Studies using these techniques have shown that around 15% of the neocortex is demyelinated at autopsy, with some outliers up to 70% of the total neocortical volume (Haider et al., 2014; Kutzelnigg et al., 2005).

Furthermore, deep GM nuclei can be heavily affected, with an average of approximately 30% demyelination. GM demyelination is more common in the cerebellum (Gilmore, DeLuca, et al., 2009; Kutzelnigg et al., 2007), hippocampus (Geurts et al., 2007), and spinal cord GM (Gilmore, DeLuca, et al., 2009; Gilmore, Geurts, et al., 2009), but essentially no areas within the central nervous system are spared. Cerebellar cortex can be almost entirely demyelinated in chronic MS cases (Kutzelnigg et al., 2007). Although the thalamus is the most frequently affected subcortical GM structure, lesions have been detected within the caudate, putamen, pallidum, claustrum, amygdala, hypothalamus, and substantia nigra (Gilmore, Donaldson, et al., 2009; Huitinga et al., 2001; Vercellino et al., 2009).

Whereas deep GM damage develops early in the disease, neocortical demyelination predominates in later stages (Haider et al., 2014). Cortical lesions are generally characterized by an intact blood–brain barrier and a lack of inflammatory cell infiltration (Bo, Vedeler, Nyland, Trapp, & Mork, 2003; Peterson, Bo, Mork, Chang, & Trapp, 2001; van Horsen, Brink, de Vries, van der Valk, & Bo, 2007; Wegner, Esiri, Chance, Palace, & Matthews, 2006). Neuronal loss is

generally limited to cortical lesions in contrast to the widespread changes observed in neurodegenerative diseases like Alzheimer's disease. Nevertheless, a neuronal density reduction of 18–23% has been reported (Vercellino et al., 2005).

Furthermore, loss of glia cells (~36%) and synapses (~47%) have also been found (Wegner et al., 2006). On occasion, signs of cortical inflammation have been observed in MS. One *post-mortem* study found rims of activated microglia at the border of cortical lesions (Kooi, Strijbis, van der Valk, & Geurts, 2012), and two others found meningeal B-cell follicle-like structures, associated with cortical demyelination (Howell et al., 2011; Magliozzi et al., 2007).

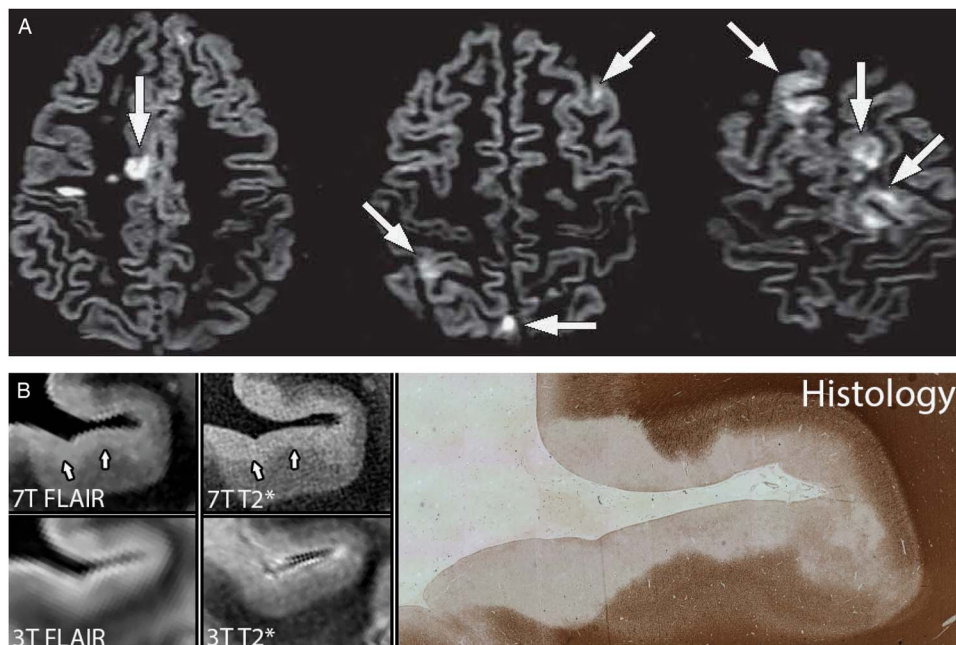
Neuropsychological investigators have come to realize that the presence and severity of cognitive impairment in MS may not be fully explained by WM pathology alone. Our understanding of the role of GM pathology in the development of cognitive dysfunction, however, is dependent on our ability to visualize these lesions *in vivo* using novel neuroimaging technologies.

