

Handbook of Clinical Neuropsychology

SECOND EDITION

Edited by:

Jennifer M. Gurd

University Department of Clinical Neurology,
John Radcliffe Hospital, Oxford, UK

Udo Kischka

Rivermead Research Centre,
Oxford Centre for Enablement,
Oxford, UK

John C. Marshall (deceased †)

Formerly of Neuropsychology Unit,
University Department of Clinical Neurology,
John Radcliffe Hospital, Oxford, UK

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The neuropsychological presentation and treatment of demyelinating disorders

Peter A. Arnett and Amanda R. Rabinowitz

1 Introduction

By far the most commonly seen and studied demyelinating disorder in clinical neuropsychology is multiple sclerosis (MS). As such, most of this section will focus on MS. Other demyelinating disorders on which some neuropsychological data are available will be reviewed in a brief section at the end.

Clinical neuropsychologists play a pivotal role in assessment and treatment of MS patients. Prior to the advent of sensitive neuropsychological tests, when cognitive evaluations involving brief mental state examinations were primarily used, cognitive difficulties were thought to affect less than 5% of patients (Rao, 1986). Prevalence estimates with use of neuropsychological tests now range from 40-60% (see below). Because cognitive deficits in MS are associated with real-world functioning, neuropsychologists can first evaluate the extent to which tested difficulties displayed by patients may map onto real-world problems, then help patients make modifications to daily routines that allow them to circumvent cognitive difficulties they display. Neuropsychologists can also help identify and treat the depression that is so common, but often overlooked, in MS patients.

2 Pathophysiology of MS

MS is a demyelinating disease of the central nervous system whose cause is not yet fully explained, although it is thought to be related to an autoimmune process, a slow-acting virus or a delayed reaction to a common virus, or epigenetic factors interacting with the environment (ie. lack of vitamin D). One specific autoimmune process identified involves antibodies against antigens located on the myelin sheath that may infiltrate the blood-brain barrier and directly cause demyelination. Various pathophysiological processes may be involved in disease progression. Also, there is considerable variability among patients with regards to structural and immunologic disease features. These observations suggest that MS may be a series of syndromes, rather than a uniform disorder with a singular etiology and disease process (Noseworthy, Lucchinetti, Rodriguez, & Weinshenker, 2000).

The defining pathological feature of the disease is the demyelinated plaque - a lesion characterized by the loss of myelin, the relative preservation of axons, and the presence of astrocytic scars. Myelin is fatty tissue comprised of oligodendrocytic glial cells. Oligodendrocytes surround the neuronal axon and facilitate the propagation of action potentials. Multiple discrete plaques that are found at demyelinated sites are formed, in part, by proliferating astrocytes. Myelin sheaths within plaques are either destroyed or swollen and fragmented. Neural conduction facilitated by myelin because an intact nerve is enclosed in myelin sheaths separated by gaps from which the nerve impulse jumps. Affected areas thus interfere with or block neural transmission by limiting this process known as saltatory conduction. Axons and cell bodies of neurons often remain intact until late stage disease. Early symptoms of disease believed to be a result of the demyelination process. Remission of symptoms attributed to reduction of inflammatory edema and partial remyelination. As disease progresses, however, irreversible axonal injury may occur. Furthermore, oligodendrocyte progenitor pool exhaustion can inhibit remyelination. Remyelination much more likely to occur during acute phases and early in the disease process; minimal remyelination occurs with chronic lesions. These fluctuating disease processes may be responsible for chronic and progressive decline in functioning observed in many patients.

Size of plaques varies from about 1.0mm to several cm. Resulting symptoms typically reflect functions associated with affected areas. Plaques can occur in the brain or spinal cord. Location of plaques is highly variable between patients: Within the cerebrum, plaques near the lateral and 3rd ventricles are most common. Frontal lobes are the next most commonly affected, even when size of frontal lobes relative to rest of brain considered. Plaques in other major lobes of the brain are also frequently observed; additionally, plaques commonly seen in the optic nerves, chiasm, or tracts, as well as the corpus callosum, brain stem, and cerebellum. Majority of plaques (about 75%) are observed in white matter, but some occur in gray matter and in the juncture between gray and white matter. Some remyelination occurs with acute MS plaques.

2.1 Clinical presentation and natural course of MS

Likely acquired before puberty, but actual disease onset occurs in most (2/3rds) patients between ages 20 and 40. Onset before age 15 rare; late onset after age 40 is commonly characterized by quicker progression and greater morbidity. Average life expectancy following onset estimated at 30+ years, but variability is great.

Environmental contribution suggested by generally higher prevalence in temperate zones away from equator with prevalence decreasing near tropics towards equator. Highest prevalence rates (greater than 30 in 100,000) are in Northern Europe, Southern Australia, and middle latitude zones of North America. The 30-40% concordance in identical twins but only 1-13% in fraternal, suggests a genetic and/or epigenetic contribution. Risk in first-degree offspring of MS patients is only 5%, but 20-40 times greater than in general population. No increased risk in adopted children of patients with MS. Presence of HLA-DR2 allele significantly increases risk for MS; populations with greater incidence

of this allele (such as Scotland) have greater risk of MS (Noseworthy, Lucchinetti, Rodriguez, & Weinshenker, 2000).

2.1.1 Symptoms

Common symptoms: Muscle weakness, urinary disturbance, and visual anomalies like diplopia, loss of visual acuity, blurry vision, and visual field defects. Fatigue, problems with balance, and paresthesias (usually numbness and tingling in the limbs, trunk, or face) are also common. Significant cognitive difficulties and problems with depression constitute very common symptoms as well. Most common symptoms at MS onset are muscle weakness, paresthesias, visual disturbances, and gait/balance problems. About 50% of patients require assistance walking within 15 years of disease onset (Noseworthy, Lucchinetti, Rodriguez, & Weinshenker, 2000). Mode of symptom onset is typically acute or subacute. Many MS symptoms are 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 symptoms, it is not uncommon for patients in early stages before formal diagnosis to be labeled with hysterical/somatization disorders.

