The Neuropsychiatry of Multiple Sclerosis

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This review describes the many neuropsychiatric abnormalities associated with multiple sclerosis (MS). These may be broadly divided into 2 categories: disorders of mood, affect, and behaviour and abnormalities affecting cognition. With respect to the former, the epidemiology, phenomenology, and theories of etiology are described for the syndromes of depression, bipolar disorder, euphoria, pathological laughing and crying, and psychosis attributable to MS. The section discussing cognition reviews the prevalence and nature of cognitive dysfunction, with an emphasis on abnormalities affecting multiple domains of memory, speed of information processing, and executive function. The detection, natural history, and cerebral correlates of cognitive dysfunction are also discussed. Finally, treatment pertaining to all these disorders is reviewed, with the observation that translational research has been found wanting when it comes to providing algorithms to guide clinicians. Guidelines derived from general psychiatry still largely apply, although they may not always be most effective in patients with neurologic disorders.
The importance of future research addressing this imbalance is emphasized, for neuropsychiatric sequelae add significantly to the morbidity associated with MS.

(Can J Psychiatry 2003;49:157–163)

Information on funding and support and author affiliations appears at the end of the article.

Highlights

- Multiple sclerosis (MS) is the commonest cause of neurologic disability in young and middle-aged adults.
- The lifetime prevalence of major depression in MS is approximately 50%.
- The reasons for the elevated prevalence of depression can be traced to multiple factors. The cerebral lesion findings must be viewed alongside psychosocial data.
- It is likely that diffuse white matter disease rather than focal damage is the most important factor responsible for cognitive dysfunction in MS.

Key Words: *multiple sclerosis, mood, cognition, neuroimaging, translational research, treatment*

The evolution of the neuropsychiatry of multiple sclerosis (MS), with a set sequence of events unfolding over the course of a century or more, provides a historical paradigm for other neurologic disorders. According to the paradigm, a clinically astute neurologist, whom posterity will treat kindly, first describes the neurologic (and occasionally, the psychological) signs and symptoms that come to define the disorder. The new disease entity may bear his name, although this would have created taxonomic confusion in the case of MS, given Charcot's multiple seminal observations in a host of disorders. Over succeeding decades, the diagnostic criteria are refined by further observation supplemented by data from new technologies. Mental state changes either pass with little notice or are missed. A couple of generations later comes belated recognition of prominent abnormalities in mentation—neuropsychiatry redux. A flurry of research defines the prevalence of cognitive dysfunction and the phenomenology of emotional change. Invariably, the data reveal major psychiatric problems integral to the disease, and then, with few exceptions, clinical research stops. Few double-blind, placebo-controlled treatment trials in neuropsychiatry provide an evidence-based approach to treating the newly discerned behavioural abnormalities. Not content with anecdotal

evidence, the clinician is left with little choice but an uncomfortable retreat into general psychiatry and the application of principles and regimes that may not be the most effective.

Within neuropsychiatry, epidemiologic, genetic, molecular, and neuroimaging advances have generally failed to translate into new and specific behavioural treatment guidelines; however, this should not detract from what has been accomplished. Much has been learned, and this review highlights some of the progress with respect to MS.

As a prelude to this review, it is important to remember that MS is the commonest cause of neurologic disability in young and middle-aged adults. It has no cure. As such, all sources of potential morbidity must be detected and, wherever possible, treated. Here, psychiatrists can play a useful role because disorders of mood and cognition frequently accompany the more readily discernable ataxia, weakness, and loss of visual acuity.

Disorders of Mood, Affect, and Behaviour

Major Depression

The lifetime prevalence of major depression in MS is approximately 50% (1). A metaanalysis suggests that this is higher than in other neurologic disorders (2) and, depending on the reference point, is 3 to 10 times the rate in the general population (3). While the basic phenomenology of the MS depressive syndrome overlaps with that found in primary depression, certain symptoms are more typical, while others occur less commonly. Thus, irritability, discouragement, and a sense of frustration are more likely to accompany low mood than are feelings of guilt and poor self-esteem (4). It is also important to remember that symptoms such as insomnia, poor appetite, and difficulties with concentration and memory may be equally attributable to depression or to MS. Fatigue represents a particularly notable confounder in this regard. Fatigue is considered ubiquitous among MS patients, and most depression patients will also endorse it; while researchers may be able to delineate a particular type of fatigue associated with each disorder, such distinctions are likely to be beyond the scope of busy clinicians. Nevertheless, even when these potential diagnostic traps are avoided, the rates of major depression in MS remain elevated and suggest that 1 in 2 patients will develop the syndrome over the course of their lives.