## NEUROIMAGING

Initial attempts to image GM lesions using conventional T2-weighted and three-dimensional (3D) fluid-attenuated inversion recovery (FLAIR) imaging were largely unsuccessful, with detection of only 5% of the GM lesions observed at autopsy (Geurts, Bo, et al., 2005). Newly developed MRI sequences, such as 3D-double inversion recovery (see Figure 1A) (Calabrese & Gallo, 2009; Geurts, Pouwels, et al., 2005; Geurts et al., 2011; Nelson et al., 2007), phase-sensitive inversion recovery (Nelson et al., 2007; Sethi et al., 2012), 3D MPRAGE (Nelson, Poonawalla, Datta, Wolinsky, & Narayana, 2014; Nelson, Poonawalla, Hou, Wolinsky, & Narayana, 2008), and T2\* imaging (Nielsen et al., 2012) have been more successful, but still detected only the tip of the pathological iceberg (Seewann et al., 2011). Using higher MR field strengths (7T) and quantitative MRI methods, investigators have shown that subpially located cortical GM lesions, which form the bulk of the GM demyelination in progressive MS, are especially hard to find at lower field strengths (see Figure 1B) (Kilsdonk et al., 2016; Mainero et al., 2015).

Despite these technical limitations, several imaging studies have demonstrated that GM pathology is clinically relevant to the study of cognitive deficits in MS. Calabrese and colleagues found that, although patients may have similar T2-weighted WMH loads, cognitively impaired patients had more cortical lesions than patients who were cognitively intact (Calabrese et al., 2009). Other studies have shown strong correlations between cortical lesions and worse performance on measures of information processing speed, episodic memory, and learning capacity (Mike et al., 2011; Nelson et al., 2011; Roosendaal et al., 2009, 2008).

Because of the difficulty in visualizing GM lesions with current imaging technologies (Geurts et al., 2011), MS researchers have focused on comparing GM and WM



**Fig. 1.** (A) Intracortical lesions and mixed GM and WM lesions are shown (arrows) using double inversion recovery MR images obtained at 3 Tesla (T) field strength; reprinted with permission (Geurts, Calabrese, Fisher, & Rudick, 2012). (B) *Post-mortem* GM lesions detected at 7T FLAIR and 7T  $T_2^*$  images and on histology, but not detected on 3T images; reprinted with permission (Kilsdonk et al., 2016).

atrophy, measurements of which can be reliably reproduced across imaging centers despite disease heterogeneity. In a 4-year longitudinal study, Fisher et al. (Fisher, Lee, Nakamura, & Rudick, 2008) reported that WM atrophy increased three-fold, but this rate of change was similar across disease stages (relapsing-remitting, secondary progressive, and primary progressive MS, and clinically isolated syndrome). In contrast, GM atrophy increased in proportion to disease stage, that is, three-fold increase in early stage (clinically isolated syndrome converting to relapsing remitting MS) *versus* a 14-fold increase in late stage (secondary progressive MS).

MRI-based atrophy measures have been assumed to reflect a neurodegenerative process. This assumption was recently confirmed using combined *post-mortem* whole-brain *in situ* MRI imaging and histopathology in brain donors with chronic MS (Popescu et al., 2015). Neuronal and axonal pathology were identified as the predominant substrates of MRI-measured cortical volume.

Furthermore, GM atrophy has been shown to be regionally specific, with early volume loss of the thalamus and basal ganglia, as well as within the limbic system (Audoin et al., 2010; Bergsland et al., 2012; Schoonheim et al., 2012; Zivadinov et al., 2013), and to be of relevance for understanding cognitive impairment (Damjanovic et al., 2017; Preziosa et al., 2016; Tillema et al., 2016).

Regional GM atrophy appears to be topographically associated with lesion pathology in the adjacent WM, but only in relapse-onset MS. For primary progressive MS, no such correlation was found (Riccitelli et al., 2011). This, however, may be largely a technical issue, as a diffusion tensor approach did show a spatial association between GM

atrophy and adjoining diffuse WM damage (Bodini et al., 2009). The latter finding was later confirmed longitudinally (Bodini et al., 2016), and it was suggested that WM damage causes GM atrophy more so than the other way around. While this may certainly be true, second-order effects may start playing a role in later disease stages.

