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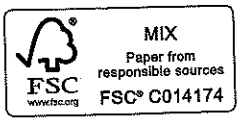

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25 Multiple Sclerosis and Related Disorders

Peter A. Arnett, Jessica E. Meyer, Victoria C. Merritt, and Lauren B. Strober

Introduction

Multiple sclerosis (MS) is the most common nontraumatic neurological condition of early to middle adulthood, and the most common demyelinating condition. Other demyelinating conditions include concentric sclerosis (also known as *Balo's disease*), Schilder's disease, Devic's disease, central pontine myelinolysis, and Marchiafava-Bignami disease. Rarer still are acute disseminated encephalomyelitis and acute hemorrhagic leukoencephalitis. Because MS is the only one of these conditions that has been adequately examined neuropsychologically, the focus of this chapter will be on MS.

Neuropathology

A central feature of MS is demyelination that is presumed to be caused by an autoimmune process, a slow-acting virus, or a delayed reaction to a common virus (Brassington & Marsh, 1998). Multiple discrete plaques at demyelinated sites are formed, in part, by proliferating astrocytes. The plaques are comprised of demyelination, inflammation, gliosis and axonal injury, and myelin sheaths within plaques are swollen and fragmented, or destroyed entirely. When intact, nerves of the central nervous system (CNS) are enclosed in myelin sheaths, which are separated by synaptic gaps from which the nerve impulse fires, facilitating neural conduction. Plaques associated with MS thus interfere with or block neural transmission by limiting this saltatory conduction process. Axons and cell bodies of neurons often remain intact. Lesions are typically found in a random or asymmetrical pattern in the periventricular, juxtacortical, and infratentorial regions.

Plaques occur in both the brain and spinal cord, and the location of plaques is highly heterogeneous among patients. Plaques in the cerebrum are most commonly located near the lateral and third ventricles and the periventricular region. The frontal lobes are next most commonly affected, but plaques in other major lobes of the brain are also frequently seen. Additionally, plaques are commonly seen in the optic nerves, chiasm, or tracts, as well as the corpus callosum, brain stem, and cerebellum. Furthermore, plaques can be found in white matter regions of the thalamus, hypothalamus, and basal ganglia.

Despite long-standing classification as a white matter disease, recent research has suggested significant involvement of gray matter, even early on in the disease (Zivadinov & Pirko, 2012). The most affected gray matter regions include the cingulate, thalamus, basal ganglia, hypothalamus, cerebellum, hippocampus, and frontal and temporal lobes (Horakova, Kalincik, Dusankova, & Dolezal, 2012). This type of cortical demyelination occurs most frequently in Progressive forms of MS and may be indicative of disease progression and potential irreversible disability (Popescu & Lucchinetti, 2012).

Epidemiology

The incidence of MS is lowest in regions close to the equator, with larger numbers of cases in northern and southern latitudes (from about 60 to 300 per 100,000, respectively). There are about 400,000 people with MS in the United States, and 2.5 million people worldwide (National MS Society, 2009). Females are approximately 2.5 times more likely than males to get MS, with some recent work suggesting this disparity is increasing (Koch-Henriksen & Sørensen, 2010), and peak onset for the disease is around age 30 (Chitnis et al., 2011). Those living north of latitude 40 degrees North are about three times as likely to have MS as are those living in the southern United States, a geographic pattern suggesting an environmental contribution to the disease. Still, the 30%–40% concordance rate in identical twins versus only 1%–13% in fraternal twins implicates a substantial genetic contribution, as well. Onset of the disease occurs between age 20 and 40 in 70% of patients (Compston et al., 2005); onset after age 40 is often characterized by quicker progression and greater morbidity. Life expectancy beyond disease onset is approximately 30 years, but there is significant variability around this mean.

Symptom Onset and Diagnosis

Early MS symptoms are variable, but the most common initial symptoms include muscle weakness, paresthesias (i.e., numbness and tingling in the limbs, trunk, or face), gait/balance problems, and visual disturbances. The latter usually involve decreased visual acuity, blurry vision, or diplopia. Urinary disturbance is also common, as are

balance difficulties. Cognitive dysfunction, fatigue, and depression are frequently observed, as well. MS symptoms are often transient and unpredictable. For example, visual disturbances and paresthesias may last for seconds or hours. Because of the short-lived and sometimes bizarre nature of the symptoms, it is not uncommon for patients to be diagnosed with hysteric/somatization disorders prior to a formal diagnosis of MS.

The diagnosis of MS is based on guidelines developed by McDonald and colleagues (2001), and these were subsequently revised in 2005 (Polman et al., 2005), and 2010 (Polman et al., 2010). The revision by Polman and colleagues in 2010 was the result of a consensus panel designed to simplify the criteria. Classifications in this new diagnostic system include "MS," "not MS," and "possible MS." Central factors for an MS diagnosis in this new system involve both clinical and paraclinical (e.g., the presence of oligoclonal bands in the cerebral spinal fluid, or CSF) assessments, lesions that are disseminated in space (DIS) and time (DIT), and disease attacks that last at least 24 hours. DIS occurs with the presence of at least one T2 lesion in at least two of four MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord), or by a clinical attack that implicates a different CNS site. DIT occurs when a new T2 and/or gadolinium-enhancing lesion(s) appears on follow-up MRI after a baseline scan has been conducted; DIT can also be demonstrated by the simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions.

Per the McDonald et al. (2001) system, MS sometimes presents with an insidious progression rather than via discrete attacks, and is known as Primary Progressive MS. For this to be demonstrated there must be evidence of at least one year of disease progression, as well as at least two of the following: (a) evidence for DIS in the brain, (b) evidence for DIS in the spinal cord based on the presence of at least two T2 spinal cord lesions, or (c) positive CSF findings (isoelectric evidence of oligoclonal bands and/or elevated IgG index).

Prior to the mid-1990s, MS was classified into two major disease course types: Relapsing-Remitting and Chronic Progressive. An updated system was then developed and is now more commonly used (Lublin & Reingold, 1996). Presently, there are four course types in this new system: Relapsing-Remitting, Secondary Progressive, Primary Progressive, and Progressive Relapsing. Relapsing-Remitting is the most common type and affects more than half of all patients. Relapsing-Remitting MS is characterized by clearly defined disease relapses where recovery can be complete or with sequelae and residual deficit; however, there is no progression of disease between relapses. Relapses typically last days to weeks, with a duration of hours or months being less common. The frequency of relapses is highly variable, and can occur weeks or even years apart.

The remaining course types are all progressive in nature and were formerly encompassed by the Chronic Progressive term. The Secondary Progressive course is next most common and always begins as a Relapsing-Remitting course, but is defined by progression occurring even between relapses, and relapses and remissions with this course may or may not occur. The median time to conversion from Relapsing-Remitting to Secondary Progressive course is 15–20 years (Loitfelder et al., 2011). The Primary Progressive type is next most common, and involves an unremitting disease progression from disease onset for most patients with no clear relapses. The least common MS course type is Progressive Relapsing, and this involves disease progression from onset that is punctuated by acute relapses from which patients may or may not fully recover.

