Troster, A. I., Fields, J, A., Pahwa, R., Wilkinson, S, B., Straits-Troster, K. A., Lyons, K., Kiellyka J., & Koller, W. C., (1999). Neuropsychological and quality of life outcome after thalamic stimulation for essential tremor. *Neurology, 53*, 1774–1780.

Troster, A. I., Woods, S. P., & Morgan, E. E. (2007). Assessing cognitive change in Parkinson's disease: Development of practice effect-corrected reliable change indices. *Archives of Clinical Neuropsychology, 22*, 711–718.

Victor, M., & Ropper, A. H. (2001). *Adams and Victor's principals of neurology* (7th ed.). New York: McGraw-Hill.

Vidailhet, M., Vercueil, L., Houeto, J. L., et al. (2005). Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. *N Engl J Med., 352*, 459–467.

Vidailhet, M., Vercueil, L., Houeto, J. L., Krystkowiak, P., Lagrange, C., Yelnik, J., et al. (2007). Bilateral, pallidal, deep-brain stimulation in primary generalised dystonia: A prospective 3 year follow-up study. *Lancet Neurology, 6*, 223–9.

Visser-Vandewalle, V., Temel, Y., Boon, P., et al. (2003). Chronic bilateral thalamic stimulation: A new therapeutic approach in intractable Tourette syndrome. A report of three cases. *Journal of Neurosurgery, 99*, 1094–1100.

Vitek, J. L. (2002). Mechanisms of deep brain stimulation: excitation or inhibition. *Mov Disord, 17* (s3), S69–72.

Voon, V., Kubu, C., Krack, P., Houeto, J., Troster, A. I., (2006). Deep brain stimulation: Neuropsychological and neuropsychiatric issues. *Movement Disorders, 21*, 305–326.

Volkmann, J., Allert, N., Voges, J., Sturm, V., Schnitzler, A., & Freund, H. J. (2004). Long-term results of bilateral pallidal stimulation in Parkinson's disease. *Annals of Neurology, 55*, 871–875.

Ward, J., Sheppard, J.-M., Shpritz, B., et al. (2006). A four-year prospective study of cognitive functioning in Huntington's disease. *Journal of the International Neuropsychological Society, 12*, 445–54.

Watkins, L. H., Sahakian, B. J., Robertson, M. M., et al. (2005). Executive function in Tourette's syndrome and obsessive-compulsive disorder. *Psychological Medicine, 35*, 571–82.

Weaver, F. M., Follett, K., Stern, M., Hur, K., Harris, C., Marks, W. J., Jr., et al. (2009). For the CSP 468 study group. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson's disease. *The Journal of the American Medical Association, 301*, 63–73.

Wechsler, D. (1987). *Wechsler memory scale – revised (WMS-R) manual*. San Antonio: The Psychological Corporation.

Wechsler, D. (1997). *Wechsler Memory Scale – 3rd Edition (WMS-III) manual*. San Antonio: The Psychological Corporation.

Weintraub, D., & Hurtig, H. I. (2007). Presentation and management of psychosis in Parkinson's disease and dementia with Lewy bodies. *The American Journal of Psychiatry, 164*(10), 1491–8.

Windels, F., N. Bruet, et al. (2000). "Effects of high frequency stimulation of subthalamic nucleus on extracellular glutamate and GABA in substantia nigra and globus pallidus in the normal rat." *Eur J Neurosciences, 12*, 4141–4146.

Winikates, J., & Jankovic, J. (1994). Vascular progressive supranuclear palsy. *Journal of Neural Transmission, 42*, 189–201.

Wolters, E Ch, & Braak, H. (2006). Parkinson's disease: Premotor clinico-pathological correlations. *Journal of Neural Transmission Supplementum, 70*, 309–19.

Woods, S. P., Fields, J, A., Troster, A. I., (2002). Neuropsychological sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: A critical review. *Neuropsychology Review, 12*, 111–126.

Woods, S. P., & Troster, A. I. (2003). Prodromal frontal/executive dysfunction predicts incident dementia in Parkinson's disease. *Journal of the International Neuropsychological Society, 9*, 17–24.

Wu, L. J., Sitburana, O., Davidson, A., & Jankovic, J. (2008). Applause sign in Parkinsonian disorders and Huntington's disease. *Movement Disorders, 15*, 2307–2311.

York, M. K., Dulay, M., Macias, A., Levin, H. S., Grossman, R., & Simpson, R., et al. (2008). Cognitive declines following bilateral subthalamic nucleus deep brain stimulation for the treatment of Parkinson's disease. *J Neurol Neurosurg Psychiatry, 79*(7), 789–795.

