

## CHAPTER 15

### Cognitive Functioning and Everyday Tasks in Multiple Sclerosis

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Ecological validity is a central issue for the field of clinical neuropsychology. Neuropsychologists routinely extrapolate the neuropsychological test results of their patients to real-world activities, yet, in many cases the actual empirical data supporting such an extrapolation is limited or nonexistent. If patients are impaired on tasks such as the Wisconsin Card Sorting Test or the California Verbal Learning Test, will they have difficulty with real-world tasks that purportedly require the cognitive functions measured by these tasks? As a more specific example, if patients perform poorly on tasks measuring information processing speed and attention, such as the Symbol Digit Modalities Test or the Paced Auditory Serial Addition Test (PASAT), will their driving skill or their ability to carry out daily household tasks such as cooking be impaired? The goal of the present chapter is to provide a review of some of the existing data relating to the ecological validity of neuropsychological tests in patients with multiple sclerosis (MS). Cognitive problems are very common in MS, and there is a growing body of literature suggesting that such cognitive difficulties have consequences for important real-world tasks. Before reviewing this literature, we summarize what is known about some of the basic characteristics of MS, including pathophysiology, symptom profile and diagnostic issues, epidemiology and disease characteristics, and cognitive functioning and depression. We turn to these issues now.

#### General Characteristics of MS

##### *Pathophysiology*

MS is thought to be caused by an autoimmune process that results in demyelination in the central nervous system; a slow-acting virus or a delayed reaction to a common virus is also considered as a possible cause of this demyelination (Arnett, 2003; Brassington & Marsh, 1998; Compston et al., 2005; Pary & Ebers, 1998; Tröster &

Arnett, 2006). Multiple discrete plaques are formed, in part, by proliferating astrocytes that result in demyelination. Myelin sheaths within plaques are either destroyed or swollen and fragmented. This process disrupts neural transmission by limiting the saltatory conduction process whereby the nerve impulse jumps between gaps in the myelin sheaths. In the normal brain, myelin encloses intact nerves, and the nerve impulse moves fluidly across the gaps in myelin. MS plaques appear as ill-defined, pale, pink-yellow lesions in the untreated brain. Axons and cell bodies of neurons often remain intact, though some cell death is thought to occur with progression of the disease (Brass, Benedict, Weinstock-Guttman, Muntschauer, & Bakshi, 2006). MS plaques can occur in the brain and/or spinal cord, and their location is highly variable among patients. Within the brain, plaques near the lateral and third ventricles are most common. The frontal lobes are the next most commonly affected, even when the size of the frontal lobes, relative to the rest of the brain, is taken into account. Plaques are also frequently observed in other major lobes of the brain, the optic nerves, optic chiasm, or optic tracts, as well as the corpus callosum, the brainstem, and the cerebellum. Plaques are also found in white matter regions of the thalamus, hypothalamus, and basal ganglia. The majority of plaques (about 75%) are observed in the white matter, but some occur in the gray matter and in the juncture between the gray and white matter (Pitroock & Lucchinetti, 2007).

### Symptom Profile and Diagnosis

Symptoms from demyelination in MS most often reflect functions associated with the affected areas. The most common symptoms at MS onset are muscle weakness, paresthesias, gait/balance problems, and visual disturbances. Urinary disturbance, fatigue, problems with balance, and paresthesias (usually numbness and tingling in the limbs, trunk, or face) are also common (Arnett, 2003; Pary & Ebers, 1998). Significant cognitive difficulties and problems with depression are very common symptoms as well. These latter difficulties are discussed in more detail below. Symptom onset is typically acute or subacute, with many MS symptoms being transient and unpredictable. For example, visual disturbances and paresthesias may last for seconds or hours. Because of the short-lived and sometimes unusual nature of symptoms, it is not uncommon for patients in the early stages, prior to formal diagnosis, to be labeled with somatoform disorders.

Up until about 6 years ago, the diagnosis of MS was most often based on Poser and colleagues' (1983) criteria. In this system, there are four categories of diagnosis. "Clinically definite" MS requires two discrete disease attacks and clinical evidence of two separate lesions, or two attacks, clinical evidence of one lesion, and paraclinical evidence of another, separate lesion. "Laboratory-supported definite" MS requires two attacks and either clinical or paraclinical evidence of two separate lesions, and cerebrospinal fluid (CSF) oligoclonal bands or abnormal IgG synthesis rate. "Clinically probable" MS requires two attacks and clinical evidence of one lesion. Finally, "laboratory-supported probable" MS requires two attacks and CSF oligoclonal bands or abnormal IgG synthesis rate.

Currently, however, diagnosis guidelines published by McDonald and colleagues (2001) and Polman and colleagues (2005) are considered the gold standard for the

diagnosis of MS. Under these new criteria, lesions should be separated in both time and space. More specifically, patients must have had two or more discrete attacks of the disease lasting at least 24 hours. These attacks, or episodes of neurological change, should also implicate the presence of lesions in at least two different sites in the central white matter. An additional criterion is that at least 30 days should separate the onset of each attack. McDonald and colleagues also lay out specific criteria for defining lesions detected on MRI as abnormal and characteristic of MS. With this new diagnostic system, MRI data are considered preferable to other paraclinical tests; however, additional tests are considered useful when clear-cut MRI findings are not evident or in the case of atypical clinical presentations. In particular, the presence of oligoclonal IgG bands in the CSF different from those in the serum, or elevated IgG, can be used. Furthermore, visual evoked potentials (VEPs) are considered an acceptable supplement to the clinical examination to reveal evidence of additional lesions. In cases of insidious MS progression that do not involve discrete disease attacks, abnormal CSF findings that reflect inflammation and abnormal immune functioning are necessary. Evidence of lesions being separated in space, established by MRI or abnormal VEP, is considered essential. Lastly, there should be evidence indicating separation in time as reflected by the onset of new MRI lesions or increased level of disability over the course of at least 1 year.

New attacks, relapses, or exacerbations commonly occur in MS and imply new disease activity. MS was previously classified under two major types of disease course: relapsing-remitting and chronic progressive. A new system that includes four course types developed by Lublin and Reingold (1996) has been widely adopted. The most common course type is *relapsing-remitting*. Approximately 85% of patients have this type at initial diagnosis. It is characterized by clearly defined disease relapses. Recovery is highly variable, ranging from complete recovery back to pre-relapse baseline to sequelae and residual deficit. A central feature of this course type is the absence of disease progression between relapses. *Secondary progressive* is the next most common type of MS. It begins as a relapsing-remitting course, but progression of the disease is evident even between relapses. It is important to note, however, that relapses and remissions may or may not occur once patients enter a secondary progressive course, but disease progression occurs. Before the relatively recent development of disease-modifying drugs, approximately 50% of patients with relapsing-remitting MS developed this course of the disease within 10 years. Long-term data are not yet available to allow for an evaluation of whether such drugs delay this progression. The *primary progressive type* is the next most common course type, affecting approximately 10% of patients and involving an unremitting disease progression for most patients. That said, occasional stabilization and even improvement in functioning can occur, but there are no clear relapses. The least common type of MS is *progressive relapsing*, affecting about 5% of patients. It involves disease progression from onset that is punctuated by acute relapses from which patients may or may not fully recover. The term "chronic progressive" formerly encompassed all progressive types (Tröster & Arnett, 2006).

Complete remission is common following the initial episode of symptoms for relapsing-remitting MS. Subsequent episodes are unpredictable, occurring weeks to years later, and symptoms associated with them remit less completely or not at all.

Relapses are highly variable, lasting days to weeks, and more rarely, hours or months (Compston et al., 2005; Pary & Ebers, 1998).

### *Epidemiology/Disease Characteristics*

MS is about twice as likely to affect women compared to men, and symptom onset occurs in most (about two-thirds of) patients between the ages of 20 and 40. Onset before age of 15 in MS is rare; late onset after age 40 is also relatively uncommon and typically characterized by a quicker progression and greater morbidity. Following disease onset, the average life expectancy of patients is estimated to be greater than 30 years, but as with many aspects of this disease, variability is great (Arnett, 2003).