Cognitive Functioning

Patterns and Prevalence

Rao, Leo, Bernadin, and Unverzagt's (1991) seminal study remains the definitive examination of prevalence of cognitive dysfunction in MS in a community-based sample, as it compared 100 community-based MS patients with 100 matched healthy controls on an extensive neuropsychological battery. This study showed that individuals with MS demonstrated the greatest impairment on measures of recent memory, sustained attention, verbal fluency, and conceptual reasoning, and were less frequently impaired on measures of language, visuospatial perception, and immediate and remote memory. From this, Rao and colleagues proposed a brief battery—subsequently named the *Brief Repeatable Battery* (BRB) of neuropsychological tests likely to be most sensitive to cognitive impairment in MS, based on the tests that most differentiated MS and normal controls in their study. This initial battery included the Paced Auditory Serial Addition Test (PASAT), Controlled Oral Word Association Test (COWAT), 7/24 Spatial Recall, and the Verbal Selective Reminding Test (SRT). The Symbol Digit Modalities Test (SDMT) was subsequently added for a five-test battery that took about 30 minutes to administer, and included multiple alternate forms for each test (Rao and the Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990). Additionally, the 7/24 Spatial Recall was expanded into a 10/36 Spatial Recall test that required more items to recall to enhance sensitivity. Subsequent studies have generally supported Rao and colleagues' findings about cognitive domains most affected in MS (Benedict et al., 2006; Bobholz & Rao, 2003; Chiaravalloti & DeLuca, 2010). Benedict and colleagues conducted their study on a clinic-based MS sample consisting of 291 MS patients and 56 healthy matched controls. The prevalence rates for cognitive impairment in their MS sample were often higher than Rao et al., though the same general pattern of domains typically affected was found. When discussing the different cognitive domains below, we will primarily reference Rao et al. and Benedict et al.'s studies, with prevalence rates of impairment typical of community-based samples based on the former and rates

typical of clinic-based samples based on the latter study. The two studies used similar cutoffs for impairment, with Rao and colleagues defining impairment at the fifth percentile (relative to controls) and Benedict et al. using 1.5 standard deviations below the mean of controls.

SIMPLE AND COMPLEX ATTENTION, INFORMATION PROCESSING SPEED

Simple attention span (as measured by tests such as Digit Span) is usually intact in MS patients, but mild impairments are sometimes found. However, MS patients typically show their greatest difficulty on tasks requiring rapid and complex information processing, including those requiring swift application of working memory operations, attentional switching, or rapid visual scanning. About 25%–30% of community-based MS patients and 25–50% of clinic-based patients show impairments on such tasks of complex attention and processing speed. Some investigators have asserted that slowed information processing is the most fundamental cognitive deficit in MS, noting that such difficulties impact new learning and the ability to perform higher-order cognitive functions (Chiaravalloti & DeLuca, 2010). Working memory and processing speed are typically measured by tasks such as the PASAT and SDMT. The SDMT appears to be more sensitive than the PASAT, perhaps due to its visual nature given that many MS patients have visual problems. Supporting this hypothesis, at least one study (Bruce, Bruce, & Arnett, 2007) has shown that primary visual acuity problems contribute significantly to performance on the SDMT in MS patients, even in patient groups who have been prescreened for significant visual problems. Thus, it appears that even subtle visual anomalies can impact performance on the SDMT, and perhaps inflate sensitivity measures in MS patients. Furthermore, rudimentary oralmotor deficits contribute to group differences on tasks such as the SDMT in MS (Arnett, Smith, Barwick, Benedict, & Ahlstrom, 2008), suggesting that both primary visual and primary oral motor factors may inflate sensitivity measures of the SDMT in MS. In terms of the practical impact of these types of deficits, patients with MS often complain of problems tracking things in conversation, following details of movies or television programs, and quickly and efficiently performing work tasks. Such everyday difficulties may stem from problems with complex attention and speeded information processing.

MEMORY

Memory difficulties in MS are usually manifested as deficits with immediate recall on neuropsychological testing. Although delayed recall is also commonly impaired, this appears to be mostly a function of limited immediate recall, as opposed to actual forgetting. Tests that are most commonly used to measure memory functioning in MS include the California Verbal Learning Test, second edition (CVLT-II), Brief Visuospatial Memory Test–Revised (BVMT-R), 10/36 Spatial Recall, and story memory tests such as Logical Memory from the Wechsler Memory Scale, or the Story Recall test. In community-based MS groups, about 25%–30% of patients have impaired recall, compared with 25% to more than 50% of clinic-based patients. Regarding the upper value for clinic-based patients, this is solely due to MS patients' impairment on the BVMT-R, so this latter test appears to be unusually sensitive to cognitive impairment in clinic-based MS samples. With that said, given the visual-motor problems that are common to MS, it may be that such a test has an inflated sensitivity because it may be affected by noncognitive (i.e., motor, visual) factors in addition to cognitive factors. Consistent with such a hypothesis, Benedict and colleagues (2011) found a high inverse correlation ($r = -0.45$) between BVMT-R performance and upper extremity function (as measured by the 9-Hole Peg Test, or 9-HPT). Their interpretation of such data was different, however, as they suggested that the causal relationship may run in the other direction, with higher-order cognitive functions impacting motor performance and thus accounting for the relationship. Such an interpretation was based, in part, by the fact that the 9-HPT was inversely correlated with performance on a number of other cognitively demanding tests with significant executive components (e.g., Delis-Kaplan Executive Function System [D-KEFS] Sorting Test, PASAT, and SDMT).

The learning curve across repeated trials of memory tests (e.g., CVLT-II, BVMT-R) is typically similar in slope in MS compared with controls, but is lower in magnitude. Working memory, or the ability to maintain and manipulate information "online," is also commonly impaired in MS. However, percent retention, recognition, incidental memory following a delay, remote memory, and semantic memory are usually intact.

Because memory-impaired patients usually display intact recognition memory, MS patients' memory recall problems were initially thought to be due to problems with retrieval (Rao et al., 1991). However, based on additional work finding that patients could recall a normative amount of information if given enough initial learning trials, some investigators asserted that these memory recall problems were primarily due to initial acquisition difficulties (DeLuca, Barbieri-Berger, & Johnson, 1994; Lafosse, Mitchell, Corboy, & Filley, 2013). More recent work has suggested that information processing speed deficits are much more predictive of memory recall problems than working memory deficits, suggesting the primacy of processing speed problems in memory recall tasks (Chiaravalloti, Stojanovic-Radic, & DeLuca, 2014).

In addition to being among the most common cognitive deficits found in MS using objective tests, patients with MS often come to the clinic complaining of memory problems. In practical terms, these get manifested as complaints of difficulty remembering conversations, appointments, and work tasks that are sometimes so debilitating that patients can no longer work at cognitively demanding jobs.