# Chapter 20
# Multiple Sclerosis and Other Demyelinating Disorders

**Julie A. Bobholz and Shelley Gremley**

**Abstract** Demyelinating disorders are characterized by the destruction of the myelin sheaths of the nerves following normal myelin development. Types of demyelinating conditions can be generally characterized as immune-mediated diseases, infection-mediated diseases, inherited disorders, and toxic disorders (see (Table 20.1; and Joy and Johnston, 2001, for detailed review). This chapter will begin with a brief description of demyelinating conditions representing these categories. Multiple Sclerosis (MS) is the most common demyelinating condition and will be the primary topic of this chapter.

**Key Points and Chapter Summary**

- There are many demyelinating disorders which have CNS effects including cognitive decline.
- Demyelinating disorders often have a variable course across individuals ranging from relatively mild and transient symptoms to severe, permanent and even deadly courses. The most common presenting complaints of demyelinating disorders are rapid motor and sensory changes (i.e., paresis, visual loss, acute sensory loss)
- The most common cognitive effect from demyelinating diseases is slowed processing speed and attentional deficits which often produce working memory declines; however, focal and diffuse deficits are not uncommon and include memory impairment, and may include changes in reasoning, personality and judgment.

(continued)

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**Key Points and Chapter Summary (continued)**

- Cognitive deficits in demyelinating disorders are associated with the severity, duration and recurrence of the disorder.
- Emotional sequelae of demyelinating disorders are common and should be addressed and treated expeditiously. Untreated, these factors may compound physical and cognitive disability associated with the demyelinating disorder.

**Table 20.1** Types of demyelinating conditions that resemble MS

| |
|---|
| Immune-mediated diseases |
| • Acute disseminated encephalomyelitis |
| • Systemic inflammatory or autoimmune diseases |
| Infection-mediated diseases |
| • Progressive multifocal leukoencephalitis |
| • Human T-cell Lymphotropic Virus Type 1 |
| Inherited disorders |
| • Dysmyelinating disorders (leukodystrophies) |
| Toxic disorders |
| • Toxic optic neuropathy, subacute myelo-optic neuropathy |

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated demyelinating disease and can be a consequence of a vaccination or an infection, or without a preceding cause (Joy and Johnston 2001). The most common causes of postinfectious ADEM are upper respiratory tract infections and varicella but it can also occur after viral infections such as mumps, rubella, and influenza A and B. ADEM is characterized pathologically by widespread perivenular inflammation and demyelination. Onset of symptoms is sudden and can include monoplegia (paralysis of a single limb) or hemiplegia (paralysis on one side of the body), headache, delirium, lethargy, coma, seizures, stiff neck, fever, ataxia, optic neuritis, transverse myelitis, vomiting, and weight loss. This disorder occurs more often in children (average age around 5–8 years of age) than adults. The incidence rate is about 0.8 per 100,000 people per year. The average time to recover is 1–6 months, and 50–75% of cases experience complete recovery (Schwarz et al. 2001), although there can be recurrence of the disorder. Patients who recover tend to show good functional recovery from a neurologic standpoint; however, neuropsychological studies show that this apparent transient illness is associated with cognitive and social sequelae (Jacobs et al. 2004).

**Rule of thumb: Acute Disseminated encephalomyelitis (ADEM)**

- Immune-mediated demyelinating disease that typically involves sudden onset of symptoms and is characterized pathologically as widespread periventricular inflammation and demyelination.



Progressive multifocal leukoencephalitis (PML) is an infection mediated demyelinating disease and is a rare and usually fatal viral disease caused by the JC virus (Joy and Johnston 2001). Most patients die within 4 months of onset. It primarily occurs in people with severe immune deficiency (e.g., transplant patients on immunosuppressive medications, AIDS patients). This disorder is characterized by progressive inflammation of the white matter in the brain at multiple locations. Demyelination is most prominent in the occipital lobes and is a result of direct infection of oligodendrocytes, the cells responsible for creating the myelin sheath. Common symptoms include hemiparesis, aphasia, focal seizures, and visual disturbances.

**Rule of thumb: Progressive Multifocal Leukoencephalitis (PML)**

- Infection mediated disease that is rare and usually fatal. It is characterized as progressive diffuse inflammation of cerebral white matter.

Another infection-mediated demyelinating disease is Human T-cell Lymphotropic Virus Type 1 (HTLV-1) which is an RNA retrovirus that is sometimes associated with a syndrome called HTLV-1 associated myelopathy/tropical spastic paraparesis. Patients with this disorder have a progressive myelopathy, sensory disturbance, bladder dysfunction, and optic neuritis.

Inherited demyelinating disorders, or leukodystrophies, are characterized by specific gene defects that result in myelin abnormalities (Joy and Johnston 2001). More specifically, there is either inadequate myelin production or excess breakdown of myelin.

Toxic optic neuropathy is defined by visual impairment do to damage to the optic nerve. This disorder is uncommon and is primarily associated with specific medications, occupational exposures, or tobacco and alcohol abuse. It is more common in developing nations afflicted with famine. Subacute myelo-optic neuropathy (SMON) affects the peripheral nerves, spinal cord, and the eyes. SMON typically leads to a disabling paralysis, blindness, and sometimes death.