The incidence and prevalence of MS are quite variable geographically. Relatively few cases occur near the equator, with the greatest number of cases found in the northern and southern latitudes (from about 60 to 300 per 100,000). Thus, although it is estimated that approximately 350,000 persons have MS in the United States and another approximately 400,000 in Europe (Roistein, Hazan, Barak, & Achiron, 2006), individuals who live north of 40 degrees latitude are approximately three times more likely to have MS compared with residents living in southern regions. Such a discrepant geographic pattern implicates an environmental contribution to the disease. Nonetheless, there appears to be a likely significant genetic contribution to MS, as well, something suggested by the 30–40% concordance in identical twins but only 1–13% in fraternal twins (Poser, 1994; Tröster & Arnett, 2006).

### *Cognitive Sequelae/Profiles*

Since Rao and colleagues' (Rao, Leo, Bernardin, & Unverzagt, 1991) seminal study on the prevalence of cognitive deficits in MS, other investigators have supported their finding of close to a 45% prevalence in community-based samples (Amato, Zipoli, & Portaccio, 2006; Jonsson et al., 2006; McIntosh-Michaelis et al., 1991). Over half of patients in clinically based samples (about 55–65%) have typically been shown to have significant cognitive problems (Amato et al., 2006; Berrando, Maffei, & Ghezzi, 1983; Feinstein, 2004). In their study, Rao and colleagues (1991) compared 100 community-based patients with MS with 100 matched healthy controls on an extensive neuropsychological battery. They found that memory and complex attention/speeded information processing were the cognitive domains most affected in MS; this finding has been supported by subsequent work. Other domains commonly affected include verbal fluency, working memory, and executive functions involving problem solving and abstract reasoning (Amato et al., 2006; Benedict et al., 2002; Bobholz & Rao, 2003; Feinstein, 2004; Rao, Leo, Bernardin, & Unverzagt, 1991; Wishart et al., 2004).

As Rao and others have noted, however, about 80% of patients with cognitive deficits are relatively mildly affected. Only approximately 5% of patients experience global cognitive deficits that would be consistent with dementia. Even mild cognitive problems, however, have been shown to be associated with difficulty in everyday activities in MS (e.g., work, homemaking, personal care activities, social activities)

(Higginson, Arnett, & Voss, 2000). Thus, even mild cognitive difficulties in MS are a concern in a context of ecological validity.

### *Nature of Neuropsychological Deficits*

In the following sections the percentage of patients with deficits in a particular domain is noted. This determination is based on the percentage of patients who fell below the fifth percentile of controls in Rao, Leo, Bernardin, and Unverzagt's (1991) seminal study. We chose this study because it is the representative community sample of patients with MS and provides one of the best samples of control participants in the literature.

*Memory.* Difficulties encoding and/or retrieving both verbal and visual information are the most common type of memory deficit in MS. On neuropsychological testing these problems are typically manifested as immediate and delayed recall memory deficits. About 30% of patients have substantial problems, another 30% have moderate problems, and the remaining 40% have mild or no problems with this type of memory (Brasington & Marsh, 1998). Delayed recall deficits are usually a function of deficient immediate recall, not forgetting. The learning curve across repeated trials is similar in slope in MS compared with controls, but is lower in magnitude. Percent retention, recognition, and incidental memory following a delay, and remote memory are usually intact in MS (Arnett, 2003).

*Working Memory/Attention/Information-Processing Speed.* Working memory deficits and problems with speeded information processing are nearly as common in MS as long-term memory problems. Working memory, defined as the ability to maintain and manipulate information "online," is commonly impaired in MS (D'Esposito et al., 1996; Foong et al., 1999; Grigsby, Ayarbe, Kravcisin, & Busenbark, 1994; Grigsby, Busenbark, Kravcisin, Ayarbe, & Kennedy, 1999) in patients with relapsing-remitting (Grigsby et al., 1999) as well as progressive (Grigsby et al., 1994) subtypes. It can be difficult to separate speeded information processing from working memory/attention because attention is typically necessary for performing any speeded cognitive task. Of note is that Deluca and colleagues (Deluca, Chelune, Tulisky, Lengenfelder, & Chiaravalloti, 2004) have reported that processing speed deficits, as measured by the Processing Speed index from the Wechsler Adult Intelligence Scale-III (WAIS-III), are common to both relapsing-remitting and secondary progressive MS subtypes. In contrast, working memory deficits, as measured by the Working Memory index from the WAIS-III, only emerge in patients with a secondary progressive course. One limitation of their study is that the Processing Speed index requires fine motor speed, something that is commonly impaired in patients with MS. The authors did attempt to control for this potential confound by covarying out Finger Tapping test speed, but motor writing impairments may still have exacerbated differences with controls. Using the Sternberg task, an experimental measure that controls for perceptual and motor difficulties, Archibald and Fisk (2000) showed that both relapsing-remitting and secondary progressive MS course types demonstrated significantly slower processing speed compared with controls as the working memory demands of the task

increased. Generally, patients with MS show significant difficulty on tasks requiring rapid and complex information processing. Like those requiring swift application of working memory operations, attentional switching, or rapid visual scanning. About 20–25% of patients with MS have impairments in this cognitive domain (Rao, Leo, Bernardin, & Unverzagt, 1991). Simple attention span is usually intact, but mild impairments are sometimes found.

**Executive Functioning.** The next most common cognitive domain typically affected in MS is executive functioning, with approximately 15–20% of individuals with MS showing impairments here (Rao, Leo, Bernardin, & Unverzagt, 1991). Deficits in cognitive flexibility, concept formation, verbal abstraction, problem solving, and planning are commonly found (Amato et al., 2006; Benedict et al., 2002; Bobholz & Rao, 2003; Feinstein, 2004).

**Verbal/Linguistic Function.** Aphasias are unusual in MS (Arnett, Hussain, Rao, Swanson, & Hammeke, 1996), but mild confrontation naming difficulties are sometimes seen. Similarly, alexia, agraphia, and apraxia are very rare (Mahler, 1992). With that said, speech abnormalities such as dysarthria and hypophonia are common in MS (Harrelius, Runmarker, & Andersen, 2000; Harrelius, Runmarker, Andersen, & Nord, 2000), as are deficits in verbal fluency. A recent meta-analysis suggested that letter–word and semantic fluency tasks are equally sensitive to verbal fluency problems in MS (Henry & Beatty, 2006). Recent data from our lab indicate that the later parts of verbal fluency tasks may be most sensitive to cognitive problems in MS. In particular, we found that patients with MS did not differ significantly from controls in the first 15-second interval of the task, but robust differences were found for the overall task (Smith & Arnett, 2007). We speculated that the initial, more automatic part of the tasks, wherein examinees often produce a large proportion of their words, is not sensitive to fluency deficits in MS, but the more effortful later parts of the task requiring more controlled cognitive processing are sensitive. Overall, 20–25% of patients typically show deficits on verbal fluency tasks (Rao, Leo, Bernardin, & Unverzagt, 1991).

**Visuospatial Function.** Visuospatial deficits occur with reasonable frequency in MS, with 10–20% of patients showing substantial difficulty with higher-order visuospatial skills involving angle matching or face recognition (Rao, Leo, Bernardin, & Unverzagt, 1991).

**Intellectual Function.** Although verbal intellectual functioning is impaired in about 20% of patients with MS (Rao, Leo, Bernardin, & Unverzagt, 1991), most patients score within the broad normal range on general measures of intelligence.

#### *Possible Causes of Cognitive Deficits*

Cognitive deficits are primarily a direct consequence of the location and extent of brain damage. Because most research in cognition in MS is conducted on participants who are not experiencing acute attacks, there are limited data on cognition during a clinical exacerbation. However, Foong and colleagues (1998) exam-

ined memory and attentional performance in a small sample of patients with MS tested during and after an acute exacerbation. They report that, in a subgroup of patients in whom gadolinium-enhanced lesion load decreased following remission, attentional performance improved during recovery, whereas memory performance remained consistently impaired. These findings suggest that some limited aspects of cognitive dysfunction observed during acute exacerbation may be reversible. However, there is clear evidence that overall cognitive impairment is associated with total white matter lesion burden in MS, as measured by T1 magnetic resonance imaging (MRI) lesion volume (Brass et al., 2006; Rao, Leo, Haughton, St. Aubin-Faubert, & Bernardin, 1989). There is also more recent evidence that subcortical gray matter deterioration is associated with overall neuropsychological functioning in MS (Brass et al., 2006), in some cases more highly than lesion volume (Sanfilippo, Benedict, Weinstock-Gurtman, & Bakshi, 2006). Thus, cognitive problems caused by primary influences are generally not reversible. Additionally, there is some evidence that frontal lobe lesions are associated with deficits on executive tasks such as the Wisconsin Card Sorting Test (WCST) (Arnett et al., 1994); however, the association between lesions in other brain areas and specific cognitive deficits is less clear (Brassington & Marsh, 1998).