2.1.2 Diagnosis

Diagnosis of MS is clinical and laboratory based. Latest criteria involve various combinations of clinical and laboratory based evidence (McDonald *et al.*, 2001). Patients can get MS diagnosis from either discrete episodes or insidious progression. Regarding a diagnosis from discrete episodes, patients must have had at least one disease attack. If patients have had two or more attacks lasting at least 24 hours and separated in time (at least 30 days), combined with objective clinical evidence of two or more lesions, then that is sufficient for diagnosis. One attack can also lead to diagnosis if there is clinical evidence of at least two lesions, combined with the lesions being disseminated in time as demonstrated by MRI. Other combinations of attacks are also possible. MRI data are considered preferable to other paraclinical tests; however, additional tests can be used when clear-cut MRI findings are not present or atypical clinical presentations occur. Specifically, the presence of oligoclonal IgG bands in the cerebrospinal fluid (CSF) different from those in the serum, or elevated IgG, can be used. Additionally, Visual Evoked Potentials (VEPs) can be used to supplement the clinical examination to reveal evidence of additional lesions. Attacks, relapses, or exacerbations that imply new disease activity are common. Regarding insidious onset where discrete disease attacks are not present, positive CSF results involving presence of oligoclonal bands or raised IgG levels are necessary, combined with both abnormal VEP and various combinations of lesions disseminated in space. Furthermore, there must be MRI or abnormal VEP evidence that lesions are separated in space. Lastly, separation in time should be evident, as reflected by the onset of new MRI lesions or increased level of disability over the course of at least one year. McDonald and colleagues also lay out specific criteria for defining lesions detected on MRI as abnormal and characteristic of MS.

Several course types have been identified (Lublin & Reingold, 1996):

- 1 Relapsing-remitting (RR) - Most common and characterized by clearly defined disease relapses. Recovery can be full or with sequelae and residual deficit. Complete

remission following the initial episode of symptoms is common. Subsequent episodes are unpredictable, occurring weeks to years later. Symptoms associated with them remit less completely or not at all. Relapses are highly variable, lasting days to weeks, and more rarely, hours and months. No progression of disease between relapses. About 80% of MS patients have this type or secondary-progressive type. The RR and secondary-progressive types are more common in females than males by about a 2:1 ratio.

- 2 Secondary-progressive (SP) - Next most common type: First characterized by RR course then progression. Relapses and remissions may or may not occur. Approximately 70% of RR progress into SP.
- 3 Primary-progressive - Next most common type: Unrelenting disease progression from onset for most patients, but occasional stabilization and even improvement in functioning for others. No clear relapses. Prevalence is equivalent in males and females.
- 4 Progressive-relapsing - Least common type: Disease progression from onset. Acute relapses also occur from which patients may or may not fully recover. The term "chronic-progressive" formerly encompassed all progressive types.

Two severity outcome definitions also identified:

- 1 Benign - Patient remains fully functional 20 years post disease onset. This occurs in about 10% of patients.
- 2 Malignant - Rapidly progressing course leading to significant disability or death relatively soon after disease onset. Most patients fall in between these two extremes.

Several factors predict poor outcome including frequent relapses within first two years of onset, early motor and cerebellar findings, and male sex. Predictors of better outcome include female sex, predominantly sensory symptoms, and optic neuritis.

3 Neuropsychological deficits in MS

3.1 Prevalence of neuropsychological deficits

On average, about 45% of community based samples have been shown to have cognitive impairment (Jonsson *et al.*, 2006; Rao, *et al.*, 1991). Prevalence rates shown to be higher among clinic based samples, typically falling between 55% and 65% (Amato, Zipoli, & Portaccio, 2006). Most (about 80%) patients with deficits are relatively mildly affected. Global cognitive deficits uncommon, occurring in about 5-10% of patients (Longley, 2007). However, even mild cognitive problems in MS have been shown to relate to everyday activities (e.g., work, homemaking, personal care activities, social activities) (Higginson, Arnett, & Voss, 2000), including driving (Schultheis, Garay, & DeLuca, 2001), and even employment status (Benedict *et al.*, 2005; Rao *et al.*, 1991).

3.2 Nature of neuropsychological deficits

3.2.1 Intellectual functioning

This is affected significantly in about 20% of patients. Most patients score within a broad normal range.

3.2.2 Academic Skills

Little systematic research conducted on these in MS, but assumed to be intact in most patients.

3.2.3 Memory

One of the most commonly affected cognitive domains in MS. Problems encoding and/or retrieving both verbal and visual information are most common. It is typically manifested as immediate and delayed recall memory deficits on neuropsychological testing. About 30% of patients have substantial problems, another 30% have moderate problems, and the remaining 40% have mild or no problems with this type of memory (Brassington & Marsh, 1998). Working memory, the ability to maintain and manipulate information "on-line," also commonly impaired. Delayed recall deficits usually a function of deficient immediate recall, not forgetting. Learning curve across repeated trials is similar in slope to controls, but lower in magnitude. Percent retention, recognition, and incidental memory following a delay, and remote memory are usually intact. Clinically, memory problems often manifested as complaints of difficulty remembering conversations, appointments, work tasks, etc.