This means that WM lesions or more subtle WM damage may initially lead to local GM damage, but later GM damage will also be affected by connected, damaged cortical or deep GM, leading to an increasing GM atrophy rate over time. This would entail that WM damage will have less of an effect on the total GM damage over time, which was indeed shown (Steenwijk et al., 2016). In other words, GM damage (demyelination and atrophy) seems to grow into an independent pathological process, with potential implications for the rate of progression of cognitive dysfunction.

Numerous studies have demonstrated correlations between cognitive testing and brain volume measures (Batista et al., 2012; Benedict, Ramasamy, Munschauer, Weinstock-Guttman, & Zivadinov, 2009; Calabrese et al., 2009; Rao et al., 1985). For example, Benedict and colleagues (Benedict et al., 2009; Houtchens et al., 2007) showed that mesial temporal lobe (hippocampus and amygdala) and deep GM (thalamus and caudate) volumes correlated with recall and recognition memory, respectively. Amato and colleagues showed that overall normalized cortical volume was related to neuropsychological tests of verbal memory and fluency, as well as attention/concentration (Amato et al., 2004).

In addition to structural imaging studies, functional MRI (fMRI) is gaining increasing attention in the MS field. Combining functional and structural imaging data are indispensable to understanding the brain mechanisms responsible

for cognitive decline. Researchers have begun to look at the effects of MS related tissue changes on cognition, integrating information from multimodal imaging and demonstrating widespread functional network abnormalities to be present in MS (Rocca et al., 2015).

As an example, thalamic volume together with thalamic activation were identified as the best predictors of impaired information processing speed and executive function in RR-MS patients (Koini et al., 2016). In another fMRI study involving recognition memory, WMH load was shown to correlate positively with retrieval activation, but not with encoding activation, suggesting that the retrieval stage is more affected by disease burden than the encoding stage (Bobholz et al., 2006).

However, subsequent work showed that the association between brain pathology and retrieval difficulties was mediated by the strength or integrity of initial learning (DeLuca, Leavitt, Chiaravalloti, & Wylie, 2013). In a recent fMRI study (Nelson et al., 2017), reduced activation of prefrontal cortex was observed in cognitively impaired MS patients on a working memory task compared to MS patients who were cognitively intact.

## NEUROPSYCHOLOGICAL ASSESSMENT

Beatty and colleagues demonstrated that frequently used tests for senile dementia, including the Folstein Mini-Mental State Exam (Folstein, Folstein, & McHugh, 1975), were insensitive to MS cognitive disorders (Beatty & Goodkin, 1990). Considerable effort has focused on identifying the most psychometrically sound and valid tests for assessing cognition in MS, with the primary emphasis on the two domains, processing speed and learning/memory, that are most commonly impaired based on large-scale, controlled neuropsychological studies. In 2001 (Benedict et al., 2002), a consensus conference (including RHBB, SR, and JD) identified what was dubbed the Minimal Assessment of Cognitive Function in MS (MACFIMS), a battery that is typically administered in roughly 90 min. The MACFIMS was subsequently validated in numerous studies (e.g., Benedict et al., 2006).

The MACFIMS panel recognized several confounds to the interpretation of neuropsychological data. Major depression is related to WM and GM abnormalities in the frontotemporal region (Feinstein et al., 2010, 2004), and likely accounts for some impairment on cognitive testing (Arnett et al., 1994). The influence of dysphoria among MS patients not in the throes of a major depression episode is less certain. Fatigue, another common subjective complaint is usually not correlated with performance based neurocognitive test results (Morrow, Weinstock-Guttman, Munschauer, Hojnacki, & Benedict, 2009).

One cognitive test, in particular, the Symbol Digit Modalities Test (SDMT) (Smith, 1982) has repeatedly been found to be exceptionally reliable and sensitive, and correlated most robustly with other outcomes, such as brain MRI metrics and employment. As noted above, deep GM atrophy is a

particularly relevant MRI abnormality in MS. Third ventricle widening and thalamus volume loss are robustly correlated with SDMT performance deficits, even when analyses account for the effects of depression and education (Benedict, Carone, & Bakshi, 2004; Houtchens et al., 2007; Minagar et al., 2013). As a result, the SDMT has figured prominently in brief, widely used international monitoring tools (Benedict et al., 2012) and composites for neurological performance in clinical trials (Benedict et al., 2017). While the Brief International Cognitive Assessment for MS (BICAMS) was not designated a GM battery *per se*, deficits on the battery are strongly correlated with deep GM atrophy (Batista et al., 2012). A self-administered, computerized version of the test has recently been adapted to the iPad platform (Rao et al., 2017).