EXECUTIVE FUNCTIONING

The next most common cognitive domain typically affected in MS is executive functioning. Deficits in cognitive flexibility, concept formation, verbal abstraction, problem solving, and planning are very common. Tests most commonly used to measure these cognitive skills include the Wisconsin Card Sorting Test, D-KEFS Sorting Test, Stroop Color-Word Test, Booklet Category Test, and verbal fluency tests, among others. In community-based samples, 15%–20% of individuals with MS show impairments in this domain, whereas the range is between 10% and 25% in clinic-based samples. The range of variability is higher for clinic-based samples because in Benedict and colleagues' (2006) study, they found that very few patients displayed verbal fluency deficits on the COWAT, with more showing impairments on the D-KEFS Sorting Test. In everyday terms, problems in this very broadly defined executive functioning domain can manifest themselves in patients reporting problems planning their day-to-day activities (e.g., job tasks, meals, grocery shopping), organizational difficulties, and problems collecting their thoughts and maintaining the flow of conversation.

VERBAL-LINGUISTIC FUNCTIONING

Depending on the complexity of the task, verbal and linguistic skill deficits can be seen in MS. It is rare (though not unheard of) for patients to have aphasic disorders (Arnett, Hussain, Rao, Swanson, & Hammeke, 1996); mild confrontation naming difficulties are relatively more common, though still usually occur in less than 10% of community-based samples of MS patients. Similarly, alexia, agraphia, and apraxia are very rare. In contrast, speech abnormalities such as dysarthria and hypophonia are common in MS (Arnett, Vargas, Ukueberuwa, & Rabinowitz, 2013). As referred to earlier in the discussion of executive tasks, deficits in verbal fluency are found in 20%–25% of community-based patients, with a surprisingly lower number of clinic-based patients (less than 15% from Benedict et al.'s 2006 study) showing deficits. Still, the latter finding appears somewhat anomalous, as a meta-analysis in more severely affected (Chronic Progressive) patients (who would presumably most closely mirror Benedict and colleagues' clinic-based patients) showed a medium effect size across many studies for verbal fluency tasks in MS relative to healthy controls (Henry & Beatty, 2006). Evidence suggests that impairments in verbal fluency may be as great as impairments in speeded information processing (Henry & Beatty, 2006). This may be due to the fact that performance on verbal fluency tasks requires rapid information processing, so patients' poor performance on such measures may also be reflective of their speeded information processing deficits. It is also important to keep in mind that slowed speech in MS can contribute to patients' verbal fluency deficits (Arnett et al., 2013). In practical terms, patients who have verbal fluency deficits may complain of frequent word-finding problems in conversation, and generally feel as though their ability to readily communicate with others is impacted.

VISUOSPATIAL FUNCTIONING

Visuospatial functioning in neuropsychological terms involves perceiving relationships in space. In MS, visuospatial functioning is commonly screened using tasks such as Judgment of Line Orientation (JLO), with more complex tasks such as the Facial Recognition Test sometimes used. Deficits in this domain are relatively common in MS; in both community- and clinic-based samples, 15%–20% of patients show impairments. It is unclear whether higher order visual deficits are a function of primary visual disturbances involving blurred vision and diplopia (Rao et al., 1991). Patients who report problems in their daily lives with regard to visuospatial functioning may complain of problems running into things frequently while walking (e.g., doorways) or driving (e.g., hitting curbs) because of visual miscalculations.

INTELLECTUAL FUNCTIONING AND ACHIEVEMENT

Intellectual functioning is usually considered to be well-preserved in MS, and is in many patients. Still, in Rao and colleagues' (1991) seminal study, slightly over 20% of patients had deficits in verbal intelligence. Of note, however, few patients (less than 10%) displayed impairments in their fund of knowledge (Information subtest from the Wechsler Adult Intelligence Scale—WAIS), so the Information test may represent a reasonably good index of premorbid cognitive functioning in MS. Finally, there has been little systematic research in how achievement-related skills (e.g., reading, writing, and math) may change with MS progression, but they are generally assumed to be significantly affected in few patients.

Longitudinal Course

Cognitive impairment can occur at any stage of MS and across all disease courses. Even patients with recently diagnosed MS or clinically isolated syndrome (CIS) commonly show deficits, with 45%–49% of individuals with early MS or CIS patients in one study demonstrating impairment on at least one measure (Glanz et al., 2012). Cognitive deficits in and of themselves appear to confer risk for further cognitive decline, even over a two-to-three-year period (Kujala, Portin, & Ruutiainen, 1997). When examined longitudinally, declines in information processing speed, verbal learning and memory, visual memory, and attention/working memory are usually seen in MS, at least over relatively shorter time periods of three to five years (Glanz et al., 2012; Kujala et al., 1997; Nordin & Rorsman, 2012). Verbal fluency and executive function skills also decline during these shorter periods, but this is less common (Glanz et al., 2012; Till et al., 2012).

Longer-term longitudinal investigations (e.g., seven to ten years) reveal declines in long-term verbal memory (Feinstein, 2011), information processing speed, motor speed, reaction time, visuospatial ability, and visual short-term memory (Vattakatuchery, Rickards, & Cavanna, 2011). Amato, Ponziani, Siracusa, and Sorbi (2001) have conducted one of the most comprehensive longitudinal studies to date (spanning ten years). They reported that when individuals with MS are followed from shortly after diagnosis, they show initial deficits on indices of concentration, verbal memory, and abstract reasoning, with the development of later impairments in verbal fluency, verbal comprehension, and short-term verbal and spatial memory/attention. Most strikingly, 26% of patients displayed cognitive impairment at the time of study entry, but this increased to 56% at the ten-year follow-up point.

Relationship to Disease Variables

Studies have consistently shown that patients with a Relapsing-Remitting course type exhibit less severe cognitive impairment than those with Progressive courses. One large meta-analytic study revealed that those patients with a Chronic Progressive course (encompassing all progressive types of MS) were more likely to have frontal-executive impairments, and those with Relapsing-Remitting courses more commonly showed memory-related impairments (Zakzanis, 2000).

Measurement

For cognitive difficulties to be detected in MS, it is important to employ test batteries that assess key areas of cognitive functioning, as the precise pattern of cognitive impairment often varies significantly among individuals. MS patients who show impairment in one domain of cognitive functioning are not necessarily impaired in others (Rao et al., 1991). Optimally, test batteries should be limited to about two to three hours, or less, to circumvent secondary problems (e.g., fatigue) that may compromise performance over a long period of time. There is evidence that MS patients' performance declines more than controls over the course of a long battery (Krupp & Elkins, 2000), and even within the context of a single task, such as the PASAT (Walker, Berard, Berrigan, Rees, & Freedman, 2012). There are at least two well-validated batteries for assessing cognitive impairment in MS, and both will be discussed in the following sections. Additional approaches and considerations will also be discussed.