3.2.4 Attention & concentration/speeded information processing

One of the most commonly affected cognitive domains in MS. Difficult to separate speeded information processing from attentional functioning because the latter is necessary for performing any speeded cognitive task. Attention necessary in clinical evaluations to the possibility that memory problems in MS may, in part, be a function of deficits in these domains. MS patients show greatest difficulty on tasks requiring rapid and complex information processing, such as those requiring swift application of working memory operations, attentional switching, or rapid visual scanning. About 20-50% of MS patients have substantial difficulty with this cognitive domain, depending on the task used, with tasks like Oral Symbol Digit revealing more impairment than the PASAT (Benedict, Cookfair *et al.*, 2006). Such increased sensitivity may be due to the visual demands of the Symbol Digit, something that recent research has shown can compromise performance on the task in even MS patients with mild visual acuity problems (Bruce, Bruce, & Arnett, 2007). Simple attention span usually intact, but mild impairments sometimes found. Clinically, attention/speeded processing problems commonly manifested as difficulty tracking and keeping up with and focusing on details of conversations, work tasks, television programs, etc.

3.2.5 Verbal/linguistic deficits

Aphasias are rare in MS, but mild confrontation naming difficulties are sometimes seen. Deficits in verbal fluency are common. Important in clinical evaluations to determine if the latter deficits are associated with memory retrieval difficulties common to MS (Fischer *et al.*, 1994). Also, there is some evidence that the later parts of verbal fluency tasks are most sensitive to the fluency deficits in MS (Smith & Arnett, 2007). Because fluency tasks require rapid production of information, patients' poor performance on them may also be related

to their speeded processing deficits. Additionally, slowed speech common to MS should be considered as possible contributor to patients' verbal fluency, as well as speeded attentional deficits. 20-25% of patients have substantial problems on verbal fluency tasks (Rao, Leo, Bernardin, & Unverzagt, 1991), though some studies have reported impairment frequencies lower than 15% (Benedict, Cookfair *et al.*, 2006). Fluency problems may manifest clinically as word-finding problems impairing the flow of patients' conversations.

3.2.6 Visual-spatial deficits

About 10-20% of individuals with MS show substantial difficulty with higher-order visual-spatial skills involving angle matching or face recognition. Unclear whether higher order visual deficits are a function of primary visual disturbances involving blurred vision and diplopia (Bruce, Bruce, & Arnett, 2007; Rao, Leo, Bernardin, & Unverzagt, 1991). Clinical manifestations may involve accounts of running into things frequently while walking (e.g., doorways) or driving (e.g., curbs) because of visual miscalculations.

3.2.7 Executive skills

Executive skills are commonly affected in MS. Deficits in cognitive flexibility, concept-formation, verbal abstraction, problem-solving, and planning are found. 15-25% of individuals with MS show substantial difficulties in this cognitive domain. May manifest clinically as difficulty planning day-to-day activities (e.g., job tasks, meals, grocery shopping), verbal disinhibition and tangential speech, as well as problems organizing ideas and shifting appropriately from one topic to another in conversation.

3.3 Measurement of neuropsychological deficits

3.3.1 Brief screening batteries/repeatable batteries

An efficient way of approaching neuropsychological testing in MS is to conduct a brief screening evaluation to determine if further testing is warranted. MS patients impaired in one domain of cognitive functioning are not necessarily impaired in others (Rao *et al.*, 1991). Thus, neuropsychological assessments that evaluate major areas of cognitive functioning typically impaired in MS is critical because performance on a test in one domain provides little information about the likelihood of deficits in other domains.

Brief Repeatable Battery (BRB) Rao and colleagues have developed the Brief Repeatable Battery of Neuropsychological Tests in Multiple Sclerosis (Rao, and the Cognitive Function Study Group of the National Multiple Sclerosis Society, 1990) comprised of tests most sensitive to cognitive impairments typically seen in MS; most tests also include 15 alternate forms to allow for repeat testing. Battery includes six-trial version of the Verbal Selective Reminding Test, 10/36 Spatial Recall, Oral Symbol Digit Modalities Test, 2s and 3s Paced Auditory Serial Addition Test (PASAT), and Word List Generation (verbal fluency). Comprehensive norms for BRB can be found in Boringa *et al.* (2001). BRB takes 20-30 minutes to administer. Wechsler Test of Adult Reading (WTAR) (Psychological Corporation, 2001) also recommended and takes 5 minutes. Provides reliable and valid estimate of Full Scale WAIS-III IQ and has excellent norms. Adding the Chicago Multiscale Depression Inventory (CMDI) (Nyenhuis *et al.*, 1995), and Fatigue Severity Scale (FSS)

(Krupp *et al.*, 1988) also suggested. Together, the latter two measures take about 10 minutes and are self-administered, so could be completed in a waiting room before actual testing. Thus, in only 35-45 minutes of actual patient contact time, a reasonably comprehensive neuropsychological screen can be obtained and more extensive testing conducted if deficits are detected.

3.3.2 Minimal Assessment of Cognitive Functioning in MS (MACFIMS)

Developed by consensus from the meeting of a group of experts on neuropsychological functioning in MS (Benedict *et al.*, 2002). Somewhat longer than the BRB, taking approximately 90 minutes. The MACFIMS consists of the following five cognitive domains with tests measuring those domains listed in parentheses: Processing speed/working memory (Oral Symbol Digit Modalities Test, 2s and 3s PASAT), learning and memory (California Verbal Learning Test - 2nd Edition (CVLT-II) and Brief Visuospatial Memory Test – Revised (BVRT-R)), executive function (D-KEFS Sorting Test), visual-spatial processing (Judgment of Line Orientation), and word retrieval (Controlled Oral Word Association Test (COWAT)). In validation study, Benedict and colleagues (2006) found that nearly 60% of MS patients were impaired on at least two of these subtests. Caution required for PASAT use in lower functioning patients; can damage rapport because of their great difficulty performing. Poor performance on Arithmetic subtest of WRAT-4 (see below) may suggest that primary arithmetic calculation difficulties contribute to PASAT deficits.