Surprisingly, well-controlled longitudinal studies of MS cognitive function are few, and have yielded inconsistent results. Considering the plethora of studies on brain MRI abnormalities in MS, involving demyelinating lesions and GM atrophy, one may wonder why more patients do not suffer from cognitive impairment and evidence clear decline within a few years. Part of the answer may reside in the cognitive reserve theory which was first investigated in MS by Sumowski and colleagues (Sumowski, Chiaravalloti, Wylie, & DeLuca, 2009).

In a cross-sectional study, the investigators showed that the correlation between brain atrophy and cognitive function is moderated by cognitive reserve (Sumowski et al., 2009). The results were soon replicated in a longitudinal study showing decline on SDMT over 5 years, only in patients with low *versus* high cognitive reserve (Benedict, Morrow, Weinstock-Guttman, Cookfair, & Schretlen, 2010). Since then, other aspects of reserve including estimated brain growth capacity, leisure activities, and personality traits such as Neuroticism and Conscientiousness have also been shown to influence the trajectory of cognitive decline in this disease (Roy et al., 2016; Sandroff, Schwartz, & DeLuca, 2016).

Traditionally, MS is not thought of as a chronic, progressive neurodegenerative disease, but a disease characterized by episodes of acute exacerbation followed by remission. Until recently, MS relapses have been defined by transient neurologic signs, not mental status changes. Serendipitously, Morrow et al. discovered that during a year-long observational study, including surveillance of mental status by monthly SDMT assessments, relapses were in fact accompanied by declines in SDMT (Morrow, Jurgensen, Forrestal, Munchauer, & Benedict, 2011). Subsequently, in studies including more carefully defined MS samples and non-relapsing controls, neuropsychological assessments demonstrate that cognitive relapses do occur (Benedict, Rodgers, Emmert, Kininger, & Weinstock-Guttman, 2014; Pardini et al., 2014), and that the patient recovery falls short of baseline levels of function. In this way, neuropsychology is providing an important tool for redefining MS disease activity.

Some investigators have tried to better characterize the nature of the cognitive disruption in MS. In a particularly



creative study of episodic memory, DeLuca and colleagues (DeLuca, Barbieri-Berger, & Johnson, 1994) found that the primary MS deficit was in the acquisition or learning aspect of memory performance. When MS patients and controls were tested to a criterion level of performance, patients required more learning trials, but then recalled and recognized the learned information normally. In other words, the episodic memory deficit was ameliorated by overcoming a deficit in acquisition, subsequently found to be associated with slowed processing speed and executive dysfunction. As noted previously, while an fMRI study (Bobholz et al., 2006) noted that lesion burden correlated more with activation during retrieval than encoding, subsequent work found that the strength of initial learning mediated the relationship between brain atrophy and retrieval (DeLuca et al., 2013). Future studies are needed to resolve these differences.

## COGNITIVE DYSFUNCTION IN PEDIATRIC MS

Traditionally, MS has been thought to be a disease of adult onset. Until recently, neuropsychological studies focused exclusively on adults with MS. In recent years, epidemiological studies, with improved diagnostic criteria, have called attention to pediatric onset MS, defined as symptoms beginning before 18 years of age. While relatively rare (only 2–5% of the MS population), the majority of pediatric MS patients (80–90%) are adolescents who have already reached puberty, but children as young as 20–25 months can present with their initial episode of MS (L.B.K.'s clinical practice; Sivaraman & Moodley, 2016).

Cognitive deficits have been identified in approximately one third of individuals, with the most prominent deficits in motor and cognitive processing speed as well as in attention, verbal and visual memory, expressive and receptive language, and visuo-motor integration (Amato et al., 2014; Charvet et al., 2014; Pardini et al., 2014; Till et al., 2013). These studies suggest that language acquisition may be more vulnerable to disruption in children than in adults with MS.