THE BRIEF REPEATABLE BATTERY (RAO AND THE COGNITIVE FUNCTION STUDY GROUP OF THE NATIONAL MULTIPLE SCLEROSIS SOCIETY, 1990)

This battery consists of five tests that were shown to be most sensitive to cognitive impairments typically seen in MS from Rao's seminal MS study (Rao et al., 1991). As noted earlier, the BRB includes the SDMT, 10/36 Spatial Recall, Six-Trial version of the SRT, PASAT (2s & 3s version), and Word List Generation (WLG). Most of these tests also include 15 alternate forms (in English) to facilitate serial testing. Additionally, a two-form (A and B) version of the BRB has been developed by the European Study Group on Interferon beta-1b in Secondary Progressive MS (Boringa et al., 2001), but with some limitations noted in the comparability of the forms. The BRB has also been shown to have excellent specificity (94%) and adequate sensitivity (71%; see Rao et al., 1991). It has advantages over other batteries in that it has been translated into several languages other than English. The battery, or parts of the battery, have also been explored in Dutch (Boringa et al., 2001), Brazilian (Brooks, 2011), Serbian (Obradovic, Petrovic, Antanasijevic, Marinkovic, & Stojanovic, 2012), Greek (Potagas, Giogkaraki, Koutsis, Mandellos, & Tsirempolou, 2008), and Italian (Goretti et al., 2014) samples, among others. Even an abbreviated version administered in an Italian sample (Portaccio, Goretti, Zipoli, Siracusa, & Sorbi, 2009) showed excellent sensitivity (94%) and specificity (84%) in a group of Relapsing-Remitting patients. Regarding the latter study, the investigators included only the Selective Reminding Test, PASAT (3s version), and SDMT. The BRB takes about 20–30 minutes to administer.

One continuing limitation of the BRB is that adequate norms across the alternate forms of the tests comprising it are generally not available. Boringa and colleagues' study (2001) was a Dutch sample and included only the A and B forms developed by the European Study Group. Even examining only these two forms, the investigators found that scores were higher on the B form for three of the tests (SDMT, WLG, and 10/36 Spatial Recall), so great caution is warranted when using these two forms in repeat testing. Benedict and colleagues (Benedict et al., 2012) developed two alternate forms for the SDMT that were comparable to the original oral form of the SDMT; however, this study was based on a very small sample (25 healthy controls, including six men), so a replication of their findings is warranted before broad clinical application of these new forms takes place. In the absence of good normative data and clear-cut form equivalence for the BRB, one possible solution is to create standardized scores from these authors' control data for each form that could then be compared across different testings.

MINIMAL ASSESSMENT OF COGNITIVE FUNCTION IN MS (MACFIMS; BENEDICT ET AL., 2002)

The MACFIMS was developed as a result of a consensus conference and designed to provide a somewhat more extensive battery than the BRB. The MACFIMS takes about 90 minutes to administer and includes measures of memory (CVLT-II and BVMT-R), Attention and Concentration/ Processing Speed (SDMT [Oral Version]), PASAT [2s &

participants with confirmed MS or CIS who completed a battery of neurological, cognitive, and psychological assessments. The sample was comprised of mostly middle-aged female patients who had Relapsing-Remitting or Secondary Progressive course types. A binary logistic regression, with employment status as the dependent variable, revealed that the Multiple Sclerosis Functional Composite (MSFC; 9-HPT, 25-foot Timed Walk Test, and the PASAT) was the most robust predictor of employment status ($R^2 = 0.31$, 68% correctly classified). Although the addition of the Expanded Disability Status Scale (EDSS) to the model did not increase its predictive value, the addition of both the NEO Five Factor Inventory (NEO-FFI) Agreeableness scale and the Hospital Anxiety and Depression Scale Depression (HADS) subscale did; the addition of these variables substantially increased the predictive value of the model to 50% of the variance in employment status accounted for ($R^2 = 0.50$, 83% correctly classified). The robust predictive value of the MSFC may be related to its assessment of both cognitive and motor symptoms of MS.

The utility of the PASAT in the MSFC has been questioned, as its predictive value, independent of the motor tasks in the MSFC, has been inconsistent across studies. Strober and colleagues (2014) examined a sample of 77 mostly female and Relapsing-Remitting or Secondary Progressive MS patients. These investigators administered a comprehensive neuropsychological battery, but only the SDMT emerged as a significant predictor of employment status in a stepwise logistic regression analysis, accounting for 15%–20% of the variance with 67% overall classification accuracy. These researchers asserted that their findings provided support for the addition of the SDMT to the MSFC and the potential replacement of the PASAT with the SDMT, given the high association of SDMT performance and employment status.

For both driving and employment, then, the SDMT appears to provide excellent predictive validity, underscoring its usefulness as a core neuropsychological screening measure.

Remediating Cognitive Impairment in MS

Prospective Memory and Emotional Valence

Deficits in prospective memory (PM), or the memory for future intentions, are often seen in MS. PM is essential for the successful completion of many everyday tasks necessary for independent living and improving PM is therefore a valuable target for intervention in MS. Rendell et al. (2012) investigated the efficacy of the use of emotionally valenced information to improve PM in participants with MS. A group of 30 MS participants with confirmed MS diagnoses and 30 age, sex, and education-matched controls took part in this study. A laboratory measure of PM, Virtual Week (which is designed like a computerized board game), was used to assess PM. The MS group performed significantly worse than controls on both the event-based and time-based emotionally valenced Virtual Week tasks. Positivity and negativity enhancement/impairment indices were calculated and it was found that the MS group's performance on event-based tasks was significantly improved by the use of emotionally positive material in the tasks. These results suggest that the use of positive emotional associations and cuing might help to improve PM performance in individuals with MS.

Self-Generated Learning

O'Brien Chiaravalloti, Arango-Lasprilla, Lengenfelder, and DeLuca (2007) examined the generation effect in MS to assess whether it would improve memory functioning. With the generation effect, material that is produced by an individual is learned and remembered better than information that is provided to that individual. These investigators explored whether even cognitively impaired individuals with MS would benefit from using the generation effect. MS participants were compared with healthy controls and TBI patients. In addition to administering a few standard neuropsychological tests, these authors included a generation effect protocol. This involved 32 sentences presented individually on separate pages. In the Generated Condition, 16 sentences were presented with the last word missing. In the Provided Condition, 16 complete sentences were provided with the last word underlined. The task required participants to read the 32 (alternating) sentences presented individually on separate pages. In the Generated Condition, they had to fill in the blank at the end of the sentence with an appropriate word, and in the Provided Condition, they simply had to read the sentence, including the underlined word. Participants then performed a distractor task, and then were asked to recall the words immediately following this, at a 30-minute delay, and after one week. At both the immediate recall and 30-minute delay, MS participants displayed significantly better recall in the Generated versus Provided condition. These data suggested that MS patients may remember information better when they generate it themselves.