**Rule of thumb: Toxic Optic Neuropathy**

- Optic nerve damage that results in visual impairment and is typically associated with medications, chemical exposures, or tobacco/alcohol abuse.

## Clinical Features of Multiple Sclerosis

### *Pathophysiology*

Multiple Sclerosis (MS) is an autoimmune condition in which the immune system attacks the central nervous system (CNS), leading to demyelination. Neurons in both the brain and spinal cord can be affected. Demyelination occurs when a subset

of lymphocytes, called T cells, get trapped in the brain due to loss of integrity of the blood–brain barrier (during infection or virus) and destroy oligodendrocytes (Joy and Johnston 2001). This eventually leads to thinning or complete loss of myelin, and this demyelinating process can cause changes in motor and sensory functioning, as well as changes in cognition.

## *Common Symptoms*

The most common presenting symptoms of MS include sensory disturbance in limbs, visual loss, and motor disturbance (See Table 20.2 for summary). About 14% of MS begins with a polysymptomatic presentation (Olek 2005). Sensory changes that can occur in MS include numbness in one or more limbs, paresthesia (tingling) in the limbs, and L'hermitte's sign, which involves a sensation like an electric shock in the back and limbs on flexing the neck. Optic neuritis, internuclear ophthalmoplegia, diplopia, and changes in visual acuity can also occur in MS. Common MS-related motor changes include gait disturbance, weakness, balance problems, limb ataxia, slurred speech, decreased coordination, and swallowing difficulty. Spasticity, vertigo, pain, sexual dysfunction, and bladder disturbance are also common symptoms of MS. Paraparesis or hemiparesis can also occur.

Declines in cognitive functioning are a common symptom in MS, with about half of patients experiencing cognitive decline. The functions most frequently affected include abstract conceptualization, recent memory, attention, and information processing speed.

## *Epidemiology and Prevalence*

The onset of MS usually occurs in early adulthood (between 20 and 30 years of age) and is two to three times more common in women. The peak age of onset for

**Table 20.2** Most common presenting symptoms of MS (Adapted from Olek 2005)

| Symptom | Frequency (%) |
|---|---|
| Sensory disturbance – limbs | 30.7 |
| Visual loss | 15.9 |
| Motor disturbance (subacute) | 8.9 |
| Diplopia | 6.8 |
| Gait disturbance | 4.8 |
| Motor (acute) | 4.3 |
| Balance problems | 2.9 |
| Sensory disturbance – face | 2.8 |



most patients with MS is between 20 and 40 years of age but onset has been has been reported to be as early as 11 months of age and as late as 72 years of age. Onset is also estimated to be approximately 5 years earlier for women (Olek 2005). It is a disease that occurs predominantly in the caucasian population. The prevalence of the disease ranges between 2 and 150 per 100,000 depending on the country or specific population (Rosati 2001). MS is more common among persons of northern European heritage. It is also more common among people who live in northern latitudes during childhood. With this observation, MS is more common in the northern states of the USA. Climate, diet, geomagnetism, toxins, sunlight exposure, and infectious exposure have all been offered as possible reasons for these regional differences.

## *Disease Course*

MS is distinguished by the clinical pattern of disease activity, with current practice typically considering the following categorization of disease activity:

(A) *Relapsing-remitting MS*: The majority of cases of MS begin with a relapsing–remitting course. This course is characterized by clearly defined relapses or unpredictable attacks followed by periods of remission or complete recovery of symptoms. Reported common triggers for relapse include warm weather, infections, and emotional and physical stress.

(B) *Secondary progressive MS*: Secondary progressive course describes around 80% of those with initial relapsing–remitting MS, who then begin to have neurologic decline between their acute attacks without any definite periods of remission. This course represents the most common type of MS.

(C) *Primary progressive MS*: This course type describes approximately 10% of individuals who never had remission after their initial MS symptoms. Decline occurs continuously without clear attacks. The primary progressive subtype tends to affect people who are older at disease onset. Progressive relapsing describes those individuals who, from the onset of their MS, have a steady neurologic decline but also suffer superimposed attacks. This is the least common of all subtypes.

(D) *Progressive relapsing MS*: This disease course is characterized as being progressive since the onset of the disease but with clear acute relapses, and the period between relapses is continued progression of the disease.

Disease course is also described as having two severity outcomes: benign, which is used to describe a course of MS that remains fully functional after 15 years after disease onset, and malignant, which characterizes a rapid progressive course resulting in significant disability or death.