The authors of MACFIMS also suggest including a number of additional measures to assess potential confounds. First, they recommended employing a culturally appropriate measure of premorbid ability on the first occasion a patient is seen. Several suggestions provided, with the North American Adult Reading Test (NAART) favored by most panel members.

Second, panel recommended that a measure of depression be routinely administered. The CMDI, a depression measure that includes mood, evaluative, and vegetative scales, was recommended as a screen for depression. Because of the overlap of MS disease symptoms and vegetative depression symptoms (e.g., fatigue, sleep disturbance, concentration difficulties, sexual dysfunction), CMDI allows clinician to evaluate whether total depression score is artificially elevated due to differential contribution of vegetative scale. The panel also suggested the possibility that the Beck Depression Inventory - Fast Screen (BDI - FS) be used, though this was recommended with caution since, at the time of this publication, the BDI - FS had not been validated on an MS sample, but since then it has (Benedict *et al.*, 2003). Consists of only 7 items and does not include any vegetative symptoms, thus it circumvents the potential vegetative depression symptom/MS disease symptom confound. Raw scores greater than 3 suggest further evaluation of depression is needed.

A third confound that the consensus authors suggested needed to be addressed were potential problems with vision. They recommended that a measure like the Rosenbaum Pocket Vision Screener could be used, and that a 20/50-70 threshold at 14 inches from the corrected eye was necessary because that was similar to the small print characters presented during neuropsychological testing.

Fourth, although most tests chosen involved a spoken response to circumvent fine motor writing deficits common to MS, the authors suggested that motor confounds that could potentially interfere with performance on the BVMT-R be addressed. They suggested using the copy portion of the BVMT-R administration, in addition to the 9-Hole Peg Test.

Related to motor functioning, the authors of the MACFIMS paper also suggested that a measure of rudimentary oral motor speed be included given that many of the recommended tests required a rapid spoken response. The task they recommended, the Maximum Repetition Rate of Syllables and Multisyllabic Combinations (MRRSMC), requires examinees to repeat the phonemes “pa” “ta” or “ka” as quickly as possible in one good breath lasting at least six seconds. A fourth trial requiring the repetition of the “pa-ta-ka” sequence is also administered. Number of syllables per second is the main scoring index. Given the frequency of dysarthria in MS, it was suggested that slowed speech might impair patients’ performance on such tasks. At the time of the MACFIMS publication, no data were available on the MRRSMC. A recent publication examined this test in MS and controls and found that MS patients performed significantly slower on the task compared with controls (Arnett *et al.*, 2008). These authors also found that consideration of the MRRSMC task before comparing group differences on several standard neuropsychological tasks requiring a rapid oral motor response (e.g., COWAT, Animal Naming, Oral Symbol Digit, & PASAT) significantly reduced group differences with controls. Thus, the data suggested that a significant proportion of the variance in group differences between MS patients and controls on these standard neuropsychological tasks was due to the relatively slower speech of MS patients.

Finally, the authors suggested that fatigue be screened using the Fatigue Impact Scale. Although the authors acknowledged that the literature on the influence of fatigue on cognitive functioning in MS was mixed, they noted that fatigue may influence performance in some patients and also was known to influence other domains of quality of life in MS patients. A recent study has shown that the MACFIMS has excellent validity in detecting cognitive impairment in MS (Benedict *et al.*, 2006).

3.3.3 Comprehensive batteries

The MACFIMS provides a core battery from which a more comprehensive battery can be developed. In addition to this minimal battery, the following tests can be added if a more comprehensive evaluation is deemed clinical necessary.

Intellectual functioning Best measured using four-subtest (Vocabulary, Similarities, Matrix Reasoning, Block Design) form of WASI, which allows for derivation of reliable and valid Full Scale, Verbal, and Performance IQ estimates. Entire Wechsler Adult Intelligence Scale, 3rd Edition (WAIS-III) is not necessary in most cases. However, individual subtests are useful for measurement of specific functional areas and are highlighted below. Interpret Block Design cautiously because motor manipulation and visual demands required for it and many other WAIS-III Performance subtests make it difficult to use reliably and validly in MS patients with sensorimotor disturbance. Consider performance on 9-Hole Peg test mentioned above for assistance with interpretation.

Table 29.1 Recommended brief and comprehensive neuropsychological batteries for assessing Multiple Sclerosis patients**Brief Screening Battery (About 30 minutes)****Premorbid Intellectual Functioning**

Wechsler Test of Adult Reading (WTAR)

MemoryVerbal Selective Reminding Test (6-Trial Version) with delayed recall and recognition
10/36 Spatial Recall with delayed recall and copy**Attention & Concentration/Speeded Information Processing**Symbol Digit Modalities Test (SDMT), Oral Version
Paced Auditory Serial Addition Test (PASAT), 2s and 3s versions**Verbal-Linguistic**

Controlled Oral Word Association test (COWAT)

Affective/Emotional, FatigueChicago Multiscale Depression Inventory (CMDI)
Fatigue Severity Scale**Mid-Length Battery (about 90 minutes)****Premorbid Intellectual Functioning**

North American Adult Reading Test (NAART)

MemoryCalifornia Verbal Learning Test - 2nd Edition (CVLT-II)
Brief Visuospatial Memory Test – Revised (BVM-T-R)**Attention & Concentration/Speeded Information Processing**Symbol Digit Modalities Test (SDMT), Oral Version
Paced Auditory Serial Addition Test (PASAT), 2s and 3s versions**Verbal-Linguistic**

Controlled Oral Word Association test (COWAT)

Executive

D-KEFS Sorting Test

Visuospatial

Judgment of Line Orientation (JLO)