The Testing Effect

Sumowski and colleagues (2010) examined the testing effect in a group of MS patients that included a subgroup with significant memory deficits. The testing effect has been shown to be a robust cognitive phenomenon. It involves practicing recall rather than simply restudying something to be learned. These investigators examined this effect in an MS patient group matched to a healthy control group on a verbal paired associates (VPA) task that included three conditions: massed restudy (MR), spaced restudy (SR), and spaced testing (ST). Recall on the VPA test using cued recall was measured after a 45-minute delay. These investigators found that both MS and controls had better recall on the VPA list after they did spaced testing compared with the MR and SR conditions.

3s]), Verbal-Linguistic Functioning (COWAT), Executive Functioning (D-KEFS Sorting Test), and Visuospatial Skill (JLO). Optional measures were suggested for this battery to measure Premorbid Intellectual Functioning (North American Adult Reading Test, or NAART), Emotional Functioning (BDI– Fast Screen, or BDI-FS), Fatigue (Fatigue Impact Scale, or FIS), Sensorimotor Functioning (9-HPT, Maximum Repetition Rate of Syllables and Multisyllabic Combinations (MRRSMC), and the Rosenbaum Pocket Vision Screener. Depression should be routinely screened in MS because it is so common, and because some research has shown an association between depression and cognitive dysfunction in MS (Arnett, Barwick, & Beeney, 2008).

Besides English (Benedict et al., 2006), the MACFIMS has been validated in Czech (Dusankova, Kalincik, Havrdova, & Benedict, 2012) and Persian (Eshaghi, Riyahi-Alam, Roostaei, Haeri, & Aghsaei, 2012), with reasonably good validity data being reported in these latter languages.

At least two studies recently compared the BRB and the MACFIMS (Goksel Karatepe et al., 2011; Strober et al., 2009), and suggested that the these batteries have comparable sensitivity. The SDMT was shown to be the best predictor of MS status in both studies, but with verbal fluency and verbal memory also contributing independently. Although the SDMT has much appeal, given its high level of sensitivity and ease of administration, performance on it can be compromised by the slowed speech that is common in MS (Arnett et al., 2013), as well as relatively minor rudimentary visual problems (Bruce et al., 2007). In terms of comparing the different verbal and visual learning and memory tasks in these batteries, the SRT and CVLT-II appear to be comparable, but the BVMT-R appears superior to the 10/36 Spatial Recall.

BRIEF INTERNATIONAL COGNITIVE ASSESSMENT FOR MS (BICAMS) (BENEDICT, AMATO, ET AL., 2012)

The BICAMS has yet to be validated, but has been suggested by an international consensus panel of expert neuropsychologists and neurologists in MS. It was developed in recognition of the fact that many centers where patients with MS are tested have limited resources, and may not have the time or expertise to administer and interpret extensive neuropsychological batteries. With this in mind, this group has recommended the adoption of the following tests as targets for validation across a number of cultures and languages: SDMT, BVMT-R, and CVLT-II. Such a battery would be easier to administer than the BRB and takes only about 15 minutes. However, the validation of this protocol across cultures and languages is still in process.

These approaches to neuropsychological assessment in MS attempt to survey the core cognitive domains typically affected in the disease and differ primarily in their comprehensiveness. Selection of one battery versus another depends upon the goals for the evaluation, in addition to the setting in which the evaluation takes place.

Ecological Validity of Neuropsychological Tests in MS

An important aspect of the validity of any neuropsychological test, especially regarding its clinical applicability, is whether it relates to everyday functioning. There is an emerging literature on the ecological validity of these tests in MS that suggests they are associated with important real-world tasks. We now turn to a brief review of the literature on the association of neuropsychological tests to driving and employment.

Driving

The motor, visual, and cognitive symptoms of MS can all contribute to difficulties with driving. Akinwuntan and colleagues (2013) aimed to determine what tests would best predict driving ability as measured by performance on a road test. Forty-four mostly female, middle-aged individuals with Relapsing-Remitting MS completed a comprehensive battery of cognitive, physical, and visual tests. Although 12 cognitive and 3 visual tests were moderately correlated ($r = 0.31–0.63$) with performance on the road test, multiple regression revealed that a model containing the following five tests accounted for the most variance ($R^2 = 0.59$) of performance on the road driving test: time to complete the Stroop Color-Word test; the Stroke Driver Screening Assessment (SDSA) directions, compass, and road sign recognition subtests; and the Useful Field of View speed of processing test.

Schultheis et al. (2010) focused on the cognitive contributors to difficulties with driving by measuring cognitive functioning and driving abilities in community-dwelling participants with MS who had no reported visual impairments. Sixty-six middle-aged, mostly female, and Relapsing-Remitting participants with clinically definite MS were included. Participants underwent comprehensive neuropsychological evaluations and behind-the-wheel driving evaluations, and their state-issued driver history abstracts were obtained from the Department of Motor Vehicles to evaluate recent collision and violation involvement. Logistic regression revealed that information processing speed, as measured by the SDMT, was the strongest predictor of behind-the-wheel driving performance (marginally significant at $p = .07$) while visuospatial learning and recall, as measured by the 7/24 spatial recall test, was the strongest predictor of collision and violation frequency (marginally significant at $p = .06$).

Employment

Employment status is a critical aspect of daily functioning and an important area of MS research, as most people with MS are diagnosed well before typical retirement age. Demographic, cognitive, physical, and emotional factors of MS have been evaluated as potential predictors of employment status. Honarmand and colleagues (2011) examined 106

The effect held even for a subgroup of 16 MS patients who had objective memory impairment. These findings were extremely promising, and suggest the possibility that applying such a spaced testing method to rehabilitation of memory problems in MS could be effective.

Cognitive Rehabilitation Interventions

Parisi et al. (2014) sought to examine the effectiveness of a cognitive rehabilitation program in a group of MS patients, and to determine the relationship between functional neuroimaging (functional magnetic resonance imaging, or fMRI) and performance on neuropsychological measures. Their sample was small, consisting of 18 female Relapsing-Remitting MS patients; half of the patients were assigned to the treatment condition and the other half served as controls. Participants were administered a battery of neuropsychological tests at baseline, after completion of the 12-week cognitive rehabilitation program, and then again at six months, and resting state fMRI was acquired at baseline and at 12 weeks. These investigators found that participants who received the treatment displayed significantly better performance on measures of attention and executive function. Furthermore, the treatment group demonstrated significantly lower levels of depression and improved quality of life. With respect to the neuroimaging findings, the authors reported that better test performance was associated with greater resting state functional connectivity within default mode network regions.

Neuroimaging Studies on Cognitive Function in MS

Structural Neuroimaging

Generally, cognitive deficits are proportional to MRI-visualized total lesion load on T2 sequences (Bagert, Camplair, & Bourdette, 2002), and regional associations have been reported as well. Sperling and colleagues (2001) found that frontal and parietal region lesion load were correlated with deficits in processing speed and memory. Some studies have also reported an association between MRI lesion location and particular patterns of dysfunction, with primarily frontal lesion patterns associated with executive task dysfunction (Arnett et al., 1994).