**Rule of thumb: Multiple Sclerosis (MS)**

- MS can be difficult to diagnosis because the initial symptom(s) are variable, may remit quickly and the course is unpredictable.
- Diagnosis should be considered when individuals present with sensory/motor symptoms without obvious etiology.
  - Loss of vision/blurred vision
  - Motor weakness
  - Numbness or parasthesias (tingling) of limb(s)
- Symptom onset commonly between 20 and 40 years old.
- Careful history taking is important to appreciate past episodes of sensory/motor symptoms that may have reflected previous episodes of disease activity.
- Disease course
  - Relapsing–remitting – symptom attacks and remit with return to previous baseline level of function
  - Secondary progressive – decline between symptom attacks without return to previous baseline function
  - Primary progressive – no remission of symptoms after first symptom(s) onset
  - Progressive relapsing – progressive decline since first symptom onset, but have clear episodes of worse symptoms that remit, but function does not return to baseline

## *Etiology*

While no definitive cause of MS has been found, there are many theories regarding the etiology of MS and various risk factors have been identified. A common hypothesis is that a viral infection or retroviral reactivation primes a susceptible immune system for an abnormal reaction later in life. Another theory is that MS is a response to a chronic infection, such as Epstein–Barr virus, spirochetal bacteria infection, Chlamydophila pneumoniae, and Vericella zoster (Joy and Johnston 2001). In addition to these environmental factors, genetics have also been found to help determine risk for developing MS. A 30% concordance rate has been found for identical twins, compared to 3–5% for dizygotic twins. Also, first-degree relatives of MS patients have a 2–5% risk of developing the disease, compared to the average risk in the general population of 0.1% (Vollmer 1999).



# Neuropsychological Symptoms of Multiple Sclerosis

## *Cognitive Deficits*

Approximately half of MS patients experience decline in neuropsychological functioning, and cognitive dysfunction is more common in men (Beatty and Aupperle 2002). While it has been found that MS-related cognitive decline tends to increase with disease duration (Amato et al. 2001), studies have shown signs of decline very early in the disease process. Lyon-Caen et al. (1986) found that 85% of patients with MS with less than 2 years disease duration demonstrated some degree of cognitive impairment. Progressive disease course (secondary progressive and primary progressive MS) is associated with more severe cognitive impairment (Huijbregts et al. 2004).

Neuropsychological domains most commonly negatively affected in MS include recent memory, processing speed, and working memory (see Table 20.3 for summary). Deficits in executive functioning, verbal abstraction, and visuospatial perception have also been found (Rao et al. 1991a; Amato et al. 2001; Amato et al. 1995; Ryan et al. 1996). While researchers had initially characterized cognitive dysfunction in MS as predominantly reflective of subcortical dysfunction, studies have clearly demonstrated cognitive difficulties that are not exclusively associated with subcortical dysfunction. Indeed, this growing appreciation of the breath of dysfunction in cognition is coinciding with neuroimaging and immunological research suggesting whole brain involvement in MS.

Memory decline has been reported in approximately 40–60% of MS patients (Rao et al. 1993). Episodic or explicit memory (e.g., remembering what one had

**Table 20.3** Neuropsychological functions shown to be impaired in MS

| |
|---|
| Memory |
| • Episodic/recent memory |
| • Working memory |
| Executive functions |
| • Abstract reasoning |
| • Problem solving |
| Attention/concentration |
| • Sustained |
| • Complex |
| Language functions |
| • Verbal fluency |
| • Naming |
| Speed of information processing |
| Visuospatial skills |

for lunch yesterday) tends to be most affected, while implicit, semantic, and autobiographical memory are typically spared. While debated in the past, memory disruption is likely associated with encoding, storage, and retrieval operations. Some studies have found that MS patients were able to successfully recall information after a delay when they were given more learning trials to ensure that the information was encoded (DeLuca et al. 1994; Demaree et al. 2000). However, another study found that MS patients demonstrated increased brain activation during the recognition trial of a memory task compared to controls, suggesting that retrieval processes are more affected by the disease (Bobholz et al. 2006).

Deficits in processing speed are the most common MS-related cognitive deficit and are thought to be the key component underlying other cognitive deficits in MS. Arnett (2004) found that fewer MS patients performed poorly on a measure of story memory when the stories were presented at a slower rate. Another study found that MS patients performed similar to controls on a working memory task when they were given adequate time to process the test stimuli (Demaree et al. 1999). Deficits in processing speed can be seen in both visual and auditory tests.

Working memory deficits can also be seen in individuals with MS (Rao et al. 1993). Working memory is generally thought to be the ability to hold information in memory for a short period, while manipulating that information. Deficits in working memory are thought to be related to deficits in processing speed since these functions related to one another.

Rather consistently, cross-sectional research has found that nearly half of all MS patients show deficits on neuropsychological testing. Longitudinal research suggested that cognitive dysfunction does have some correlation with disease duration but is also associated with disease course and degree of MR abnormality including lesion burden and atrophy.

**Rule of thumb: Common neuropsychological deficits in MS**

- Recent memory
- Processing speed
- Working memory

Deficits that may also occur:

- Executive function/verbal abstraction, and
- Visuospatial perception.