There is also evidence that cognitive problems can appear very early on in the disease course. Jonsson and colleagues (2006) found that 44–48% of patients with MS displayed cognitive impairments within the first year of their diagnosis. Feullter and colleagues (2007) even found significant evidence of cognitive impairment in over 50% of patients with clinically isolated syndromes suggestive of MS. It has also been demonstrated that once cognitive problems are present, they are likely to progress. Two longitudinal studies have now shown that patients who initially display cognitive problems are most likely to show progression of such difficulties. Kujala, Portin, and Rautiainen (1997) demonstrated this outcome in a 3-year longitudinal study, and Bergendal, Fredrikson, and Almkvist (2007) showed evidence for such progression over an 8-year follow-up period.

Secondary causes of cognitive impairment arise from factors/conditions associated with the disease, such as depression, anxiety, or fatigue. Cognitive problems caused by a secondary influence are potentially reversible if the secondary influence is successfully treated. There has been less emphasis in the MS literature on these possible secondary causes of cognitive dysfunction. Although many early studies often reported null findings in this realm (Good, Clark, Oger, Pary, & Klonof, 1992; Krupp, Sliwinski, Masur, Friedberg, & Coyle, 1994; Moller, Wiedemann, Rohde, Backmund, & Sonntag, 1994; Schiffer & Caine, 1991), there is some evidence from a few older studies, but especially from more recent work, that depression is associated with impairments in speeded attentional functioning, working memory, and executive functions (Alkens, Fischer, Namy, & Rudick, 1997; Arnett, Higginson, & Randolph, 2001; Arnett, Higginson, Voss, Bender, et al., 1999; Arnett, Higginson, Voss, Wright, et al., 1999; Denney, Lynch, Parmenter, & Horne, 2004; Fischer, 1988; Landro, Celius, & Sletvold, 2004). One factor that may account for some of the discrepancies in the literature, on which we have focused in our lab, is the variable definitions of depression. We define depression more narrowly as mood disturbance (Arnett et al., 2001; Arnett, Higginson, Voss, Bender, et al., 1999; Arnett, Higginson, Voss, Wright, et al., 1999) or as a combination of mood disturbance and

negative evaluative symptoms of depression (Arnett, 2005; Arnett, Higginson, Voss, & Randolph, 2002). We have done this because of the possible overlap theorized between neurovegetative symptoms of depression and MS symptoms (e.g., sleep disturbance, sexual dysfunction, fatigue) (Mohr, Goodkin, Likosky, Beutler, et al., 1997; Randolph, Arnett, Higginson, & Voss, 2000). Nonetheless, some studies have still found associations using depression measures such as the Beck Depression Inventory (BDI) and Center for Epidemiological Studies Depression Scale (CES-D), which also include neurovegetative depression symptoms (Aikens et al., 1997; Beatty, Goodkin, Monson, Beatty, & Hertsgaard, 1988; Denney et al., 2004; Fischer, 1983; Gottberg, Einarsson, Fredriksson, von Koch, & Holmqvist, 2007; Landro et al., 2004).

The presence of unmeasured moderators might also explain some of the discrepancies in the literature on cognitive problems and depression in MS. In a recent theoretical review paper (Arnett, Barwick, & Beerey, 2008), we articulated a comprehensive model that explains how the relationship between cognitive dysfunction and depression may be moderated by factors such as stress, social support, cognitive schema, and coping. In one empirical study we found that coping strategies significantly moderated the relationship between cognitive dysfunction and depression (as measured by the combined Mood and Evaluative scales from the Chicago Multiscale Depression Inventory (CMDI; Nyenhuis et al., 1995). Specifically, patients with MS and cognitive difficulties were at risk for depression only if they used high levels of avoidance coping or low levels of active coping (Arnett et al., 2002; Rabinowitz & Arnett, in press). The influence of moderators such as coping style might explain some of the discrepancies in the literature outlined above. Longitudinally, we have found that negative evaluative depression symptoms are more consistently associated with cognitive dysfunction than mood symptoms (Arnett, 2005).

Besides depression impacting cognitive functioning or cognitive functioning resulting in depression, it is also possible that both common problems in MS could result from some third variable, for example, a common neurobiological factor such as inflammation in the basal ganglia and white matter. We have also previously proposed (Arnett et al., 2001) that, given that left frontal hypoactivation is common in depression in general (e.g., Davidson, 1992; Nímeic & Lithgow, 2005), and the left frontal brain region appears to be important in performance on executive and working memory/speeded processing tasks associated with depression in MS, differential white matter lesion damage and/or hypoactivation in this region could result in both depression and cognitive problems.

Primary problems with visual acuity as well as problems with output modalities (e.g., fine motor skills, oral-motor speed) can also compromise performance on higher-level cognitive tasks requiring these outputs and thereby confound interpretation of test results. It is unclear whether higher-order visual deficits are a function of primary visual disturbances involving blurred vision and diplopia (Rao, Leo, Benardin, & Unverzagt, 1991), though a recent study from our lab suggests that such factors may play an important role (Bruce, Bruce, & Arnett, 2007). Recent research from our lab also suggests that rudimentary problems with oral-motor speed differentially contribute to performance on commonly used cognitive tasks in evaluating MS, such as the oral version of the Symbol Digit Modalities Test (Smith & Arnett, 2007). Such problems in oral-motor speed appear to magnify the relatively poorer performance of patients with MS on such tasks.

## Depression

The prevalence of depression is high in patients with MS (Arnett, 2003; Brassington & Marsh, 1998; Dalton & Heinrichs, 2005; Fischer et al., 1994; Goldman Consensus Group, 2005; Minden & Schiffer, 1990). The lifetime risk for depression has been estimated at around 50% (Parren & Metz, 1997; Sadovnik et al., 1996), compared with a lifetime risk in the general population of around 10–15% (American Psychiatric Association, 1994). Because of its high prevalence, importance to quality of life and patients' well-being (Kenaly, Beaumont, Lintern, & Murrell, 2000), and possible influence on the disease course itself (Ackerman et al., 2000; Dalos, Rabins, Brooks, & O'Donnell, 1983; Franklin, Nelson, Heaton, Burkes, & Thompson, 1988; Mohr et al., 2000), depression has been intensively studied in MS. The significance of depression in MS is also underscored by the fact that depression scores are highly predictive of suicidal intent in patients with MS (Feinstein, O'Connor, & Feinstein, 2002).

Depression in MS has been shown to be treatable through brief and even telephone-based cognitive-behavioral therapy (CBT; Mohr et al., 2000) as well as group therapy. In addition, cognitive-behavioral stress management training has been shown to reduce emotional distress in patients with MS (Fischer et al., 1994), and psychopharmacological treatments have been shown to be effective in treating depression in these patients (Mohr & Goodkin, 1999). Nonetheless, depression has been historically undertreated in MS, despite the fact that successful treatment of depression is associated with greater adherence to immunotherapy (Mohr, Likosky, et al., 1999).