Atrophy measures have proven to be as or more associated with patterns of cognitive impairment in MS than lesion burden. Atrophy measures such as bi-caudate ratio, third ventricular width, and brain parenchymal fraction have all been shown to be significantly associated with cognitive impairment in MS (Tekok-Kilic, Benedict, & Zivadinov, 2006; Zivadinov et al., 2001), with some specificity in terms of brain region affected and the types of cognitive impairments observed. Regional frontal volume has been shown to be correlated with performance on measures assessing executive function, attention, and processing speed, while left temporal atrophy has been shown to be predictive of poor verbal memory and both left and right temporal atrophy associated with visual memory performance (Tekok-Kilic et al., 2006).

Several recent studies have also shown that fiber tract integrity in the brain, as measured by diffusion tensor imaging (DTI), is associated with cognitive impairment in MS. Hulst et al. (2013) compared "Cognitively Impaired" and "Cognitively Preserved" MS patients on common DTI measures. They found that, compared with the Cognitively Preserved patients, the Cognitively Impaired patients demonstrated significantly greater white matter integrity changes in a number of brain regions. Koenig et al. (2013) sought to investigate the relationship between common DTI measures (specifically in the fornix) and cognitive performance in mostly Relapsing-Remitting MS patients and healthy controls. Compared with healthy controls, the MS group showed significantly greater mean diffusivity and longitudinal diffusivity, as well as lower fractional anisotropy, suggesting compromised fiber tract integrity in the MS group. Additionally, the MS group demonstrated significantly worse performance than the healthy controls on a neuropsychological test battery consisting of measures of episodic memory, working memory, and attention. Llufriu et al. (2014) examined the relationship between cognitive performance and structural brain damage using DTI in a sample of Relapsing-Remitting MS patients and healthy controls. They found that MS patients demonstrated widespread abnormalities on DTI indices in both gray matter regions and white matter tracts as compared to control participants. Interestingly, the abnormalities observed within the white matter tracts accounted for more of the variance in cognitive dysfunction.

Functional Neuroimaging

Initial studies using functional neuroimaging measures showed that MS patients displayed *greater* increases in brain activation relative to non-MS controls when performing complex cognitive tasks (Forn et al., 2006; Hillary et al., 2003). More recently, Loitfelder and colleagues (2011) reported similar findings. They examined fMRI activation patterns during a Go/No Go Discrimination Task and found that Relapsing-Remitting and Secondary Progressive patients displayed greater activation increases during task performance compared with controls. Interestingly, the patterns of increased activation were more pronounced in the Secondary Progressive patients who showed more widespread activation, and also less deactivation.

Findings from other studies have supported a general increase in brain activation in MS patients; however, this pattern has not been consistently observed across all brain areas. On the Computerized Test of Information Processing, Smith and colleagues (2012) found that, compared with controls, MS patients displayed a significant increase in activation in the prefrontal cortex (PFC) and right temporal gyrus;

however, the MS patients displayed *decreased* activation in areas of the left temporal gyrus. This study suggested that the broadly greater task activation in MS patients versus controls may not always hold true across brain areas. Additional research is needed to clarify the conditions under which increased versus decreased activation occur in MS during task performance.

Wojtowicz, Mazerolle, Bhan, and Fisk (2014) sought to explore the relationship between performance variability (on measures of processing speed) and resting-state functional connectivity in a sample of age-matched Relapsing-Remitting MS participants and healthy controls. The authors reported that performance variability was greater in MS patients as compared to healthy controls. Furthermore, MS patients were found to have decreased functional connectivity between regions associated with the default mode network. Finally, with respect to MS patients, those exhibiting less performance variability (better performance) showed increased connectivity between the ventral medial prefrontal cortex (PFC) and the frontal pole.

Psychiatric Issues

Depression

The risk for lifetime major depression in MS is approximately 50% (Arnett, Barwick, et al., 2008; Chwastiak et al., 2002; Sadovnick et al., 1996), a figure much higher than the 8% lifetime risk in the general population, but also greater than many other neurological disorders and chronic illnesses.

SCREENING FOR DEPRESSION

A common problem associated with the assessment of depression in MS pertains to the overlap between neurovegetative symptoms of depression and MS disease symptoms. Symptoms such as fatigue, sleep disturbance, sexual dysfunction, and concentration difficulties are all neurovegetative symptoms of depression, but they are also symptoms of MS itself. This makes the assessment of depression in MS complicated, because the meaning of such symptoms in MS is unclear. One solution that has been suggested in the literature is to simply discard such symptoms, focusing instead on mood and negative evaluative depression symptoms. Nyenhuis et al. (1995) developed the Chicago Multiscale Depression Inventory (CMDI) for this purpose. The test consists of three 14-item scales, each measuring a different domain of depression. These investigators suggested using only the Mood subscale of the CMDI, as it was least potentially overlapping with MS disease symptoms.

An alternative to the CMDI is the BDI-FS (Beck, Steer, & Brown, 2000). This measure was explicitly developed with medical patients in mind, and includes only mood and negative evaluative symptoms in its seven-item format. There is much to be said for the BDI-FS as a screening measure for depression in MS. It takes only a few minutes to administer, and has been shown to be valid for detecting depression in MS by Benedict and colleagues (2003). They found that it was highly correlated with other self-report measures of depression, other-report measures of depression, and also distinguished between depressed MS patients in treatment and those not being treated.

Another approach to addressing the neurovegetative depression symptom/MS symptom overlap has been suggested by Strober and Arnett (2010). These investigators proposed a "trunk and branch" model of depression in MS. Rather than disregard neurovegetative symptoms entirely, this model distinguishes between symptoms common to the medical condition ("trunk" symptoms), and those independent of the medical condition that are likely to reflect depression ("branch" symptoms). To test this model, a criterion group of likely depressed MS patients was identified. They were compared to a nondepressed MS group and a group of healthy controls on the BDI (Beck & Steer, 1987). Trunk symptoms were those on which the MS group (depressed and nondepressed combined) endorsed significantly more often than the healthy controls (see Figure 25.1). Branch symptoms were those that were endorsed significantly more often by depressed compared with MS compared with nondepressed MS. The researchers also found that there were some trunk symptoms that were more severe in the depressed compared with nondepressed MS group, so these were also considered core MS depression symptoms. As shown in Figure 25.1, the initial branch symptoms and these latter additional symptoms comprised 12 items from the original BDI.

Strober and Arnett (2015) followed up this study and examined the new 12-item "MS-BDI" relative to existing depression measures commonly used in MS, including the BDI-FS, the CMDI, and the BDI-II. The BDI-FS and the CMDI-Mood subscale had the best sensitivity at 94%. The MS-BDI, however, had the highest specificity and corresponding Positive Likelihood Ratio (PLR) of 12.81. PLR is a measure of the increase in the likelihood an individual has a condition (i.e., depression in this case) if he or she scores above a cutoff. A PLR greater than 10 is almost conclusive for the condition, so the MS-BDI fared extremely well when a cutoff of 7 was used.