Depression is an important reason for so many MS patients' thoughts of self-harm: suicidal intent occurs in approximately 30% of MS patients and is linked to the presence and severity of depression and social isolation (5). Given that thoughts of suicide are harbingers of suicidal attempt, these figures help explain, albeit indirectly, why suicide rates in MS patients are up to 7 times higher than rates in the general population and higher than in most other neurologic disorders, as well (6).

The elevated prevalence of depression can be traced to multiple factors, although it needs to be acknowledged at the outset that etiologic data are at best inconsistent and incomplete. While there does not appear to be a clear genetic diathesis to depression in MS (7), a recent dissenting voice exists (8). It is also unclear whether depression may be linked to disease exacerbation, with evidence for (9) and against (10) available. It is, however, incorrect to conclude that depression is simply a patient reaction to having a disabling, incurable, and difficult-to-predict neurologic disease (11). More rewarding clues come from neuroimaging data that reveal an association between low mood and various indices of structural (12) and functional (13) brain abnormalities. Focusing on a single index of cerebral pathology is, however, likely to miss the bigger picture. For example, Pujol and others reported that hyperintense lesions localized to the arcuate fasciculus was the single magnetic resonance imaging (MRI) variable that distinguished between patients with depression and euthymic patients; alone, however, it could account for only 17% of the depression score variance (14). These findings were extended by other researchers who reported that MS patients suffering from depression were more likely to have greater hypointense lesion volume as well as discrete areas of cerebral atrophy (15). Nevertheless, combining measures of lesion load and cortical atrophy have only improved the depression score variance to 40% (16). These cerebral findings must be viewed alongside psychosocial data: a constellation of perceived helplessness, uncertainty, and disability has been shown to be equally important in explaining depression (17).

A final observation with respect to the etiology of depression is germane. In the early 1990s, disease-modifying therapies for MS were introduced—an exciting development, although concern was expressed about depression as a side effect of treatment. In particular, the first trial of interferon beta-1b was marred by 1 case of suicide and other casess of attempted suicide (18). Subsequent studies that have addressed potential mood-altering effects of interferon beta-1b (19) and interferon beta-1a (20) have not found increased rates of depression on treatment, which also holds true for a third disease-modifying drug, glatirimar acetate (21).

Bipolar Affective Disorder

In MS patients, the lifetime prevalence of bipolar affective disorder is twice the prevalence in the general population (22). This increase cannot be attributed to the effects of steroid treatment alone (23). Unlike major depression, there may be a genetic predisposition to bipolar affective disorder in some female MS patients (24).

Euphoria

This refers to a state of mental and physical well-being in the presence of significant neurologic disability. Euphoric MS patients have advanced MS with an Expanded Disability Status Scale score in the upper range. MRI studies have demonstrated a high T2-weighted lesion load, with frontal areas particularly affected, while CT scan findings have shown enlarged ventricles (25). Cognitive abnormalities are invariable (25). Given the skewed clinical profile of advanced MS, the prevalence figure for this syndrome is a median, as opposed to a mean, of 25%.

Pathological Laughing and Crying (PLC)

This syndrome encompasses laughter without mirth and tears without sadness. The incongruent outward display of emotion is not, however, devoid of subjective distress, for patients find the symptoms troubling. Approximately 10% of MS patients are affected, with varying degrees of severity (26). Patients with PLC are more likely to have frontally mediated cognitive deficits (27). The pathogenesis of these symptoms is an enduring conundrum. Although considered synonymous with pseudobulbar affect, inappropriate laughing or crying or a mixture of both can occur in the absence of a pseudobulbar palsy. Case reports from the MS and non-MS literature have implicated such widely dispersed regions as the dominant prefrontal cortex (28), the cerebellum (29), and the supplementary motor cortex (30). No neuroimaging study has been undertaken in a sample of patients with MS.