## *Impact of Cognitive Dysfunction in MS*

Research has shown that the presence of cognitive dysfunction can have significant impact on daily living. The rates of unemployment are high in MS, with some estimates as high as 70–80% just 5 years after diagnosis. Furthermore, studies have shown that individuals who have cognitive dysfunction are more likely to have problems with employment compared to those without cognitive deficits (Rao et al. 1991a, b; Beatty et al. 1995). Recent studies have also raised concern regarding driving safety in MS patients with cognitive dysfunction. Cognitive dysfunction has been associated with poorer performance on computerized assessment of driving skill and accident rates (Shawaryn et al. 2002; Kotterba et al. 2003; Schultheis et al. 2002).



## Correlates with Neuropsychological Deficits

Some general trends have become apparent in the research examining correlates of neuropsychological dysfunction. Disease course tends to be associated with severity of neuropsychological dysfunction, with primary progressive and secondary progressive disease course typically performing more poorly than patients with relapsing–remitting MS. Disease duration is also a relatively strong correlate of neuropsychological dysfunction, with longer periods of disease associated with increasing cognitive deficits (Thorton and Naftail 1997).

While MS more commonly affects women, MS-related cognitive dysfunction tends to occur more frequently in men (Beatty and Aupperle 2002).

Fatigue is thought to be the most common symptom associated with MS, and can significantly impact performance on neuropsychological measures. In fact, MS patients performance on cognitive measures that were repeated worsened following an effortful cognitive task, while controls demonstrated the inverse relationship, such that their performance improved on cognitive measures that were repeated (Krupp and Elkins 2000).

Sleep disturbance is another symptom of MS that can act as a potential correlate of MS-related neuropsychological dysfunction. Research has shown that poor sleep is twice as prevalent in MS patients compared to controls and can be due to a variety of factors, including pain, depression, medication side effects, and nocturnal movement disorders (Lobentanz et al. 2004).

Acute, sub-acute and chronic pain, including Trigeminal neuralgia, tonic spasms, continuous dysesthetic pain, acute radicular pain, and optic neuritis, muscle cramps, headache, and back pain may interfere with test performance. Approximately 55–65% of MS patients experience pain, and cognitive complaints are common among individuals with chronic pain (Roth et al. 2005). Currently, the relationship between pain in MS and cognitive is not well researched, but likely has some impact on performance on cognitive testing and day-to-day functioning. Worth noting is that disease modifying medications typically are not associated with cognitive side effects.

Mood disturbance is another common symptom in MS. There is an estimated lifetime prevalence of 50% of major depression. Brain lesions and psychosocial issues are considered risk factors for mood disturbance, while physical disability does not appear to be closely associated with depression (Goldstein Consensus Group 2005). Mood disturbance has also been found to be associated with cognitive deficits.

Arnett et al. (1999) found that deficits in attention, executive functioning, and processing speed were related to changes in affect and personality, suggesting that mood disturbance may be due to a disruption of frontal-subcortical pathways. Fortunately, mood disturbance associated with MS can be treated. Cognitive Behavioral Therapy (CBT) has been found to have a similar, positive effect to antidepressant medications (Mohr et al. 2001), and both treatments have been found to help improve quality of life (Hart et al. 2005).

Earlier studies examining neuroanatomical variables with standard magnetic resonance imaging (MRI) typically found moderate correlations between cognitive performances on T2 lesion burden. More recent imaging research has demonstrated greater magnitude of correlation between measures of atrophy as measured by third ventricle dilation and cognitive dysfunction. Furthermore, this association appears to be strongly related to thalamic and neocortical atrophy.

Many MS patients remain cognitive intact, despite having positive MR findings. Functional MRI (fMRI) research has shown considerable evidence to suggest that, to some extent, functional reorganization or recruitment of cortical regions occur during cognitive, motor, and visual challenges.

## *Evidence-Based Neuropsychology: Predicting Outcome*

Cognitive dysfunction is a symptom of MS that is typically not a primary feature of the disease used for diagnosis. However, patients often present with cognitive dysfunction as their initial disease symptom and, for some, this can remain their primary symptom throughout their disease. In MS, neuropsychological evidence-based practice/research is in its early stages and has potential to address outcome variables related to disease progression, the impact the disease has on quality of life and day-to-day functions such as employment status, and the effects of treatments (Chelune, 2010). Chelune and Stone (2005a) performed a study that was designed to determine if processing speed was useful in distinguishing patients with relapsing–remitting MS from those with secondary progressive MS. The authors examined performances on three measures of processing speed and found the WAIS-III Processing Speed Index (PSI) was most useful in differentiating the two MS groups. Using contingency table analyses, the authors determined that individuals in their sample were nearly 6 times more likely to have secondary progressive MS, rather than relapsing–remitting MS, if their PSI T-score was 36 or less. Chelune and Stone (2005b) also reported data that showed patients with secondary progressive MS were more likely than patients with relapsing–remitting to perform below the 5th percentile on WAIS-WMS-III factors, with reported odds ratios ranging between 2.7 and 8.3. Further analysis of these data also showed that there was slightly greater risk for men to have lower auditory memory than women (odds ratio of 1:76) but that sex differences were not apparent with the other factors examined. This study also showed an interaction between sex and disease course, as men were found to be 5.2 times more likely than women to have verbal memory deficits if they had secondary progressive MS.