Strober and Arnett (2015) examined the validity of the depression measures in another way, by comparing the point prevalence rates they produced with that of the criterion group. When selecting the criterion depressed group from the larger sample of 84 individuals with MS, the point prevalence rate for depression was 20%. Importantly, the MS-BDI also produced a point prevalence rate of 20% when the cutoff of 7 was again used, suggesting that scores on it are tightly linked to more rigorous approaches to diagnosing depression that include clinical interviews. An important caveat to this consideration of the MS-BDI is that the data are based on one study only. With that said, the MS-BDI is appealing because it has the highest PLR of any of the

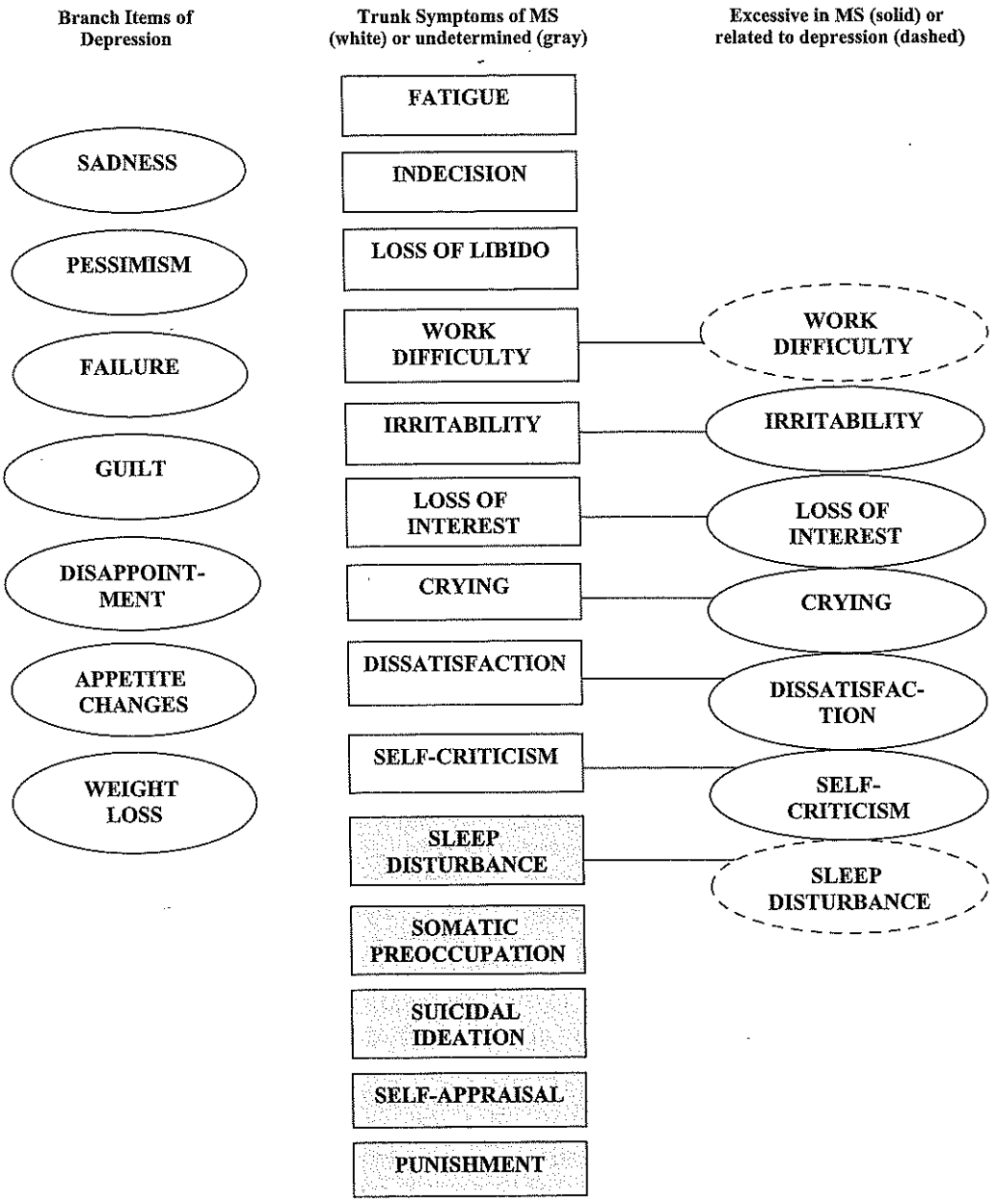

Figure 25.1 Trunk and branch model of depression in MS

Used with permission (Strober & Arnett, 2010)

depression measures assessed, is theoretically driven in relation to MS, incorporates some neurovegetative symptoms, and has prevalence rates comparable to those derived from using a rigorously identified criterion group of depressed MS patients. Still, a cross-validation study on a larger sample will be necessary before clinical application of the MS-BDI would be appropriate.

Another depression measure that has been frequently used in MS is the HADS. This 14-item measure has advantages over the other depression scales already discussed in that it also measures anxiety, which, as will be discussed, is very common in MS. Honarmand and Feinstein (2009) examined the Depression scale of the HADS in an MS sample and found excellent sensitivity (.90) and specificity (.87). Using a cutoff of 8, it also resulted in a point prevalence rate of depression in their sample of 16%, a value close to the 20% for the MS-BDI and the criterion group from Strober and Arnett's (2015) study.

As far as clinical recommendations, at this stage of our knowledge, the BDI-FS clearly appears to be the best screening measure for depression in MS. Its sensitivity is very high, and a cutoff of 4 or above has been demonstrated to be best in at least two studies, a cutoff that is also consistent with what is recommended in the BDI-FS manual for medical

patients in general. The sensitivity and specificity of the HADS Depression scale are also excellent; the one caveat is that it has been validated in one MS study only, so greater caution in its use is recommended.

Because of the high prevalence of depression in MS, patients should be routinely screened, with particular optimal approaches for this outlined earlier. Also, it is very treatable through brief and even telephone-based cognitive behavioral therapy (Hind et al., 2014; Mohr et al., 2005; Mohr et al., 2000), as well as group therapy. Still, depression has historically been undertreated in MS, despite the fact that it is unlikely to remit spontaneously.

COPING AND DEPRESSION

Depression in MS has also been consistently found to be associated with the increased use of generally less effective emotion-focused or avoidant-focused coping strategies, and the decreased use of more adaptive active or problem-focused strategies (Arnett, Higginson, Voss, & Randolph, 2002; McCabe, McKern, & McDonald, 2004; Mohr, Goodkin, Gatto, & Van Der Wende, 1997; Pakenham, 1999; Rabinowitz & Arnett, 2009). Despite this, coping strategies are not routinely screened for in clinical evaluations. There is a need for reliable and well-validated coping measures for clinical use, but to our knowledge, none have been fully validated in MS patients. This is unfortunate, because knowledge of coping strategies, especially in psychotherapy contexts, would be useful in guiding therapy. In addition to providing a potential treatment target, and improving quality of life and well-being, altering maladaptive coping strategies in MS patients might also mitigate the impact of cognitive dysfunction on mood (Arnett et al., 2002; Rabinowitz & Arnett, 2009), and fatigue (Ukueberuwa & Arnett, 2014).