Affective/Emotional, FatigueChicago Multiscale Depression Inventory (CMDI) or BDI – Fast Screen
Fatigue Impact Scale (FIS)**Sensorimotor**9-Hole Peg Test
Maximum Repetition Rate of Syllables and Multisyllabic Combinations (MRRSMC)
Rosenbaum Pocket Vision Screener**Standard Comprehensive Battery (About 3 hours)****Orientation**Information and Orientation subtest from Wechsler Memory Scale, 3rd Edition (WMS-III)**Intellectual Functioning**

Four- subtest form of the Wechsler Abbreviated Scale of Intelligence (WASI)

Academic Functioning

Wide Range Achievement Test, 4th Edition (WRAT-4)

(continued)

Table 29.1 (continued) Recommended brief and comprehensive neuropsychological batteries for assessing Multiple Sclerosis patients**Memory**

California Verbal Learning Test - 2nd Edition (CVLT-II)
 Brief Visuospatial Memory Test - Revised (BVM-T-R)
 10/36 Spatial Recall with delayed recall and copy
 Logical Memory subtests from WMS-III
 Information subtest from Wechsler Adult Intelligence Scale, 3rd Edition (WAIS-III)

Attention & Concentration/Speeded Information Processing

Symbol Digit Modalities Test (SDMT), Oral Version
 Paced Auditory Serial Addition Test (PASAT), 2s and 3s versions
 Digit Span subtest from WMS-III
 Spatial Span subtest from WMS-III
 Letter-Number Sequencing subtest from WMS-III

Verbal-Linguistic

Controlled Oral Word Association test (COWAT)
 Boston Naming Test

Executive

Tower subtest from Delis-Kaplan Executive Function System (D-KEFS)
 Card Sorting subtest from D-KEFS, free-sorting condition only
 Similarities subtest from WAIS-III

Visuospatial

Judgment of Line Orientation (JLO)

Affective/Emotional, Fatigue

Chicago Multiscale Depression Inventory (CMDI) or BDI - Fast Screen
 Hospital Anxiety and Depression Scale (HADS)
 Fatigue Impact Scale (FIS)

Sensorimotor

9-Hole Peg Test
 Maximum Repetition Rate of Syllables and Multisyllabic Combinations (MRRSMC)
 Rosenbaum Pocket Vision Screener

Disability

Multiple Sclerosis Functional Composite

Academic functioning Best evaluated using the Wide Range Achievement Test (WRAT-4), a battery that takes approximately 30-45 minutes to administer, and assesses reading, writing, and arithmetic skills. Significantly worse performance on subtests compared with Full Scale IQ can suggest possibility of a developmental learning disability contributing to pattern of cognitive test performance observed. Such a possibility should be explored in interview, as well, when discussing developmental history.

Memory The Logical Memory subtests (I & II) from the Wechsler Memory Scale - 3rd Edition (WMS-III) are a useful supplement to the memory tests suggested for the MACFIMS. The 10/36 Spatial Recall is also useful, as many patients have significant motor-writing difficulties and 10/36 tests visual memory without any drawing component. Remote memory screened by Information subtest of WAIS-III, orientation by Information and Orientation subtest from WMS-III.

Attention & concentration/speeded information processing In addition to PASAT and Oral Symbol Digit to assess this cognitive domain, Digit Span forward and Spatial Span forward from WMS-III most useful as measures of simple attention span. Letter-Number Sequencing, Spatial Span – Backward, and Digit Span – Backward subtests from WMS-III are recommended as measures of working memory relatively independent of speed.

Verbal/linguistic Confrontation naming may be assessed by Boston Naming Test, 2nd Edition, which is useful only as a screen for verbal function. In addition to the COWAT, semantic fluency (e.g., animal naming) can be useful. Significantly better animal naming than letter-word fluency can suggest that letter-word fluency problems are, in part, a function of semantic memory retrieval difficulties. Comprehensive review has suggested that semantic fluency is just as sensitive as letter-word fluency to verbal fluency problems in MS (Henry & Beatty, 2006), and can be more easily interpreted in non-English speakers (but base-line speaking rate needs to be measured, to rule out artifacts due to slowed articulation).

Executive Wisconsin Card Sorting Test (WCST) has traditionally been used to measure cognitive flexibility and concept formation in MS. However, a study by Beatty and colleagues (1996) suggested that the California Card Sorting Test (CCST) may be better because it allows for differentiation of perseverative responding and concept formation, unlike the WCST. It is important to note that MS patients tended to show impaired concept formation but not perseverative responding. The Delis-Kaplan Executive System battery (D-KEFS; (Delis *et al.*, 2001)) now includes a subtest analogous to CCST called the Card-Sorting Test that can be used and has excellent norms. Because of lengthy administration time, however, only administration of the free-sorting condition is recommended. The Tower Test from D-KEFS is recommended for measuring planning ability, and the Similarities subtest from WAIS-III is a good index of verbal abstraction.

3.4 Possible causes of cognitive deficits

Primary causes of cognitive deficits emanate from a direct consequence of location and extent of brain damage. Thus, cognitive problems caused by primary influences are generally not reversible. There is clear evidence that overall cognitive impairment is associated with total lesion damage in the brain (Rao *et al.*, 1989), gray matter hypointensities (Brass *et al.*, 2006), and especially atrophy (Benedict *et al.*, 2006). There is some evidence that frontal lobe lesions are associated with deficits on executive tasks like Wisconsin Card-Sorting Test (WCST). The association of lesions in other brain areas and specific cognitive deficits is less clear.