Psychosis

Psychosis is an unusual behavioural consequence of MS. Prevalence rates are unknown but are thought not to exceed chance (31). One possible reason for this is that MS is predominantly a white matter disease, whereas psychosis is more typically linked to grey matter abnormalities. Small sample size limited the single MRI study that looked for cerebral correlates of psychosis, attesting to the rarity of the association (32). This study defined psychosis as the presence of delusions or hallucinations in the absence of dementia or delirium and used a 1-for-1 case–control matching; its main finding was that MS patients with psychosis, as opposed to those without, were significantly more likely to have a higher temporal horn lesion load (32).

Treatment of Mood Disorders

Major Depression

Although MS patients frequently experience major depression, data show that the diagnosis is frequently missed, even when patients with depression are suicidal (5). This situation is not unique to MS. Overlooking depression as a treatable cause of morbidity may help explain why there is only 1 published double-blind, placebo-controlled trial of antidepressant medication in MS patients (33). In that trial, the tricyclic desipramine was found to be more effective than placebo; however, patients had difficulty tolerating the full therapeutic dosage because of anticholinergic side effects (33). There have been several subsequent open-label trials of various selective serotonin reuptake inhibitors (SSRIs), and good results have been reported with fluoxetine (34) and sertraline (35). Similarly, the reversible monoamine oxidase inhibitor moclobemide was found to be effective (36). A major drawback of the SSRIs, however, is their side effect of sexual dysfunction, which may further compromise function already disturbed to varying degrees in up to 80% of patients. In this regard mirtazepine, with its combined noradrenergic and serotonergic actions, may prove a useful treatment. Its mechanism of action, targeting the 5-HT_1 receptor while blockading the 5-HT_2 and 5-HT_3 receptors, sets it apart from the SSRI drugs. Consequently, rates of sexual side effects are low and similar to placebo. However, sedation is a potential problem and may aggravate complaints of fatigue.

When clinicians are confronted by a patient with MS who does not respond to an SSRI or a selective norepinephrine reuptake inhibitor (SNRI)–SSRI, they must turn to the general psychiatry literature for guidance. Lithium may prove a useful adjunct, although lithium-promoted diuresis can lead to incontinence in MS patients with bladder dysfunction. Occasionally, electroconvulsive therapy (ECT) is required for intractably low mood. It is generally well tolerated, although a reported serious side effect is an exacerbation in the MS itself. The presence of contrast-enhancing lesions on MRI at the time of treatment signifies the possibility of an ECT-induced flare in disease (37).

Psychotherapy, particularly cognitive-behavioural therapy, has been shown to be as affective as sertraline in treating depression in MS patients (38). Further, this treatment may be administered via telephone to patients whose immobility precludes regular and frequent clinic attendance (39).

A fledgling attempt at providing a treatment algorithm for major depression associated with MS has been undertaken by the Consortium of Multiple Sclerosis Treatment Centers. The aim is to publish and distribute the consensus treatment guidelines (personal communication, Schitter RB and colleagues, 2004).

Other Disorders of Mood, Affect and Behaviour

There are no published guidelines for treating a manic episode in MS, and once again, medication regimes used in general psychiatry provide direction, with the cautionary advice of starting low and going slow with dosing. Lithium or valproic acid as mood stabilizers of choice may need to be bolstered with benzodiazepines for sedation. Should delusions accompany the mania, one of the newer antipsychotic agents, such as

olanzapine or quetiapine, will be needed. The latter will also be required to treat patients who become psychotic in the absence of prominent mood symptoms. Treating these patients presents a considerable challenge, particularly if their delusional thinking is accompanied by marked agitation or motor overactivity. What is necessary pharmacologically to control behaviour is frequently countertherapeutic for MS: antipsychotic medication may further compromise balance, coordination, and strength already adversely affected by demyelination. A fine line separates adequate and necessary sedation from falls, incontinence, and incapacitating fatigue; finding the correct regime is often no more sophisticated than trial and error.

No treatment exists for euphoria, while PLC responds well to low-dosage amitriptyline (40), SSRIs (41), or dopamine-enhancing drugs such as levodopa and amantadine (42).