OTHER FACTORS ASSOCIATED WITH DEPRESSION

Even though depression is treatable in many MS patients, treatments are effective in reducing depression to remission only about 50% of the time (Ehde et al., 2008; Mohr, Boudewyn, Goodkin, Bostrom, & Epstein, 2001). Depression in MS negatively affects quality of life, adaptive functioning, and well-being (Vargas & Arnett, 2010); interferes with medication adherence (Bruce, Hancock, Arnett, & Lynch, 2010); and may increase mortality (Feinstein, O'Conner, & Feinstein, 2002). There is a need for developing models with greater explanatory power that could result in the development of better treatments to reduce depression in MS.

A history of depression appears to increase risk for future depressive or manic states in MS. Some studies show that depression is associated with cognitive dysfunction, with impairments in complex attention and information processing speed, as well as executive deficits, showing the greatest associations (Arnett, Barwick, et al., 2008; Sundgren, Maurex, Wahlin, Piehl, & Brismar, 2013). These associations are most likely to be seen when depression symptoms contaminated by MS symptomatology (e.g., neurovegetative symptoms) are excluded from the measurement of depression and the focus is on mood and negative evaluative depression symptoms (Arnett, Higginson, & Randolph, 2001; Sundgren et al., 2013). Coping may also be an important moderator between cognitive dysfunction and depression in MS, with cognitive deficits most likely to predict depression if patients rely on avoidant coping or minimally use active coping (Arnett et al., 2002; Rabinowitz & Arnett, 2009). The severity of neurologic disability is inconsistently related to depression in MS (Arnett, Barwick, et al., 2008).

Numerous factors appear to be associated with depression in MS, including high levels of perceived stress, low levels of perceived social support, and disease exacerbation/pharmacological treatment (Arnett, Barwick, et al., 2008). Depression in MS is unlikely to be governed by genetic factors, because studies show that unipolar major depression is not more common in first-degree relatives of depressed MS patients compared with first-degree relatives of non-depressed MS patients. Still, biological factors are clearly associated with depression in MS, as indicated by research showing that depression is predicted by both neuroanatomical and functional neuroimaging parameters.

PHYSICAL ACTIVITY AND DEPRESSION

The mood-boosting effects of physical activity have been observed in healthy controls as well as psychiatric populations, leading it to be studied as a potential cost-effective treatment for depression. Physical activity may be an optimal intervention for those with MS, as this disease is often characterized by high rates of depression and low levels of physical activity. Kratz and colleagues (2014) established physical activity as a successful intervention for depression in MS and additionally evaluated positive and negative affect as mediators for the effects of physical activity counseling on depressive symptoms. Ninety-two individuals with clinically definite MS were randomized into a treatment condition (n = 44) and a waitlist control condition (n = 48). The groups were well-matched in terms of sex and course type. Depressive symptoms and positive and negative affect were evaluated before and after a 12-week motivational interviewing intervention focused on increasing physical activity. Mediational analyses showed that motivational interviewing had significant effects on both positive and negative affect, and these in turn both significantly influenced depressive symptoms. When physical activity, as measured by the 7-day Physical Activity Recall Interview, was included in the model, however, only positive affect mediated the relationship between changes in physical activity and depressive symptoms. These results suggest that physical activity may improve depressive symptoms through an increase in positive affect, and supplementary treatment should be pursued to decrease negative affect and further reduce depressive symptoms.

NEUROPATHOLOGY AND DEPRESSION

Neuropathology has generally been shown to be associated with depression in MS (Feinstein, 2004). Together, lesion load, brain atrophy, and white matter fiber tract integrity account for up to 43% of depression variance in MS (Bakshi et al., 2000; Feinstein et al., 2010), with temporal and frontal brain regions most often implicated (Arnett, Barwick, et al., 2008; Feinstein et al., 2010). However, a study by Gobbi et al. (2013) was not as conclusive. These investigators examined structural neuroanatomical correlates of both depression and fatigue in MS and failed to find any significant relationships between lesion distribution and depression or fatigue. Similarly, there were no significant relationships between white matter atrophy and depression or fatigue. However, gray matter atrophy in several brain regions (including frontal, parietal, and occipital lobes) was significantly related to both depression and fatigue, and the left middle frontal gyrus and right inferior frontal gyrus were associated with depression but not fatigue. With these studies in mind, the mechanisms by which this type of structural brain damage leads to depression in MS are unclear. It may be that such structural changes lead to characteristic functional brain changes that in turn predict depression in MS.

Functional brain variables in relation to emotional functioning in MS have been examined in only a limited way in one study. Passamonti and colleagues (2009) explored emotional processing in a small group (N = 12) of Relapsing-Remitting MS participants. They found that, compared with controls, MS participants showed a lack of functional connectivity between the amygdala and the PFC during an emotional processing task involving the matching of affective faces. Although the MS participants in the study were not clinically depressed, they reported significantly higher scores on depression measures than controls. These authors hypothesized that reduced functional connectivity could reflect a disruption in an important affective processing system in the brain of MS patients early in the disease process that might ultimately put them at risk for emotional difficulties such as depression. Clearly, further work examining functional neuroimaging and depression in MS is warranted.

Anxiety

Anxiety has sometimes been shown to be more common than depression in MS, but has been studied far less extensively. The point prevalence of clinically significant anxiety is thought to be about 25%, but lifetime prevalence is unknown. The cause of anxiety in MS is unknown, but it tends to be prominent in the early stages of the disease when the diagnosis and prognosis are most uncertain. Decline in distress is associated with more definitive diagnostic statements by treatment professionals. There are no published studies treating specific anxiety disorders in MS. At least one study has shown that comorbidity of anxiety and depression in MS is more associated with thoughts of self-harm, social dysfunction, and somatic complaints than either alone (Feinstein, O'Connor, Gray, & Feinstein, 1999). The only other emotional disorder occurring with any significant frequency in MS is bipolar disorder, with point prevalence estimated at 0%–2% and lifetime prevalence at 13%–16%. There are no published treatment studies of bipolar disorder in MS.

Conclusion

MS is the most common nontraumatic neurological condition of early to middle adulthood, and the most common demyelinating condition. In this chapter, we have reviewed common sequelae associated with MS, especially focusing on neurocognitive impairments and emotional difficulties including depression and anxiety. We have also included practical suggestions for neuropsychological assessment and for the assessment of depression. Neuropsychologists can play a critical role in the assessment and treatment of cognitive and emotional difficulties in MS. This chapter provides some evidence-based suggestions that can optimize patient care.

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