A number of factors has been found to have a strong association with depression, including reduced social support (McCabe, McKern, & McDonald, 2004; McIvor, Riklan, & Reznikoff, 1984), dysfunctional attitudes and negative cognitive schema (Bruce & Arnett, 2005; Shnek, Foley, LaRocca, Smith, & Halper, 1995), stress and maladaptive coping (Jean, Paul, & Beatty, 1999; Pakenham, 1999), and the extent of lesion damage in the brain (Bakshi et al., 2000; Feinstein et al., 2004; Pujol, Bello, Dues, Marrí-Viñata, & Capdevila, 1997; Zorzon et al., 2002). Not surprisingly, depression has also been shown to be related to sexual dysfunction in MS (Demirkiran, Sarica, Ugunz, Yerdelen, & Aslan, 2006; Zivadinov et al., 2003). Additionally, research has consistently demonstrated that depression is highly negatively correlated with quality of life in MS (D'Alisa et al., 2006; Janardhan & Bakshi, 2002; Janssens et al., 2003; Patri et al., 2003; Wang, Reimer, Metz, & Parren, 2000) and that effective treatment of depression may alleviate this effect (Hart, Ponareva, Meruzzi, & Mohr, 2005). Effective treatment of depression in patients with MS has also been found to improve adherence to disease-modifying treatment (Mohr, Goodkin, Gatto, & Van Der Wende, 1997).

There is no consensus regarding the nature of depression in the MS literature. Some investigators have presented evidence that neurovegetative symptoms of depression are not valid indicators because of their overlap with MS symptoms (e.g., sleep disturbance, fatigue, sexual dysfunction) (Beerey & Arnett, 2008; Mohr, Goodkin, Likosky, Beutler, et al., 1997; Randolph et al., 2000), whereas others have provided evidence to the contrary (Aikens et al., 1999; Moran & Mohr, 2005). This debate suggests that caution is warranted in interpreting neurovegetative symptoms of depression as such in any individual patient with MS.

### Ecological Validity of Cognitive Tests in MS

Perhaps the seminal study examining the ecological validity of cognitive tests in MS was Rao, Leo, Ellington, and colleagues' (1991) comprehensive examination of the impact of cognitive dysfunction on employment and social functioning. These investigators divided their sample of 100 patients with MS into groups of 52 "cognitively intact" and 48 "cognitively impaired" patients. To demarcate their groups, they first determined the mean number of "failed" tests from a comprehensive neuropsychological battery of 31 test indices that a matched control group of 100 participants had taken. These investigators determined that less than 5% of controls failed (scored below the fifth percentile) four or more tests in the battery. Thus, failing four or more tests was operationalized as failing the entire battery. Participants were then administered a number of measures pertaining to real-world skills, including the Expanded Disability Status Scale (EDSS; Kurtzke, 1983), the Incapacity Status Scale (ISS; Kurtzke, 1981), and the Environmental Status Scale (ESS; Mellertup, Fog, & Raun, 1981). The EDSS is a standard measure of physical/neurological disability in MS that focuses primarily on ambulation; the ISS measures basic activities of daily living (ADLs) such as stair climbing, dressing, and bed and chair transfers; the ESS assesses degree of social handicap from illness in seven domains, including employment, social activities, personal assistance required, community assistance required, financial status, need for transportation, and modifications to personal residence. An occupational therapist also conducted a 2-hour evaluation in patients' homes. Patients were rated on the Barthel Index (BI; Mahoney & Barthel, 1965), the Klein-Bell ADL (Activities of Daily Living) Scale (Klein & Bell, 1982), and a homemaking evaluation. In the latter assessment patients performed three tasks: cooking a simple dessert, demonstrating the operation of household appliances, and making a bed. The Klein-Bell scale includes ratings in six ADL domains (i.e., dressing, elimination, mobility, bathing/hygiene, eating, and communication). Finally, the BI provides an overall summary score reflecting level of dependence on others for ADLs. Patients and significant others also completed various self-report measures pertaining to emotional functioning, as well as a measure of sickness-related disability. Because of its relevance to the topic at hand, the results of Rao and colleagues' seminal study are variously described in the relevant sections that follow.

### Independent Activities of Daily Living

ADLs involve a variety of basic functions such as dressing oneself, bathing and hygiene, eating, and communicating, among others. Impairments in ADLs are extremely common in MS. In one of the most representative samples of patients with MS reported in the literature to date, Sarah Minden and her colleagues (2006) noted that almost two-thirds of over 2,000 patients with MS in the Songya Sifika Longitudinal MS Study needed help from another person to perform routine or instrumental activities of daily living. Several studies have now examined the relationship between cognitive dysfunction and ADLs in MS; Rao, Leo, Ellington, and colleagues' 1991 study is perhaps the first in the literature to examine this relationship. They found that the cognitively impaired and cognitively intact groups were not significantly different in EDSS scores or for noncognitive scales from the ISS. Compared with cognitively

intact patients, cognitively impaired patients required more personal assistance, as rated on the ESS; were significantly more dependent in their ADLs on the BI; and in the homemaking evaluation displayed significantly greater difficulty following recipes and demonstrating proper utensil use. Of note, the finding regarding utensil use was not statistically significant when differences between the groups in upper extremity incoordination were covaried out of the analysis.

In a study examining 31 cognitively and functionally impaired patients with MS, Higginson and colleagues (2000) used standard clinical neuropsychological tests of memory and attention in addition to two batteries of memory and attentional tests designed to be more ecologically valid, to predict ADLs in MS. The standard clinical tests included the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987), 7/24 Spatial Recall Test (Rao, Leo, Bernardin, & Unverzagt, 1991), PASAT, and oral Symbol Digit Modalities Test (Smith, 1982); the ecologically valid batteries were the Rivermead Behavioural Memory Test (RBMT; Wilson, Cockburn, & Baddeley, 1985) and the Test of Everyday Attention (TEA; Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994). The ESS (described earlier) was used to measure ADLs. The standard neuropsychological tests were quantified into one index based on the number of scores below the 16th percentile of the MS sample; a comparable strategy was conducted using the subtests from the ecologically valid batteries. These investigators found that both summary indices were significantly ( $\geq .40$ ) correlated with the ESS. More specifically, the following standard subtests were significantly ( $p < .05$ ) correlated with the ESS: CVLT Long-Delay Free Recall, PASAT, and Symbol Digit; on the RBMT, the Name, Belonging, and Story-Delayed subtests; and on the TEA, the Elevator Counting with Distraction, Elevator Counting with Reversal, and Time per Switch from the Visual Elevator task. In a stepwise regression analysis including the two summary indices, only the ecologically valid cognitive index significantly predicted ESS score after level of physical disability (EDSS score) was controlled for.

Grasso, Troisi, Morelli, and Paolucci (2005) examined the relationship between two measures of ADLs (the BI and the Rivermead Mobility Index [RMI]) and cognitive functioning in a group of 230 patients with primary and secondary progressive MS who had undergone a 3-day-a-week, 8-week rehabilitation treatment program. Cognitive functioning was categorized in EDSS format for functional systems (none, minimal, moderate, and severe impairment) by using the results of a neuropsychological evaluation. These investigators found that worse overall scores on the BI were significantly associated with worse cognitive performance. They also found that patients who were not severely impaired cognitively had a probability of improvement on the RMI that was almost twice as high as that of the severely impaired group. These authors speculated that cognitively impaired patients with MS may not be able to benefit from rehabilitation treatment because they may be unable to collaborate with the rehabilitative team in an effective way. One limitation of this study is that, given the broad-based nature of a measure such as the BI, it is unclear which aspects of ADLs were associated with cognitive impairments. Also, the authors did not describe the neuropsychological battery used, nor did they attempt to examine the association between ADLs and specific types of cognitive difficulties.

In a study with implications for rehabilitation, Basso and colleagues (Basso, Lowery, Ghormley, Combs, & Johnson, 2006) examined whether self-generated encoded-

ing improved memory for names, appointments, and object locations in a sample of patients with MS and moderate to severe memory problems. They found that, compared with a didactic procedure for encoding information, even patients with moderate-to-severe memory problems had better recall in ADLs when the information was self-generated. As these authors speculate, it may be that memory-impaired patients with MS would be able to improve their ability to remember names, appointments, and object locations—basic ADLs—if they developed strategies to encode this information themselves.