Cognitive Dysfunction

Although Charcot noted an "enfeeblement of memory" in MS patients, cognitive dysfunction was largely unrecognized for a century. The reason for this can be traced to the more subtle nature of cognitive impairment in MS, compared with quintessential dementing disorders such as Alzheimer's disease. The more readily discernable deficits of aphasia, apraxia, and agnosia—so characteristic of predominantly cortical diseases—are generally absent in MS, where pathology is largely, but by no means exclusively, confined to subcortical white matter. Further, neurologists' and psychiatrists' reliance on the Mini-Mental State Examination (MMSE) (43) as the preferred means to rapidly screen for cognitive impairment may have contributed to the mistaken belief that cognition is spared in MS. Cited over 13 000 times in the behavioural sciences literature, the MMSE has been used in MS research, where scores in cognitively impaired patients were found to be significantly lower than in patients whose cognition was intact. However, even in patients with cognitive impairment, the mean MMSE is well above the cut-off point used to denote dementia, thereby compromising the clinical utility of the scale.

Prevalence of Cognitive Impairment

A neuropsychological study of 100 community-based MS patients and 100 healthy control subjects found that 43% of MS patients failed 4 or more tests on a 31-test battery, the yardstick for deeming whether a patient is impaired (44). A subsequent community-based study of 147 patients arrived at the same prevalence rate (45). This figure rises to approximately 60% if the sample selection is confined to clinic attenders.

The Nature of the Cognitive Deficits

The first point that needs emphasizing with respect to cognition in MS is that considerable individual variation exists in performance on neuropsychological testing. Therefore, using group means risks obscuring abnormalities limited to a small subset of patients. A second point is that composite scores on a particular test may conceal deficits on one aspect of that test. For example, the Digit Span subtest of the Wechsler Adult Intelligence Scale determines the ability of an individual to recall a series of numbers, first forwards and then backwards. When analyzed together, MS patients are thought to perform normally. However, analyzing the components separately reveals that deficits masked by total score become apparent on the backwards recall (46).

The most widely researched aspect of cognitive dysfunction in MS is memory, where multiple domains are adversely affected. Deficits in working (47), semantic (48), and episodic (49) memory have been reported and replicated. MS patients also have difficulty both in acquiring and in retrieving information (50), and their ability to accurately assess their own memory—a function termed "metamemory"—is impaired (51). Conversely, procedural memory is unaffected (52).

A hallmark of a "subcortical" dementia is impaired attention and slowness of thinking (53). The poor performance of MS patients on such neuropsychological paradigms as the Paced Auditory Serial Addition Task (PASAT) (54) and the Symbol-Digit Substitution Test illustrate this well (55). Studies that have broken down information-processing speed into automatic processing of information (not requiring conscious effort), controlled processing of stimuli (conscious and tapping into working memory), and motor processing (also thought to be automatic) have found deficits across all domains in cognitively impaired MS patients (56).

Problems with concept formation and abstract reasoning also occur in MS (57). An attempt to ascertain the constituent abnormalities in problem solving led Beatty and Monson to conclude that the central difficulty for MS patients is their difficulty in identifying concepts rather than perseveration (58). The functional integrity of the frontal lobes is considered central to these cognitive processes, although the delineation of widely dispersed neural networks helps explain why patients with nonfrontal pathology may on occasion perform poorly as well (59). Similarly, MS patients have difficulty with verbal fluency when measured by the Controlled Oral Word Association Test (COWAT). Like problem solving, verbal fluency is sensitive to frontal function, but it is not wholly subserved by it (60).

Detecting Cognitive Dysfunction

Neuropsychological testing is the most sensitive means of detecting cognitive difficulties, but testing is time consuming, expensive, and not always available. To that end, several brief screening instruments have been developed that do not require neuropsychological expertise and may be completed in 30 minutes or less. It should be remembered, however, that these brief

batteries lack the sensitivity of a complete neuropsychological assessment; therefore, they should only be used to screen patients. Most widely used is the Brief Repeatable Neuropsychological Battery (BRNB) (44), which comprises 4 tests: the COWAT, the PASAT, and measures of verbal (the Consistent Long-Term Retrieval measure from the Selective Reminding Test) and nonverbal (total recall from the 7/24 Spatial Recall Test) memory. With a sensitivity of 71% and a specificity of 94%, the BRNB has alternative versions, making it a useful research tool. More recently, a self-report index of cognitive impairment has been developed (61). This comprises 2 sets of 15 questions each, one for the patient to complete and the other for an informant. While results from patient self-assessments correlate more closely with mood, the informant ratings, which take only a few minutes to complete, are consistent with objective indices of cognitive function. Sensitivity and specificity are superior to the BRNB.