Secondary causes of cognitive impairment are a consequence of something associated with a disease such as depression, anxiety, or fatigue. Cognitive problems caused by these secondary influences are potentially reversible if the secondary influence is successfully treated. Relative to primary causes, less attention has been paid in the MS literature to these possible causes of cognitive dysfunction. Recent work shows that depression is associated with impairments in speeded attentional functioning, working memory, and

executive functions, but this link is still controversial (Arnett, 2005; Landro *et al.*, 2004). There is little evidence that self-reported fatigue or anxiety are significantly associated with cognitive deficits in MS, but these associations are relatively infrequently examined to date. However, one study suggests that MS patients show greater decline in performance on cognitively demanding tasks over the course of an evaluation with other demanding cognitive tasks. This suggests the possibility that there is greater susceptibility to cognitive fatigue during testing in MS (Krupp & Elkins, 2000), something that should be taken into consideration when ordering tests in a battery.

3.5 Relationship between cognitive deficits and illness variables

Kurtzke's Expanded Disability Status Scale (EDSS; (Kurtzke, 1983)) has been the most commonly used measure of disability in MS. Occasional studies have reported a relationship between EDSS scores and cognitive impairment, but the majority of studies have not found this. Because of problems with EDSS as a measure of disability, the Multiple Sclerosis Functional Composite (MSFC; (Fischer *et al.* 1999)) was developed. It assesses three clinical dimensions: Leg function/ambulation, arm/hand function, and cognitive function, and is now recommended for use in standard clinical evaluations.

Recent longitudinal work on cognitive decline in MS paints a variable picture. Most studies show relative stability over about a 3-4 year period (Longley, 2007). However, patients identified as cognitively impaired are the most likely to show cognitive decline (Kujala, Portin, & Ruutiainen, 1997), even over a relatively short period of time (e.g., three years). The most extensive longitudinal study to date (10 years) has shown that nearly 50% of MS patients unimpaired initially, remained so 10 years later (Amato *et al.*, 2001). These investigators also found, however, that whereas 26% of patients were mild/moderately impaired at baseline, 56% were impaired at the 10-year follow-up. Visual and verbal recall memory, verbal fluency, visuospatial function, processing speed, and verbal intelligence may be most susceptible to decline over an 8-10 year period (Achiron *et al.*, 2005; Bobholz & Rao, 2003; Piras *et al.*, 2003). Compared with relapsing-remitting patients, progressive patients show greater cognitive dysfunction; one study estimated that secondary-progressive patients had seven times greater risk of cognitive impairment than relapsing-remitting patients (Chelune *et al.*, 2004). Nonetheless, relapsing-remitting patients shown to be cognitively impaired relative to healthy matched controls even when they are in remission.

4 Related emotional disorders

4.1 Depression

Very common in MS with lifetime prevalence around 50% for major depression. Point prevalence rates vary between about 15-50%, depending on diagnostic approach. Studies using clinical interviews and diagnostic criteria report lower prevalence; those using cut-offs from self-report measures report higher. Accurate screening and diagnosis of depression is extremely important, given the increased risk of suicide in MS; the latter may be the cause of death in up to 15% of MS clinic patients (Chwastiak & Ehde, 2007).

Depression has been shown to be treatable through brief and even telephone-based cognitive-behavioral therapy (Mohr *et al.*, 2000), as well as group therapy. Also, cognitive-behavioral stress management training shown to reduce emotional distress in MS (Fischer *et al.*, 1994). Nonetheless, depression/distress historically undertreated in MS. Successful treatment of depression associated with greater adherence to immunotherapy.

There has been no consensus regarding the nature of depression in the MS literature. Some investigators have presented evidence that neurovegetative symptoms of depression are not valid indicators of depression because of their overlap with MS symptoms (e.g., sleep disturbance, fatigue, sexual dysfunction), while others have provided evidence to the contrary. This debate suggests caution is warranted in interpreting neurovegetative symptoms of depression as depression symptoms in any individual MS patient.

The cause of depression in MS unknown, but high levels of perceived stress, low levels of social support, and disease exacerbation/pharmacological treatment of shown to be associated with increased emotional distress. Depression is associated with reduced quality of life and employment of generally less effective (emotion-focused, avoidant) coping strategies in MS. Negative cognitive schema associated with depression, and these also may moderate the impact of pain (Bruce *et al.*, 2007) and stress (Beeney & Arnett, 2008) on depression in MS. Lesion burden, especially in temporal brain regions, associated with depression in MS, and may represent a neural substrate (Feinstein, 2004). Premorbid history of depression is no greater than in non-MS. However, patients with history of depression, before or after MS onset, may be at increased risk for future depressive and manic states.

4.2 Anxiety

Possibly more common than depression, but infrequently studied in MS. Data are limited, but point prevalence of clinically significant anxiety thought to be about 25% with lifetime prevalence estimates around 35% (Korostil & Feinstein, 2007). Lifetime prevalence of specific anxiety disorders has only been minimally studied, but most frequent include generalized anxiety disorder, followed by panic disorder, and then obsessive compulsive disorder. Cause of anxiety in MS unknown, but prominent in early stages of disease when diagnosis and prognosis most uncertain. Decline in distress associated with more definitive diagnostic statements by treatment professionals. Best predictors of anxiety disorders include being female, a co-morbid diagnosis of depression, and limited social support. Drinking to excess, higher social stress, and contemplation of suicide also associated with anxiety (Korostil & Feinstein, 2007). Comorbidity of anxiety and depression more associated with thoughts of self-harm, social dysfunction, and somatic complaints than either alone (Feinstein *et al.*, 1999). Limited existing research suggests that anxiety disorders are undetected and untreated in the majority of patients.