One limitation of the studies that have been conducted on cognitive dysfunction and ADLs in patients with MS is that most have used subjective reports of ADLs (but cf. Rao, Leo, Ellington, et al., 1991). As Goverover and her colleagues (2005) have noted, subjective reports may be limited in their accuracy, in that the relationship between subjective and objective indicators of ADLs is often weak. In response to this gap in the literature, Goverover et al. conducted a study that examined instrumental ADLs using subjective (Functional Assessment of Multiple Sclerosis [FAMS]) and Functional Behavior Profile questionnaire completed by both patients and significant others), and objective measures (Executive Function Performance Test [EFPT]). In the EFPT patients carry out six ADLs, including hand washing, simple cooking, telephone use, medication management, and bill paying (a more complex cooking task was also included). These investigators found that self-reported measures of ADLs were not significantly correlated with EFPT scores. These results suggest caution in interpreting self-reported ADLs in MS, because they may not accurately reflect patients' ability to actually perform various ADLs. However, it is also notable that the authors failed to find significant correlations between self-reported ADLs and EFPT scores in the healthy controls, suggesting that self-report measures and the EFPT measures may be tapping into different aspects of ADL functioning. It may also be the case that the novelty of the environment in which the EFPT tasks were completed provided an additional executive challenge that the participants do not experience in their home environments (e.g., using an unfamiliar stove and utensils to prepare a casserole vs. preparing a familiar recipe at home with frequently used appliances and utensils). This additional executive demand may result in poorer performance and a discrepancy between participants' self-ratings and their performance on the objective measure.

Overall, the existing data on the association between cognitive dysfunction and performance of ADLs in patients with MS indicate that there is a consistent relationship whether ADLs are measured via actual performance or self-report, despite the fact that there may be little association between objective and subjective measures of these ADLs. The data also suggest intriguing clues regarding what might be helpful to patients in rehabilitation. Patients with mild-to-moderate (but not severe) cognitive impairments appear to show some benefit from rehabilitation programs, even if the outcome measure for the rehabilitation is not cognitive (i.e., mobility). That said, even patients with more severe memory impairments appear to be able to improve their memory of important everyday activities if they self-generate the information that needs to be remembered. Caution is warranted with such an extrapolation, however, because in each of these latter cases, only one study reports the finding.

### Driving Ability

Several studies on the relationship between cognitive functioning and driving in MS have been published in recent years. Schultheis, Garry, and DeLuca (2001) appear to have published the first empirical study examining this issue. These investigators compared 13 patients with MS and cognitive impairments with 15 cognitively normal patients with MS and 17 healthy controls on two computerized measures of driving ability. Most of the patients with MS had a relapsing-remitting course type, though of note, a definitive course type could not be ascertained for almost 30% of the sample. Cognitive functioning was assessed with a brief battery of commonly used neuropsychological tests. Participants with MS were included in the cognitively impaired group if they scored below the 5th percentile of controls on at least two of the neuropsychological tasks. The computerized driving tasks included the Neurocognitive Driving Test (NDT) and the Useful Field of Vision (UFOV) test. The UFOV quantifies the visual field area in which drivers rapidly process visual information; it consists of three subtests involving visual information processing, divided attention, and selective attention. The UFOV generates an overall score and also categorizes participants according to risk level (low, moderate, high). The NDT is also computerized and assesses driving-related skills in an ecologically valid format. There are five sections to the NDT that are quantified into two composite scores, with one composite involving response latency and the other involving errors. Schultheis and colleagues found that cognitively impaired patients with MS performed significantly more slowly than both cognitively intact patients with MS and healthy controls on the response latency score from the NDT, and the effect size for the comparison between MS groups was very large (Hedge's  $g$  for effect size = 1.84). The groups did not differ on errors on the NDT. On the UFOV test, significantly more cognitively impaired patients with MS (29%) were classified in the high-risk group for probability of driving difficulties compared with both the cognitively intact participants with MS and the healthy controls (0% for both). The cognitively impaired group with MS also performed significantly worse than the other two groups on the central vision and processing section of the UFOV; additionally, cognitively impaired patients with MS performed significantly worse than healthy controls on the selective attention subtest of the UFOV. Thus, these investigators reported the first clear evidence that cognitive impairment in MS was associated with driving difficulties on a simulated test, especially on driving-related activities involving rapid information processing. These findings dovetail nicely with the numerous studies that have demonstrated that deficits in information processing speed are one of the most commonly observed cognitive problems in patients with MS.

Korretba, Orth, Eren, Fangerau, and Sindern (2003) extended Schultheis and colleagues' (2001) work by comparing the performances of 31 patients with relapsing-remitting MS in a driving simulator with those of 10 healthy matched controls. The driving simulation, conducted using the computer-aided risk (CAR) simulator, involved participants driving for 60 minutes on a "highway." Various obstacles were presented to the drivers, as well as a variety of driving conditions. Concentration errors were identified, including errors of omission—disregarding the speed limit, traffic lights, or the right of way—as well as of commission—turning too far to the right or left or touching curbstones or the opposite lane. Finally, accidents were

talled. Participants were also administered the MS Functional Composite (MSFC) and the EDSS. As noted earlier, the latter is primarily a measure of ambulation that has been most commonly used to quantify disability in MS. The MSFC is a more recently developed measure of disability that measures ambulatory function, arm-hand function, and cognition. Kortebe and colleagues found that the accident rate and the number of concentration faults were significantly higher in patients with MS compared with controls. Interestingly, neither the EDSS nor the two physical components of the MSFC were correlated with either of these difficulties; however, the cognitive index from the MSFC was significantly correlated with concentration errors on the CAR. One important finding from the study that the authors noted is that most accidents occurred during the daytime and in sunny conditions. They reasoned that such situations may have been monotonous, leading to low arousal levels in the participants with MS, and thus making them differentially susceptible to accidents.

One limitation of Kortebe and colleagues' (2003) study is that differential levels of fatigue may have played a role in the poorer performance of patients with MS; however, the authors did not report on fatigue levels of the sample. Another limitation of this study is that the authors used only one test to measure cognitive dysfunction, the PASAT, which is the only measure used to assess cognition on the MSFC. Though the PASAT is conceptualized as a measure of working memory and speeded information processing, it draws upon a number of other cognitive abilities as well. Thus, it is difficult to identify the kinds of cognitive mechanisms that might underlie the driving difficulties of patients with MS in this type of study—a limitation that a future study could rectify by including a broader-based assessment of cognitive functioning that would allow for more precise quantification of the specific types of cognitive problems that were the primary contributors to driving difficulties.

Shawarzyn, Schulteis, Garay, and DeLuca (2002) conducted a study similar to Kortebe's (2003) investigation in that they examined the relationship between MSFC scores and driving indices in 29 mostly relapsing–remitting patients with MS. In addition to using the NDT and UFOV measures described above, these investigators included number of self-reported motor vehicle collisions (MVCs), as well as the number of violations and crashes formally reported to the Department of Motor Vehicles (DMV) from the states in which participants lived. These investigators found that the cognition index from the MSFC was significantly inversely correlated with all three UFOV indices, in addition to the response latency index from the NDT. The hand and leg/ambulation components of the MSFC were significantly correlated with the measure of selective attention from the UFOV, and the MSFC hand index was also significantly associated with response latency on the NDT. These authors also found that the overall MSFC (but none of the subcomponents) was inversely correlated with number of reported DMV crashes. One limitation of this study is that they found that education was significantly correlated with overall UFOV score. It was unclear from their follow-up analyses whether this overall UFOV score would still have been significantly predicted by the cognitive component of the MSFC if education had been covaried out of the equation. Other limitations (acknowledged by the authors) included relatively small sample size, in addition to a limited range of physical disability in the sample.

Schulteis, Garay, Mills, and DeLuca (2002) compared 13 cognitively impaired and 14 cognitively intact patients with MS with 17 healthy controls on the numbers of formal MVCs and motor vehicle violations (MVs) during the previous 5-year period. Most of the patients had relapsing–remitting MS. The cognitively impaired group with MS showed a significantly greater incidence of one or more MVCs compared with both other groups; the groups did not differ on the number of MVs. The authors' findings on MVCs were especially striking in that the cognitively impaired group with MS also reported driving fewer days per week than the other groups. One potential limitation of this study is that the cognitively impaired group with MS also had significantly less education than the cognitively intact group with MS; however, the cognitively impaired group was very similar to the healthy control group in this regard, so educational differences among the groups in the study are less likely to explain the authors' findings. Another limitation with this study is that a fairly high proportion (almost 30%) of the patients' diagnoses could not be confirmed.