A recent multimodal imaging study (Rocca et al., 2014) identified several brain MRI differences among pediatric MS participants classified as cognitively preserved versus cognitively impaired. The two groups differed most on verbal and visual memory performance as measured by the Brief Repeatable Neuropsychological Battery (Rao, 1991). On multivariate analysis, cognitive impairment was linked to diffusivity abnormalities in the cingulum and corpus callosum, and reduced resting state functional connectivity of the precuneus. Increases in resting state functional connectivity of the anterior cingulate cortex were noted among cognitively preserved pediatric MS participants relative to healthy controls (Rocca et al., 2014).

Among pediatric-onset MS patients who underwent fMRI while completing the SDMT (Akbar et al., 2016), those with MS and normal performance showed increased activation in the frontal lobes relative to healthy controls, with faster response times associated with increased activation. The

increased activation could reflect adaptive changes used to overcome MS associated brain injury.

Results from longitudinal studies of cognitive functioning in pediatric MS have been variable. In a United States cohort tested twice over a mean of 1.6 years, approximately one-third were impaired relative to published normative data both at baseline and at follow-up, but little change in test scores occurred over time (Charvet et al., 2014). In contrast, among an Italian cohort of pediatric MS patients serially assessed at baseline and at 2 and 5 years, more than half declined at the 5-year follow-up (Amato et al., 2014).

In the only study in which the same set of both healthy controls and pediatric MS patients were tested twice over approximately 12 months (Till et al., 2013), healthy controls compared to those with MS were much more likely to improve on repeated testing (69% vs. 18%), with 25% of pediatric MS demonstrating a decline in performance over time. Neither clinical features nor neuroimaging findings predicted who declined. However, those whose parents had 16 years or more of education were more likely to show improvement. Taken together, it is reasonable to conclude that many children and adolescents with MS show cognitive deficits at any point in time and that they are less likely than healthy controls to show age appropriate gains on serial cognitive testing.

Cognitive difficulties take a toll. Interviews of the parents with pediatric MS (Amato et al., 2014) uncovered that a third (all of whom had cognitive impairment) were having serious academic problems requiring grade retention or tutorial support (Amato et al., 2014). This study also showed that 75% of cognitively impaired children experience negative effects on family or social relationships. Other studies (Charvet, Cersosimo, Schwarz, Belman, & Krupp, 2016) indicated that pediatric MS patients with cognitive dysfunction are more likely to report behavioral and emotional problems than those without cognitive impairment. Securing support services and special school accommodations can therefore be very helpful.

## COGNITIVE REHABILITATION

Given the frequency and severity of cognitive impairments in MS and the impact on everyday life, the next question is its rehabilitation. The latest Cochrane review (das Nair, Martin, & Lincoln, 2016) indicates that there is significant support for memory rehabilitation for immediate and long-term follow-up, which significantly improves quality of life. For instance, a randomized control trial by Chiaravalloti and colleagues (Chiaravalloti, Moore, Nikielshpur, & DeLuca, 2013) provided class I evidence that a behavioral intervention (i.e., modified Story Memory Technique, mSMT) designed to improve the acquisition of new learning, significantly improved learning and memory as well as reported everyday life functioning. Several other authors have shown similar improvements from behavioral interventions in persons with MS focusing on attention, working memory, and executive functions (for a review, see Sandry, Akbar, Zuppichini, & DeLuca, 2016).

The success of the mSMT is based on the concept of compensation or memory strategy training. Specifically, persons with MS are trained to use specific techniques (i.e., context and imagery) to improve or strengthen the learning of new information, thus improving retrieval. Several other memory strategy training techniques have been shown to be effective in improving the acquisition and retrieval of newly learned information, including spaced learning, self-generated learning, and retrieval practice (or the Testing effect) (Sandry et al., 2016).

Other studies have focused on restoring or strengthening cognitive constructs such as memory, attention and executive functions, or even preventing cognitive decline by holding it stable. Such restorative cognitive training programs have primarily used computer interventions, including home-based programs (Stuifbergen et al., 2012). The majority of these studies have shown positive effects in improving cognition (Sandry et al., 2016). However, such computerized programs that have been designed to serve as rehabilitation intervention tools must be distinguished from commercially available programs that advertise cognitive improvements. These products have generally not been studied in persons with MS and, thus, should not be viewed as rehabilitation or treatment (for a review, see Simons et al., 2016).