4.3 Other emotional disorders

Only other emotional disorder occurring with any significant frequency in MS is bipolar disorder. Point prevalence estimated at 0-2% and lifetime prevalence 13-16%. No published treatment studies of bipolar disorder in MS. Cause unknown. Pseudobulbar affect, a condition where patients laugh or cry out of proportion to any underlying emotion,

occurs in some patients and is sometimes referred to as pathological laughing or crying (Chwastiak & Ehde, 2007). The cause is not well understood, but thought to represent some type of disconnection syndrome where there is a loss of brainstem inhibition of laughing and crying. It occurs in about 10% of patients.

4.4 Measurement of emotional disorders

There is no consensus on how depression is best measured in MS because of neurovegetative symptoms debate outlined above. However, CMDI recommended because it has been validated in MS and allows for breakdown of depression into mood, evaluative, and neurovegetative symptoms of depression in separate scales. Mood and evaluative scales are more likely to reflect depression in MS because they are not confounded with MS symptoms like neurovegetative scale. Nonetheless, neurovegetative symptoms may reflect depression in some patients, so should not be dismissed, just interpreted with caution. BDI – Fast Screen is also a useful screening tool that has been validated in MS. Clinical interview can be used to follow-up initial screening with CMDI, if necessary.

There is no consensus on how anxiety is best measured in MS, but the Hospital Anxiety and Depression Scale been shown to be useful (Feinstein *et al.*, 1999); a measure that takes only about 5 minutes to complete and can be followed up with clinical interview, if necessary. It is unclear how bipolar disorder is best measured in MS. Diagnostic interviews are the only reliable method reported to date.

5 Neuropsychological/cognitive rehabilitation in MS

Approaches to cognitive rehabilitation in MS have been suggested, but few have convincing empirical validation. Many early empirical studies of cognitive retraining interventions were characterized by small sample sizes, absence of control groups, and disappointing results in terms of their effect on cognitive functioning (Brassington & Marsh, 1998). However, more recent and well-designed studies have demonstrated positive initial results for some interventions. Given that many patients remain relatively stable cognitively over long periods of time, they may be more likely than patients with other neurological conditions to benefit from cognitive rehabilitation (Longley, 2007).

The story memory technique (SMT) is designed to train individuals to make use of imagery and context in order to improve learning. This intervention was investigated in a randomized clinical trial as a treatment for memory impairment in a group of MS patients with memory deficits. MS patients with moderate to severe impairments showed a significant improvement on the Selective Reminding Test compared with patients in the control condition. The treatment group also reported significant self-reported improvement in memory, suggesting that improved performance on the neuropsychological measure may be reflective of meaningful improvements in real life cognitive functioning (Chiaravalloti *et al.*, 2005; Krupp *et al.*, 2004).

Recent research on self-generated learning in MS patients has yielded promising results as well. Items generated by an individual are better remembered than items that are simply presented; this phenomenon is robust within the general population, and has been labeled the generation effect (Slamecka & Graf, 1978). Chiaravalloti and DeLuca (2002)

demonstrated the generation effect in a sample of MS patients with mild to moderate memory impairment, reporting significantly better recall and recognition of self-generated stimuli compared with presented stimuli. These results were replicated and extended in a study by Basso and colleagues (2006). This study examined self-generated encoding for information related to activities of daily living - specifically names, appointments, and object locations. In a sample of MS patients with moderate to severe memory impairment, the investigators found significantly better memory for self-generated, compared with didactically presented, stimuli. The results of these two studies suggest that cognitive rehabilitation interventions based on self-generated learning could improve memory performance in MS patients. The findings reported by Basso and colleagues (2006) indicate that such an intervention may promote memory improvements that are relevant to real-life functioning.

Other interventions have focused on improving attentional functioning in MS patients. One study examined the efficacy of computer-aided retraining of memory and attention in a randomized, double-blind, controlled trial. The study treatment - a computer-assisted memory and attention retraining intervention - was compared with a control intervention - a visuo-constructional and visuo-motor coordination computer-assisted intervention. Although the results did not support superiority of the study treatment, in both groups about 45% of patients demonstrated significant improvement on measures of neuropsychological functioning (Solari *et al.*, 2004). These results may suggest that computer-assisted cognitive intervention is helpful in MS patients, irrespective of specificity (Penner *et al.*, 2006); however, as the authors acknowledge, improvements by all study participants could simply have been a function of practice effects.

Failure of some large well-designed studies to detect significant treatment effects of cognitive retraining interventions has suggested that cognitive rehabilitation may not be viable for MS patients. However, some have argued that certain methodological limitations are in part responsible for the disappointing findings to date. Chiaravalloti and colleagues (2005) suggest that future studies should focus on including only those patients who are selectively impaired in the cognitive domain targeted by the experimental intervention. This methodological consideration, in conjunction with some recent promising findings, suggests that cognitive retraining may be effective in some MS patients. However future work is needed to continue to develop effective treatments, and better identify patients who will respond to specific interventions.

The inconsistent findings in the literature regarding cognitive retraining have led some to suggest that pursuing compensatory strategies for MS patients may be more promising; however, cognitive retraining has not been sufficiently studied to rule out the possibility that it may work for some patients. Nonetheless, because compensatory strategies have been studied more extensively in other neurologic populations (e.g., traumatic brain injury) and been shown to be beneficial, it may be useful to apply them to MS patients (Fischer *et al.*, 1994). These include strategies such as:

- 1 Using external aids (e.g., date books, wristwatches with alarms, electronic planners) for tracking and prompting for important information such as appointments, to-do lists, and medication times;

- 2 keeping things that must be remembered in one place; and
- 3 putting calendars in prominent locations and having family members use them so that the affected individual can track family and her/his own activities better.