Marcotte and colleagues (2007) evaluated the relative influence of physical versus cognitive difficulties on driving in 17 patients with MS who had some complaints of spasticity and 14 healthy matched controls. Using spasticity as an index of physical difficulties and a battery of commonly used neuropsychological tests to measure cognitive problems, these investigators examined participants' performance on lane-tracking and car-following tasks in a driving simulator. The patients with MS performed significantly worse on both driving tasks. Additionally, the number of impairments on neuropsychological tests was most predictive of difficulty attending to multiple stimuli in the simulator, as well as slowed reaction to speed changes in the car that patients were following. The Trail Making Test Part B, Hopkins Verbal Learning Test—Revised, and Symbol Digit Modalities Test were the most predictive of deviations in lateral position while driving in the simulator. Spasticity was most predictive of difficulties making pedal movements in the simulator. The authors concluded that both cognitive impairments and spasticity could undermine patients' driving performance and that clinicians should attend to both when evaluating patients' suitability for continued driving.

These recent studies examining the ecological validity of neuropsychological tests in the context of driving are provocative. One limitation is that the sample sizes for all of the studies have been relatively small and, with the exception of Marcotte and colleagues' (2007) study, usually limited to patients with minimal physical disabilities. Most of these studies intentionally screened their samples for such patients so that the investigators could more clearly examine the influence of cognitive dysfunction uncontaminated by serious physical problems. Nonetheless, as these authors acknowledge, such an approach limits the generalizability of their findings. With that said, Marcotte and colleagues' study shows that, even in patients with physical problems, cognitive difficulties still make some independent contribution to particular driving problems. Another limitation is that two of the five existing studies used only one task (the PASAT) to measure cognitive dysfunction. Reliance on one task such as this does not allow for a thorough examination of the different cognitive factors that may be critical for an adequate driving performance that is relatively free of driving errors and MVCs. Two of the other three studies, though using more comprehensive

cognitive batteries, nonetheless used approaches whereby it was not possible to discern which cognitive impairments (e.g., in memory, attention, information-processing speed, executive functioning) identified on testing were most predictive of driving difficulties.

A final limitation in these studies is that the possible mediating role of depression was not examined. In fact, depression was not reported in any of the above studies. As noted earlier, data published in recent years shows that depression is associated with cognitive dysfunction in some MS samples (e.g., Arnett, 2005; Denney et al., 2004; Landro et al., 2004). This issue has important treatment implications, because if depression results in cognitive dysfunction in some patients with MS, which in turn leads to driving problems, then treatment of depression could improve cognitive functioning and lead to improvements in driving. Of course, such a scenario is speculative, but nonetheless, not implausible. A follow-up study examining the possible role of depression in this equation thus seems warranted.

### **Medication Management/Adherence**

Individuals with MS often have complicated medication regimens, including disease-modifying medications as well as multiple symptom-specific agents such as those for bladder dysfunction or spasticity. Four of the disease-modifying treatments (Avonex, Betaseron, Copaxone, and Rebif) are self-injectable, and dosing varies from daily to once a week. Maintaining adherence to variable medication schedules places demands on executive, attentional, memory, and to some degree, motor skills. Given that the efficacy of disease-modifying treatments has been well established (Burks, 2005; Copola et al., 2006; Sandberg-Wollheim, 2005), as has the long-term nature of damage done by increasing lesion loads, it is critical to examine any factors that negatively impact treatment adherence. This issue is particularly important when one considers that disease-modifying treatments such as Interferon beta-1a and 1b not only prevent deterioration, but may actually improve cognitive functioning in patients with MS (Barak & Achiron, 2002; Fischer et al., 2000; Pliskin et al., 1996). Investigators have examined psychological factors that contribute to treatment adherence, such as self-efficacy, hope, and perception of physician support (Fraser, Hadjimichael, & Vollmer, 2001; Fraser, Morgante, Hadjimichael, & Vollmer, 2004); perception of medical staff empathy (Mohr, Goodkin et al., 1999); therapeutic expectations (Mohr et al., 1996); and depression (Mohr, Goodkin, Likosky, Gatto, et al., 1997). However, to our knowledge, there are no published reports of empirical studies of the relationship between cognitive functioning and medication adherence in MS.

Examination of other literatures reveals a similar dearth of empirical research. However, some recent work has examined this question in medical populations such as hyperlipidemia, hypertension, and HIV/AIDS. Stille, Seretka, Muldoon, Ryan, and Dunbar-Jacob (2004) found, in a sample of 158 adults with hyperlipidemia, that higher IQ, mental flexibility, and visuospatial-constructional ability predicted better adherence to a cholesterol-lowering drug. It is worth noting that overall, this sample was not cognitively impaired. In a study of adherence in 48 adults with hypertension, Morrell, Park, Kidder, and Martin (1997) found that working memory was not a significant predictor of total antihypertensive adherence errors in regression analy-

ses, but was correlated with treatment nonadherence for other (nonantihypertensive) medications. In a study of medication adherence in 57 adults who were HIV-positive Albert and colleagues (1999) found that cognitive functioning significantly predicted performance on a test of medication management. More specifically, the researchers reported that poorer performance on an executive functioning measure and a test of fine motor speed and coordination was associated with poorer performance in a test of pill dispensing. Poorer scores on a test of memory predicted poorer performance on a "medication inference" component of the medication management test that involved figuring out whether a mock dose had been missed and predicting how long a prescription would last.

Although these studies may offer clues as to the relationship between cognitive functioning and medication adherence in MS, it is important to note that patients with hypertension, hypercholesterolemia, or HIV face different challenges and experiences than patients with MS. It will be important for future research to address which elements, if any, of cognitive functioning are related to medication adherence and to address possible methods of remediation of deficits that are associated with nonadherence. Adapting a paradigm such as that used by Albert and colleagues (1999) might provide a good starting point in this regard.

### **Vocational Status**

Unemployment rates in MS populations have been reported as high as 80% (Scheinberg et al., 1980), with some research showing that 70–80% of patients with MS are unemployed within 5 years following diagnosis (Kornblith, LaRocca, & Baum, 1986). Because MS affects many individuals in the early stages of their careers, work disability due to MS may affect attainment of life goals, worsen financial difficulties, and exacerbate caregiver stress. In addition to its obvious financial importance, employment has also been found to be related to quality-of-life ratings in MS (Koch, Rumrill, Roesler, & Fitzgerald, 2001). Considering the immense importance of mitigating disability due to MS, clinicians should be aware of factors that reliably predict change in employment status in order to assist patients with treatment planning and better focus rehabilitation efforts.

Several studies have examined factors associated with work status change in MS. Greater physical disability (Beatty, Bianco, Wilbanks, Paul, & Hames, 1995; Edgley, Sullivan, & Dehoux, 1991; Kornblith et al., 1986; LaRocca, Kalb, Scheinberg, & Kendall, 1985; Smith & Arnett, 2005), increased age (Beatty et al., 1995; Edgley et al., 1991; Kornblith et al., 1986), and less education (Edgley et al., 1991; Kornblith et al., 1986; LaRocca et al., 1985) have been found to be related consistently to unemployment in MS. Factors that have less consistent support include gender (males more likely to be employed) (LaRocca et al., 1985) and longer diagnosis duration (Bauer & Firthaber, 1965; Beatty et al., 1995). Depression has been found to be related consistently to unemployment in general population samples (Dooley, Catalano, & Wilson, 1994; Üstün, 2001) but not in MS (Beatty et al., 1995; Smith & Arnett, 2005).

Due to the cognitive challenges that many people encounter as a part of their work, one might expect cognitive impairment to be a contributing factor to unemployment in individuals with MS. Additionally, Kalechstein, Newton, and van Gorp

(2003) have reported that cognitive functioning is associated with employment status in neurological populations, though patients with MS were not included in this review.