## Assessment of Neuropsychological Deficits in MS

The assessment of cognitive functioning varies depending on the reason the MS patient is being referred for neuropsychological evaluation. Often, MS patients are referred for an evaluation in order to establish a baseline before treatment and to monitor disease progression. At other times, an evaluation is helpful in determining the reasons for difficulties at work and/or home, and in determining whether changes in treatment approach are necessary. Many times, a neuropsychological evaluation is needed to determine one's work capacity and/or application for disability. Therefore, the length and depth of the evaluation may differ based on the purpose of the assessment. While some of these referral questions require comprehensive evaluation to best characterize one's cognitive status, patients with MS often fatigue easily and have difficulty tolerating testing sessions that last several hours. Comprehensive test batteries are not always necessary to answer referral questions.

In 2001, an international panel was convened in order to develop an ideal, minimal record of neuropsychological function (Benedict et al. 2002). The panel developed a 90-minute neuropsychological battery called the Minimal Assessment of Cognitive Function in MS (MACFIMS). The MACFIMS is composed of seven tests designed to assess the cognitive domains commonly affected in MS (see Table 20.4). The tests included in this consensus battery are the Paced Auditory Serial Addition Task (working memory/processing speed), Symbol Digit Modalities Test (processing speed), California Verbal Learning Test-II (verbal memory), Brief Visual Memory Test-Revised (visual memory), Judgment of Line Orientation (visuospatial perception), Controlled Oral Word Test (verbal fluency/executive functioning), and Sorting subtest from DKEFS (executive functioning/novel).

In addition to the MACFIMS, there are several other brief neuropsychological batteries that have been developed to assess cognitive functioning in MS. The Brief Repeatable Battery assesses verbal memory, spatial memory, attention, and verbal fluency. The Basso Screening Battery assesses verbal learning, verbal fluency, and auditory attention, and the Screening Evaluation for Cognitive Impairment measures verbal memory, general verbal ability, and attention. Another method for addressing assessment of cognitive dysfunction is the use of the MS Neuropsychological Questionnaire, which is a brief screening questionnaire that can be completed by

**Table 20.4** Tests included in the Minimal Assessment of Cognitive Function in MS (MACFIMS) battery (Benedict et al. 2002)

| Test | Function |
|---|---|
| Controlled oral word association test | Language |
| Judgment of line orientation test | Spatial processing |
| California verbal learning test, 2nd edition | New learning and memory |
| Brief visuospatial memory test – revised | New learning and memory |
| Symbol digit modalities test | Processing speed and working memory |
| Paced auditory serial addition test | Processing speed and working memory |
| Delis-Kaplan executive function system – sorting test | Executive function |

the MS patient and significant others in the clinic setting. Unlike the batteries of objective measures described above, this measure would assess subjective experience to assist the clinician in management of this symptom. A high rate of cognitive complaints would likely trigger more comprehensive neuropsychological evaluation to better appreciate the concerns and to assist with treatment plans.

There are clinical challenges of assessing cognitive dysfunction in MS that should be considered. While a brief screen of cognitive functions (e.g., Mini Mental State Exam) will likely result in missing or under appreciating the cognitive deficits that can be associated with MS, on the other hand, long comprehensive evaluations can sometimes be difficult for MS patients to tolerate due to issues such as fatigue. The clinician is encouraged to carefully consider the reason for evaluation and to assess accordingly. In cases where the referral question relates to the individual's ability to work or academic functions, a more comprehensive evaluation may be warranted. In contrast, some individuals are referred for evaluation to assess for cognitive problems or monitor course of symptoms. As with motor symptoms or sensory symptoms, neurologists are often requesting neuropsychological evaluations to monitor cognitive symptoms. Often, a relatively briefer evaluation still targeting the areas vulnerable to decline may be considered.

While it is important for the clinician to characterize the nature and severity of cognitive problems, consideration of other issues such as depression, sleep deprivation, pain, and fatigue must be considered when developing treatment recommendations. As with any situation of repeat cognitive testing, clinicians must also consider issues such as test–retest reliability and practice effects.

## Treatment Neuropsychological Deficits in MS

As noted above, cognitive dysfunction occurs rather frequently in MS. While neuroanatomical correlates are important in understanding the underlying cause of cognitive difficulties in MS, clinical attention to variables such as mood disturbance, sleep disturbance, fatigue, and pain is also important in considering treatment directions for those MS patients who present with cognitive difficulties.