Although also not systematically studied to date, making workplace modifications that involve things such as reducing distractions and minimizing requirements for speed in the work area might be especially beneficial to persons with MS who suffer from attentional and speeded processing difficulties. Also, because even MS patients with memory difficulties typically show learning with repetition, providing opportunities for recording important meetings, lectures, etc. for later review/rehearsal may be helpful to some patients. Given how common speeded processing difficulties are in MS, making changes in patients' day-to-day environments that allow for adequate time to process information may improve their accuracy in performing day-to-day cognitive tasks (Demaree *et al.*, 1999).

Some recent studies suggest that medications are a promising option for treating MS related cognitive impairment. An acetylcholinesterase inhibitor (donepezil) has been used to treat cognitive impairment in Alzheimer's disease. A recent study found that donepezil is also effective in improving memory performance on the Selective Reminding Test (SRT) in MS patients compared with placebo matched controls. This effect remained significant when controlling for physical disability, MS subtype, β -interferon use, gender, baseline SRT score, and other covariates (Christodoulou *et al.*, 2006).

Another study by Fischer and colleagues (2000) examined the efficacy of a β -interferon medication for improving cognitive functioning. 166 persons with relapsing forms of MS from the original double-blind, placebo-controlled trial of IFN β -1a were compared at baseline then after two-year follow-up on a variety of neuropsychological tests. Compared with the placebo group, the IFN β -1a group improved significantly more on the CVLT (trials 1-5 total), Tower of London, and Ruff Figural Fluency Test. Additionally, significantly fewer IFN β -1a group patients showed sustained PASAT decline by treatment end. Because study sample restricted to patients with relapsing MS between ages 18-55 and very restricted range of EDSS scores (1-3.5), however, caution warranted in applying results to patients not meeting such criteria. Effect of depression treatment on neuropsychological functioning in MS has been studied systematically in only one study (Rodgers *et al.*, 1996). Significant improvement in performance on tests of word-list learning and verbal abstraction corresponded to significant reduction in depression in a cognitive therapy treatment group. Although characterized by non-random assignment of patients to treatment groups, non-clinically depressed patients, and relatively small n, results were promising and suggest that depression treatment (even in subclinical patients) could have beneficial cognitive effects in MS. Therefore, beyond improving the well being of individuals with MS and making them more likely to adhere to important disease-modifying medication regimens (see above), successful treatment of depression may improve patients' cognitive functioning in some domains.

6 Other considerations for MS

Sleep problems are common in MS, but poorly understood. High and debilitating levels of fatigue reported by MS patients appear likely to be related to sleep problems, disease

severity, and depression (Strober & Arnett, 2005). Recommended that fatigue be briefly screened using FSS or examined in more detail using Fatigue Impact Scale (FIS) (Fisk *et al.*, 1994). The latter allows for evaluation of physical, social, and cognitive fatigue in separate scales. Cutoff score of 75 for total score recommended to identify those with significant functional limitations relating to fatigue. Providing breaks throughout testing day may help minimize possible impact of fatigue on test performance.

7 Other demyelinating diseases

Demyelinating diseases other than MS are comparatively rare, have been only minimally studied neuropsychologically, and are infrequently seen by clinical neuropsychologists. What follows is a brief discussion of two other demyelinating diseases.

7.1 Marchiafava-Bignami disease

This is characterized by focal demyelination in the medial zone of corpus callosum and most commonly associated with chronic alcoholism. Rare but well-documented cases have been reported in nonalcoholics. Degeneration of anterior and posterior commissures, centrum semiovale, middle cerebellar peduncles, subcortical white matter, and long association bundles also sometimes seen. Symptom onset is usually insidious and nonspecific with both focal and diffuse manifestations of cerebral disease common; acute presentations involving deteriorating speech, gait, orientation, and consciousness also seen. Psychiatric symptoms are frequently present including delusional states, paranoia, mania, and depression. Psychomotor slowing, apathy, and dysarthria also seen. Neuropsychologically, nonspecific dementia is most common. Callosal signs also characteristic. For example, patients may be able to name objects placed in one hand or presented to one visual field, but not in the other hand or field. Hemispheric disconnection signs also include unilateral apraxias and agraphias in the absence of aphasia, in addition to unilateral sensory (i.e., auditory, tactile, visual) simultaneous extinction. Alien hand syndrome is sometimes seen, most often on the left side or bilaterally.

7.2 Central Pontine Myelinolysis (CPM)

This involves destruction of the myelin sheaths in the central portion of the basis pontis, and is most often found in young to middle-aged adults. Myelinolytic lesions are not restricted to the brain stem and are observed in the cerebral cortex, thalamus, basal ganglia, subcortical white matter, amygdala, centrum semiovale, internal capsule, cerebellum, and corpus callosum. It is associated with chronic alcoholism and/or malnutrition in most cases, but also with liver, kidney, and brain disease and organ transplants. More recently it has been seen with AIDS, chemotherapy, and viral infections. Definitive causes are unknown, but rapid correction of hyponatremia is suspected. Acute symptoms include altered levels of consciousness, seizures, lethargy, mutism, pseudobulbar palsy, and quadriparesis. Course of disease can be rapid, with death ensuing within days or weeks of symptom onset, but more patients have survived acute phase of illness in recent years. Neuropsychological data to date are limited to case reports that indicate persistence

of deficits beyond the acute stage involving global intelligence and reasoning, learning and memory, visual- and fine-motor speed, and attention and concentration. Confusional states most likely associated with underlying metabolic problem that causes CPM are not uncommon. Neuropsychiatric features including pressured and tangential speech, restlessness and agitation, and impaired insight and judgment have been reported as initial presenting symptoms of CPM.

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Correspondence concerning this article should be addressed to: Peter Arnett, Psychology Department, Penn State University, 522 Moore Building, University Park, PA 16802-3105. Electronic mail: paa6@psu.edu.

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