In published empirical studies examining neuropsychological test data and their relationship to unemployment in MS (Beatty et al., 1995; Benedict et al., 2005; Smith & Arnett, 2005), results have been mixed. In the study described earlier, Rao, Leo, Ellington, and colleagues (1991) reported that, compared with cognitively intact patients, the cognitively impaired patients with MS were less likely to be employed. Beatty and colleagues (1995) examined 38 employed patients with MS and 64 patients with MS who had retired due to their illness. The authors reported that, in addition to age and physical disability, memory (as measured by the verbal Selective Reminding Test [SRT]) and the Brown-Peterson Test of Short-Term Memory) and verbal fluency (as measured by the Controlled Oral Word Association Test [COWAT]) significantly predicted employment status in a regression model. The employed participants also performed significantly better on neuropsychological measures than those who were no longer employed. Benedict and colleagues (2005), in a study utilizing a clinic sample of 120 patients with MS, found that performance on three cognitive tests (the Judgment of Line Orientation test, Symbol Digit Modalities Test, and the perseverations index on the WCST) significantly predicted employment status (employed vs. unemployed due to MS) in a regression model that included disease duration and a measure of conscientiousness.

We reported findings that were inconsistent with these results (Smith & Arnett, 2005). In a community-based sample of 50 individuals with MS, we controlled for the effect of participants' education levels, depression levels, medication effects, and age on their test performance. After doing this in a multivariate analysis, we found that participants who cut back on their hours due to MS, participants who left their jobs due to MS, and participants who remained employed full time were not significantly different on a variety of cognitive measures commonly found to detect impairment in MS (the PASAT, the oral Symbol Digit, the SRT, the Tower of Hanoi, the COWAT, and the 7/24 Spatial Recall Task). Additionally, when asked what MS symptoms precipitated their employment status change, only a relatively small percentage (10% of the group that cut back on hours, and 29% of the group that left jobs) of participants reported that cognitive symptoms were responsible. This finding is consistent with the results of Edgley and colleagues (1991), who found that only 12% of their unemployed sample reported cognitive symptoms (when asked in an open-ended format) as a primary reason for having discontinued employment. It may be that, although cognitive impairment is common in patients with MS who have had to stop working, it is not the deciding factor for patients who are considering leaving their jobs. This hypothesis is supported by the finding that the majority (86%) of the unemployed patients with MS in our (Smith & Arnett, 2005) sample reported that they left their jobs due to physical or neurological symptoms. It may be that, although patients with MS experience difficulties at work due to their cognitive symptoms, physical symptoms pose the greatest challenge and result in the most disability.

There are many areas for future research to explore in this area. The extent of the impact of cognitive impairment on employment in MS is still unclear, though most studies support a relationship. Additionally, to our knowledge no published empirical studies have examined which cognitive domains may be most influential in affect-

ing employment in individuals with MS. Further investigations into these questions will improve our understanding of the impact of cognitive symptoms in MS and may help cognitively impaired individuals with MS decide between struggling to maintain employment or facing early retirement on disability.

### **Social Functioning and Quality of Life**

Quality of life (QOL) is a somewhat vague concept that often includes a person's life satisfaction, happiness, and standard of living. Within the health sciences, health-related quality of life (HRQOL) is frequently the focus of investigation. The concept of HRQOL specifically refers to the amount a person or group is affected by physical or mental health problems. HRQOL is distinct from QOL, which is decidedly "more difficult to conceptualize and operationalize because it is affected by economic, political, cultural, and spiritual factors that are not the primary focus for health-care providers" (Shawaryn, Schiaffino, LaRocca, & Johnston, 2002, p. 310). "Social functioning" represents another difficult-to-define concept, closely related to QOL. In the current review, we explore the literature regarding the relationship between cognitive dysfunction, social functioning, and HRQOL in MS.

In an exploration of the relationship between cognitive functioning, fatigue, depression, and dyadic adjustment in MS, King and Arnett (2005) found that neither patient nor significant-other ratings of dyadic adjustment were significantly correlated with performance on measures of speeded attention/working memory or long-term memory. However, they reported that executive dysfunction was a significant predictor of significant-other-rated dyadic adjustment, indicating that the significant others of patients experiencing greater executive dysfunction rated the quality of their relationships more negatively. It is important to note that in this investigation, cognitive dysfunction was found to be a weaker predictor of poor dyadic adjustment than fatigue or depression.

Overall, individuals with MS experience poorer QOL when compared with neurologically healthy individuals (Benedict et al., 2005; Shawaryn, Schiaffino, et al., 2002) and individuals with other chronic illnesses (Rudick, Miller, Clough, Gragg, & Farmer, 1992). However, QOL has often been neglected as an outcome measure for treatment of MS (Janardhan & Bakshi, 2000) in favor of physical disability as measured by the EDSS. More recently, investigators have attended to QOL measures as a better reflection of the true impact of MS on an individual's life and, more specifically, research has examined the effect of cognitive dysfunction on HRQOL.

Benedict and colleagues (2005) found that performance on the Brief Visual Memory Test—Revised (BVMTR) Recognition index was a significant predictor of QOL as measured by the MSQOL-54P, an expansion of the Short Form Health Survey 36 (SF-36) questionnaire, though performance on a variety of other measures sensitive to deficits typically seen in MS (the COWAT, the Judgment of Line Orientation test, the CVLT-II, the Symbol Digit Modalities Test, the PASAT, and the WCST) was not significant. Additionally, the BVMTR Recognition index was no longer a significant predictor when noncognitive variables were entered into the regression model. In contrast, Shawaryn, Schiaffino, and colleagues (2002) reported that performance on the PASAT was a significant predictor of HRQOL as measured by the SF-36 Mental Component Summary, a measure of mental and emotional aspects of

HRQOL. However, despite the authors' assertion that depression has not been found to be related to measures of cognitive functioning, our earlier review on this topic illustrates that many studies have now demonstrated that depression is significantly associated with worse performance on measures of complex information processing, such as the PASAT. These data suggest that Shawarzyn and colleagues' results should be interpreted with caution, as depression may be partially driving the effect in the relationship they reported between HRQOL and the PASAT. The researchers also found that verbal memory (as measured by the CVLT) was a significant predictor of "physical aspects" of HRQOL, along with EDSS scores. In a similar study including a sample of 52 patients with MS, Barker-Collo (2006) found that a composite score of information-processing speed measures (PASAT, Stroop, COWAT, and the Computerized Test of Information Processing) was not a significant predictor of scores on the SF-36. However, the author reports that the effect size indicates that information-processing speed does influence QOL ratings. Unfortunately, Barker-Collo did not consider the possibility of depression influencing this relationship. In other words, if the patients who are experiencing more depression are also experiencing more information-processing dysfunction, then it may be that depression is a moderator in this relationship, as depression has, not surprisingly, been found to be significantly negatively correlated with HRQOL (Amato et al., 2001; Spain, Turbidity, Kilpatrick, Adams, & Holmes, 2007).

Curafar and colleagues (2000) found that performance on the Rivermead Behavioral Memory Test was significantly negatively correlated with the emotional subscale of the SF-36 in 40 patients with MS. The authors also report that performance on the Luria Frontal Lobe Syndrome Test (LFST) was significantly negatively correlated with scores for physical functioning and life satisfaction on the SF-36. However, LFST performance was also positively correlated with depression, which was not controlled for in the analyses. In another study using the SF-36, Spain and colleagues (2007) found that performance on the Symbol Digit Modalities Test did not predict overall physical and mental health subscale scores in a regression model when other disease variables (e.g., EDSS, depression, fatigue, pain) were entered.

Ryan and colleagues (2007) examined predictors of psychological distress, global life satisfaction, and HRQOL in a sample of 74 individuals with MS. They found that cognitive functioning (as measured by a composite score based on performance on the SDMT, the Brief Test of Attention, Judgment of Line Orientation—Short Form, WAIS-III Letter-Number Sequencing, a Stroop test, the COWAT, the CVLT-II, and the WCST) was a significant predictor of life satisfaction and HRQOL (i.e., more cognitive impairment was related to poorer life satisfaction and HRQOL), though the effect size was small. The authors report that psychological distress and cognition were not significantly related in their sample and note that this is in contrast to previous findings suggesting that patients with MS with higher levels of depression tend to perform more poorly on neuropsychological measures. However, rather than using a measure assessing depression symptoms such as the BDI, they examined the relationship between cognition and psychological distress in general, which may explain the discrepancy in their findings.