Numerous studies have shown that cognitive rehabilitation not only improves cognitive functions and everyday life activity, but does so by promoting adaptive changes in brain activity *via* neuroplasticity. For example, Chiaravalloti et al. have shown that the cognitive and behavioral improvements observed using the mSMT behavioral intervention was associated with increased activity in several brain networks, increased resting state functional connectivity between the hippocampus and other brain structures, and that these effects were maintained at long-term follow-up. There are now dozens of research studies showing similar adaptive plasticity changes following various types and forms of cognitive rehabilitation in persons with MS (for a review, see Chiaravalloti, Genova, & DeLuca, 2015). How cognitive reserve, that is, effects of early life experiences, moderates the outcomes of cognitive rehabilitation has not received adequate attention as yet.

Finally, there have been mixed, but generally negative, results of pharmacological interventions to improve memory in MS (Krupp et al., 2004, 2011; Morrow et al., 2013). Several recent studies have focused on exercise as a means to improve cognition in persons with MS. While promising, definitive effects of exercise on cognition awaits further research with improved methodological designs (Sandroff, Motl, Scudder, & DeLuca, 2016). To date, cognitively based interventions remain the most efficacious approach to treating cognitive impairment in persons with MS.

## FUTURE DIRECTIONS

Much progress has been made in understanding the neuropsychological aspects of MS over the past three decades

The authors have defined several areas of inquiry that may define the field over the next decade.

## Improved Detection of Cognitive Dysfunction in the MS Clinic

Despite the existence of brief, reliable cognitive tests like the SDMT, neuropsychological assessments are not uniformly applied in MS clinics. Referrals for assessment are typically generated by patient or caregiver reports of cognitive symptoms or the need to document impairment for disability claims. Unfortunately, self-reported cognitive deficits exhibit weak correlation with neuropsychological testing (Carone, Benedict, Munschauer, Fishman, & Weinstock-Guttman, 2005; O'Brien et al., 2007) and healthcare professionals, without the benefit of neuropsychological testing, are also inaccurate in detecting the often subtle cognitive deficits associated with MS (Romero, Shammi, & Feinstein, 2015).

That said, perspectives are changing (Langdon, 2016), and we predict that MS clinics will increasingly use brief measures like the SDMT for screening purposes to detect subtle progression of dementia or transient declines associated with MS relapses. Computerized cognitive tests that are patient self-administered are an attractive option for routine clinic visits (for examples, see (Charvet, Shaw, Frontario, Langdon, & Krupp, 2017; Rao et al., 2017)). Another model involves telemedicine in which cognitive tests are administered *via* telephone or the Internet; for an example, see Barcellos et al. (2017). Comparing routine tests to baseline measures might identify “cognitive” exacerbations, monitor disease progression, and the baseline measures themselves may be used to screen patients for the need for more comprehensive evaluation. With additional large-scale data collections, research may demonstrate that the prevalence, severity, and longitudinal progression of cognitive dysfunction may be different when we move from convenience sampling to whole clinic populations.

## Neuroimaging

Future studies will increasingly use approaches that combine multiple structural (volumetrics, WM and GM lesions, diffusion tensor imaging) and functional techniques (task activation and resting state fMRI) to better understand how MS disrupts the efficiency of interacting brain circuitry. Longitudinal studies using such technologies will capture the transition from adaptive to maladaptive cognitive functions, thus providing a window to understanding how the brain’s “functional reserve” becomes exhausted by this disease.

## Pediatric MS

An unresolved question is whether the disease affects the course of adolescent brain development. Specifically, what are the consequences of demyelination and inflammation in

the context of ongoing myelination? With the emergence of collaborative worldwide networks of pediatric MS centers, we will see the emergence of controlled longitudinal studies using MRI, cognitive and academic testing, and quality of life assessments on large samples of children and adolescents with MS.

### Cognitive Rehabilitation

Future work will focus on providing more class I studies specifically aimed at questions such as proper dosage, time when services should be provided (e.g., early vs. late), examining longer term consequences, and the impact on everyday life activities. The cognitive rehabilitation literature has focused almost exclusively on relapsing-remitting MS patients; future research will examine the effects on progressive MS patients. Ultimately, we believe rehabilitation of cognitive functions in persons with MS will likely be a combination of behavioral (cognitive and exercise) and pharmacological approaches. But given the current lack of evidence of pharmacological and exercise approaches, cognitive rehabilitation is the current intervention of choice.

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