Studies in the past decade have begun to consider medication treatment options for managing the symptom of cognitive dysfunction in MS. Studies examining the effects of disease modifying medications may help in prevention of cognitive decline (Fischer et al. 2000). However, more recently, efforts to manage the symptom of cognitive dysfunction have focused on donepezil (Krupp et al. 2004), amantadine and pemoline (Geisler, et al. 1996), Prokarin (Gillson et al. 2002) and have found promising results. Porcel and Montalban (2006) offer a review of generally promising research in use of anticholinesterase inhibitors in managing cognitive dysfunction in MS.

Finally, studies have considered treatment options using cognitive rehabilitation and cognitive behavioral therapy for managing cognitive dysfunction in MS.



These studies have focused on strategies aimed at helping patients adapt and cope with cognitive dysfunction. O'Brien and colleagues (2008) have provided a recent review of studies examining cognitive rehabilitation in MS and offer some strong suggestions for future directions.

## References


Amato, M., Ponziani, G., Pracucci, G., et al. (1995). Cognitive impairment in early-onset multiple sclerosis: Pattern, predictors, and impact on everyday life in a 4-year followup. *Archives of Neurology, 52*, 168–172.

Amato, M., Ponziani, G., Siracusa, G., et al. (2001). Cognitive dysfunction in early- onset multiple sclerosis: A reappraisal after 10 years. *Archives of Neurology, 58*, 1602–1606.

Arnett, P. (2004). Speed of presentation influences story recall in college students and persons with multiple sclerosis. *Archives of Clinical Neuropsychology, 19*, 507–523.

Arnett, P., Higginson, C., Voss, W., et al. (1999). Depressed mood in multiple sclerosis: Relationship to capacity demanding memory and attentional functioning. *Neuropsychology, 13*, 434–446.

Beatty, W. W., & Aupperle, R. L. (2002). Sex differences in cognitive impairment in multiple sclerosis. *The Clinical Neuropsychologist, 16*, 472–480.

Beatty, W. W., Blanco, C., Wilbanks, S., & Paul, R. (1995). Demographic, clinical and cognitive characteristics of multiple sclerosis patients who continue to work. *Journal of Neurologic Rehabilitation, 9*, 167–173.

Benedict, R., Fischer, J., Archibald, C., et al. (2002). Minimal neuropsychological assessment of MS patients: A consensus approach. *The Clinical Neuropsychologist, 16*, 381–397.

Bobholz, J., Rao, S., Lobeck, L., et al. (2006). fMRI study of episodic memory in relapsing-remitting MS: Correlation with T2 lesion volume. *Neurology, 67*, 1640–1645.

Chelune, G.J. (2010). Evidence-based research and practice in clinical neuropsychology. *The Clinical Neuropsychologist, 24*, 454–467.

Chelune, G. J., & Stone, L. (2005a). Risk of processing speed deficits among patients with relapsing and remitting and secondary progressive multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology, 11*, 52.

Chelune, G. J., & Stone, L. (2005b). Relative risk of cognitive impairment is mediated by disease course and sex in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology, 11*(SI), 42–43. (S2), 52.

DeLuca, J., Barbieri-Berger, S., & Johnson, S. (1994). The nature of memory impairments in multiple sclerosis: Acquisition versus retrieval. *Journal of Clinical and Experimental Neuropsychology, 16*, 183–189.

Demaree, H., DeLuca, J., Gaudino, E., et al. (1999). Speed of information processing as a key deficit in multiple sclerosis: Implications for rehabilitation. *Journal of Neurology, Neurosurgery and Psychiatry, 67*, 661–663.

Demaree, H., Gaudino, E., DeLuca, J., et al. (2000). Learning impairment is associated with recall ability in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology, 22*, 865–873.

Fischer, J. S., Priore, R. L., Jacobs, L. D., et al. (2000). Neuropsychological effects of interferon beta-1a in relapsing-remitting multiple sclerosis. Multiple Sclerosis Collaborative Research Group. *Annals of Neurology, 48*(6), 885–892.

Geisler, M. W., Sliwinski, M., Coyle, P. K., et al. (1996). The effects of amantadine and pemoline on cognitive functioning in multiple sclerosis. *Archives of Neurology, 53*(2), 185–188.

Gillson, G., Richard, T. L., Smith, R. B., & Wright, J. V. (2002). A double-blind pilot study of the effect of Prokarin on fatigue in multiple sclerosis. *Multiple Sclerosis, 8*(1), 30–35.

Goldman Consensus Group. (2005). The Goldman consensus statement on depression in multiple sclerosis. *Multiple Sclerosis, 11*, 328–337.

Hart, S., Fonareva, I., Merluzzi, A., et al. (2005). Treatment for depression and its relationship to improvement of quality of life and psychological well-being in multiple sclerosis patients. *Journal of Consulting and Clinical Psychology, 69*, 942–949.

Huijbregts, S., Kalkers, N., de Sonneville, L., et al. (2004). Differences in cognitive impairment of relapsing remitting, secondary, and primary progressive MS. *Neurology, 63*, 335–339.