In a large sample of MS patients, Benito-Leon, Morales, and Rivera-Navarro (2002) examined the relationship between cognitive dysfunction and HRQOL using the FAMIS QOL questionnaire. This 52-item measure has six subscales that measure

mobility, symptoms, emotional well-being, general contentment, thinking/fatigue, and family/social well-being. Cognition was measured by the Mini-Mental State Examination (MMSE) and the clock-drawing test. The researchers reported that both cognitive tests were significantly negatively correlated with all six subscales of the FAMIS, indicating that low HRQOL was associated with higher levels of cognitive impairment. The authors also found that physical disability, as measured by the EDSS, and depression and anxiety, as measured by the Hamilton Depression Rating Scale and the Hamilton Anxiety Rating Scale, were significantly correlated with decreased HRQOL. A positive aspect of this study is that as a cognitive screening tool, performance on the clock-drawing test is typically not affected by an individual's level of depression (Herrmann, Kidron, & Shulman, 1998; Wolf-Klein, Silverstone, & Levy, 1989), and it may be therefore concluded that the association between performance on this test and HRQOL was not likely due to depression.

In a sample of 30 extremely impaired patients with MS, Kenaly and colleagues (2000) found that patients with intact autobiographical memory, as measured by the Autobiographical Memory Interview, reported the highest levels of depression, as measured by the Hospital Anxiety and Depression Scale, and the lowest levels of HRQOL, as measured by the SF-36. Surprisingly, the patients with impaired autobiographical memory (60% of the sample) reported higher levels of HRQOL than their intact counterparts. The authors interpreted these findings to suggest that severe cognitive impairment may affect the ability to accurately judge one's own HRQOL. This study suggests that cognitive impairment may not only negatively affect QOL, but also, in cases of severe impairment, might affect the ability of patients with MS to make accurate self-ratings.

The results of the research summarized above are difficult to interpret, given that most studies did not employ consistent measures of cognitive functioning. Additionally, a number of researchers did not control for the possibly confounding effects of comorbid depression on the relationship between cognitive dysfunction and HRQOL. However, it is clear that cognitive dysfunction has some negative impact on HRQOL, though the magnitude of this relationship, the role of depression, and the specific cognitive domains involved remain unclear.

### **Sexual Dysfunction**

Sexuality is influenced by a complex interplay of psychological and physiological factors. Recent functional imaging research has indicated that sexual arousal and response are linked to activity in many areas of the brain, including the cerebellum, limbic system, and multiple other cortical and subcortical regions (Rees, Fowler, & Maas, 2007). In general, people with MS experience lower levels of sexual activity, sexual relationship satisfaction, and sexual satisfaction (McCabe, McKern, McDonald, & Vowels, 2003). Disruption of sexual functioning in MS may be influenced by a variety of symptoms such as impaired mobility, depression, spasticity, impaired sensation, and bowel and bladder functioning. Deminkiran and colleagues (2006) assert that spinal cord lesions are considered to be the major cause of sexual dysfunction in MS; however, Zivadinov and colleagues (2003) found that in a magnetic resonance imaging (MRI) study of 31 patients with MS, sexual dysfunction was predicted only

by T1 lesion load of the pons. Not surprisingly, rates of sexual dysfunction are high in MS populations and have been reported at 50–90% (Dupont, 1995). Iatrogenic sexual dysfunction is also seen in MS, typically associated with antidepressants and antispasmodic agents (Dupont, 1995). In McCabe and colleagues' (2003) sample of 120 men with MS, the top three sexual problems reported were erectile problems (37.3%), lack of sensation (35.9%), and lack of sexual interest (31.7%), all of which were significantly higher than the rates reported by their sample of 79 neurologically healthy men. In the same investigation, the 201 female participants with MS reported the top three sexual problems were anorgasmia (45.1%), lack of sexual interest (42.9%), and lack of sensation (36.2%). Out of these problems, only lack of sensation occurred at a statistically significantly higher rate in the women with MS compared to the 160 neurologically healthy participants.

Because sexuality is often considered a sensitive topic, it has been historically underresearched. This problem is compounded by the fact that the sexuality of women with MS (who are disproportionately affected) and people with disabilities has typically been neglected (Dupont, 1995; Schmidt, Hofmann, Niederwieser, Hapflammer, & Bonelli, 2005). More recently, however, investigators have begun to explore this issue in MS.

Despite Rao, Leo, Ellington, and colleagues' (1991) finding that cognitively impaired patients with MS reported more sexual dysfunction relative to healthy controls, to our knowledge, there are few empirical studies of the relationship between objective cognitive measures and sexual dysfunction in MS and little research in this area in neurological populations in general. Demirkiran and colleagues (2006) found that, out of a clinic-based sample of 67 patients with MS, 41 reported sexual dysfunction. Although the groups did not differ on MMSE scores, the patients with sexual dysfunction were more likely to report memory and concentration problems. This self-report of cognitive problems was significantly correlated with decreased libido, impaired genital sensation, and decreased lubrication or difficulties with erection. However, it is difficult to interpret whether these groups were truly different in terms of memory and concentration functioning. Given that the MMSE is a screening measure and not sensitive to the cognitive deficits typically seen in MS, the finding that the groups were not different on this measure does not indicate that there are no cognitive differences to be found. However, self-report of cognitive dysfunction has been demonstrated to be associated with depression (Bruce & Arnett, 2004; Carone, Benedict, Munschauer, Fishman, & Weinstock-Gurtman, 2005; Maor, Omer, & Mozes, 2001; Randolph, Arnett, & Freske, 2003), a common correlate of sexual dysfunction. This finding indicates that the correlation between sexual dysfunction and self-reported cognitive impairment may be due, at least in part, to level of depression. Such an inference is supported by findings that depression in MS is associated with negative cognitive biases (Bruce & Arnett, 2005), something that might result in both differentially high self-reports of both sexual dysfunction and cognitive difficulties.

Zivadinov and colleagues (2003) found that sexual dysfunction had a significant, large, negative correlation with performance on the MMSE in a sample of 31 patients with relapsing-remitting MS. However, in this investigation, the patients with sexual dysfunction were also significantly older, more depressed and anxious, and had lon-

ger disease durations than the patients who did not report sexual dysfunction, and these factors were not controlled for in the analyses.

In the traumatic brain injury (TBI) literature, Crowe and Ponsford (1999) reported that, in a sample of 14 men with TBI who reported sexual dysfunction subsequent to their injury and 14 age- and education-matched healthy controls, the TBI group scored lower on the Sexual Imagery subscale of the Imaginary Processes Inventory, after controlling for differences in depression as measured by the BDI. The authors interpreted this result as suggesting that cognitive impairment secondary to brain injury was inhibiting sexual imagery required for arousal. If this can be assumed to be the case, it provides a hint to possible relationships between complex cognition and sexual functioning.

As noted previously, many questions remain as to the relationship between cognitive dysfunction in MS and sexual dysfunction. Although an investigation of this relationship would certainly be complicated by the myriad psychosocial and physiological factors that also contribute to sexual functioning, the studies noted above suggest that this may be a fruitful avenue of exploration.

### Summary and Conclusions

Research over the past 15–20 years has produced evidence to support the ecological validity of neuropsychological measures commonly employed to measure cognitive dysfunction in individuals with MS. These measures have been shown to predict driving difficulties, impairments in ADLs, reduced HRQL, and work/vocational difficulties. The literature on sexual dysfunction is sparse and inconclusive at this point, and there are as yet no published reports on the relationship between cognitive functioning and medication adherence in MS. Overall, however, the weight of existing research suggests that the tests most often used in assessing cognitive status in patients with MS are predictive of important real-world behaviors. As research moves toward a greater understanding of the pattern and prevalence of cognitive impairments seen in MS, it is important for our field to understand how these impairments affect patients in their daily lives. Future work is needed to replicate some findings, fill in some of the gaps outlined above, and define more precisely the kinds of dysfunctional cognitive operations that are problematic for specific daily tasks and activities. Such latter work should aid rehabilitation efforts that could be oriented toward circumventing the specific impaired cognitive functions necessary to perform everyday tasks, and developing alternative strategies that allow patients with MS to function more effectively as they attempt to cope with what can be a devastating disease. Additionally, more work examining the possible role that treatable factors such as depression may play in the relationship between cognitive dysfunction and everyday activities is likely to be fruitful.

### Author Note

This chapter represents an equal contribution by both authors.

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