Jacobs, R. K., Anderson, V. A., Neale, J. L., & Kornberg, A. J. (2004). Neuropsychological outcome after acute disseminated encephalomyelitis: impact of age at illness onset. *Pediatric Neurology, 31*(3), 191–197.

Joy, J. E., & Johnston, R. B. (Eds.). (2001). *Multiple Sclerosis: Current status and strategies for the future*. Washington: National Academy Press.

Kotterba, S., Orth, M., Eren, E., Fangerau, T., & Sindern, E. (2003). Assessment of driving performance in patients with relapsing-remitting multiple sclerosis by a driving simulator. *European Neurology, 50*(3), 160–164.

Krupp, L., & Elkins, L. (2000). Fatigue and declines in cognitive functioning in multiple sclerosis. *Neurology, 55*, 934–939.

Krupp, L. B., Christodoulou, C., Melville, P., et al. (2004). Donepezil improved memory in multiple sclerosis in a randomized clinical trial. *Neurology, 63*, 1579–1585.

Lobentanz, I., Asenbaum, S., Vass, K., et al. (2004). Factors influencing quality of life in multiple sclerosis patients: Disability, depressive mood, fatigue, and sleep quality. *Acta Neurologica Scandinavia, 110*, 6–13.

Lyon-Caen, O., Jouvent, R., Hauser, S., et al. (1986). Cognitive function in recent-onset demyelinating diseases. *Archives of Neurology, 43*, 1138–1141.

Mohr, D., Boudewyn, A., Goodkin, D., et al. (2001). Comparative outcomes for individual cognitive-behavior therapy, supportive-expressive group psychotherapy, and sertraline for the treatment of depression in multiple sclerosis. *Journal of Consulting and Clinical Psychology, 69*, 942–949.

O'Brien, A. R., Chiaravalloti, N., Goverover, Y., & DeLuca, J. (2008). Evidence-based cognitive rehabilitation for persons with Multiple Sclerosis: A review of the literature. *Archives of Physical Medicine and Rehabilitation, 89*, 761–769.

Olek, M. J. (Ed.). (2005). *Multiple Sclerosis: Etiology, diagnosis, and new treatment strategies*. Totowa: Humana Press.

Porcel, J., & Montalban, X. (2006). Anticholinesteraaics in the treatment of cognitive impairment in multiple sclerosis. *Journal of the Neurological Sciences, 245*, 177–181.

Rao, S., Leo, G., Bernardin, L., et al. (1991a). Cognitive dysfunction in multiple sclerosis: Frequency, patterns, and prediction. *Neurology, 41*, 685–691.

Rao, S. M., Leo, G. J., Ellington, L., et al. (1991b). Cognitive dysfunction in multiple sclerosis II: Impact on employment and social functioning. *Neurology, 41*, 692–696.

Rao, S., Grafman, J., & Dijkerman, H. (1993). Memory dysfunction in multiple sclerosis: Its relation to working memory, semantic encoding, and implicit learning. *Neuropsychology, 7*, 364–374.

Rosati, G. (2001). The prevalence of multiple sclerosis in the world: An update. *Journal of the Neurological Science, 22*(2), 117–139.

Roth, R., Geisser, M., Theisen-Goodvich, M., et al. (2005). Cognitive complaints are associated with depression, fatigue, female sex, and pain catastrophizing in patients with chronic pain. *Archives of Physical Medicine and Rehabilitation, 86*, 1147–1154.

Ryan, L., Clark, C., & Klonoff, H. (1996). Patterns of cognitive impairment in relapsing-remitting multiple sclerosis and their relationship to neuropathology on magnetic resonance images. *Neuropsychology, 10*, 176–193.

Schultheis, M. T., Garay, E., Millis, S. R., & DeLuca, J. (2002). Motor vehicle crashes and violations among drivers with multiple sclerosis. *Archives of Physical Medicine and Rehabilitation, 83*(8), 1175–1178.



Schwarz, S., Mohr, A., Knauth, M., Wildemann, B., & Storch-Agenlocher, B. (2001). Acute disseminated encephalomyelitis: A follow-up study of 40 adult patients. *Neurology, 56*, 1313–1318.

Shawaryn, M., Schultheis, M., Garay, E., & DeLuca, J. (2002). Assessing functional status: Exploring the relationship between the multiple sclerosis functional composite and driving. *Archives of Physical Medicine and Rehabilitation, 83*, 1123–1129.

Thorton, A. E., & Naftail, R. (1997). Memory impairment in multiple sclerosis: A quantitative review. *Neuropsychology, 11*, 357–366.

Vollmer, T. L. (1999). Multiple Sclerosis: The disease and its diagnosis. In S. van den Noort & N. J. Holland (Eds.), *Multiple Sclerosis in clinical practice* (pp. 1–22). New York: Demos Medical Publishing, Inc.