Cerebral Correlates of Cognitive Dysfunction

Unlike the search for cerebral correlates of depression, the yield for cognition is more robust. Correlations between indices of cognitive impairment and total lesion area (62) or more localized brain abnormalities, such as atrophy of the corpus callosum (63) and frontal lobe lesion score (64), have been noted. However, it is likely that diffuse white matter disease rather than focal damage is the most important factor responsible for cognitive dysfunction in MS. This pathology may not be visible on conventional spin-echo MRI sequencing; more specialized imaging techniques, such as magnetization transfer ratios, may be needed to demonstrate the association (65).

Longitudinal Course of Cognitive Change

There is evidence that cognitive problems may exist when the first symptoms of demyelination manifest (66). However, further progression of deficits is not invariable and will be determined by the extent to which brain pathology increases (67). Thus, a deterioration in the brain MRI becomes the best indicator of further cognitive decline. Should the MRI picture improve, evidence from a case report suggests that cognitive difficulties may lessen (68).

Treatment of Cognitive Dysfunction

As with disorders of mood and affect, few data exist related to treating cognitive problems in MS. Rehabilitation strategies have conventionally been divided into compensatory and remedial categories, with efforts in MS patients focused on the former. Thus, applying structure and organization to the lives of patients mitigates in part the deleterious effects of poor memory (69). There have been few remedial efforts that attempt to reverse deficits in poor attention and memory (70), and it is not clear whether the considerable resources required translate into significant therapeutic gain.

More recent evidence suggests that pharmacologic approaches may offer cognitive benefits. The first approach focuses on the use of cholinesterase-inhibitor therapy. An open-label, 12-week trial of donepezil hydrochloride was undertaken in 17 MS patients whose MMSE scores were less than 25. Dosage began at 5 mg daily for the first 4 weeks, followed by 10 mg daily for a further 8 weeks (71). Patients were assessed with a battery of cognitive tests at baseline, at 4 weeks, and at 12 weeks. Significant improvements in attention, memory, and executive function were reported. While promising, this result awaits replication in a larger sample. The second treatment strategy investigates the effects of disease-modifying agents on cognition. The strongest evidence that treatment may have cognitive benefits comes from a 2-year longitudinal study of interferon beta-1a (72). Significant improvements in information processing and learning or memory were noted, with a trend toward improved visuospatial and problem-solving abilities. However, similar improvements in cognitive status have not been noted with glatiramer acetate (73); a more modest effect, limited to improved delayed visual reproduction with interferon beta-1b, has been reported (74).

The Importance of a Cognitive Assessment

There is evidence that even if cognitive deficits are more subtle than those in Alzheimer's disease, their impact on MS patients may still be considerable, adversely affecting work, relationships, and activities of daily living (75). Detection and management therefore assume added importance.

Summary

Behavioural difficulties are integral to MS. Ranging from diverse disorders of mood and affect to a particular profile of cognitive impairment, they can profoundly effect patients' lives, adding to both the morbidity and the mortality associated with this disease. Over the past few years, much has been learned about these difficulties, although a better appreciation of prevalence and etiology have yet to translate into empirically derived treatment algorithms. Future research will largely be driven by technology, just as the recent history of this field has been dominated by MRI techniques that first appeared in the mid-1980s. That technology will inevitably outstrip clinical research should, however, stimulate rather than deter psychiatrists and neurologists from gaining a better understanding of behavioural treatments extending beyond mere anecdote and the occasional open-label pilot trial. The absence of concerted translational research in the neuropsychiatry of MS is mirrored in most other neuropsychiatric disorders and presents a pressing challenge.

Acknowledgement

Dr Feinstein is supported by Grants 15001 and 36535 from the Canadian Institute of Health Research.

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Manuscript received and accepted December 2003.
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Résumé : La neuropsychiatrie de la sclérose en plaques

Cette étude décrit les nombreuses anomalies neuropsychiatriques associées à la sclérose en plaques (SEP). Celles-ci peuvent se diviser en deux grandes catégories : les troubles de l'humeur, de l'affect et du comportement, et les anomalies affectant la cognition. En ce qui concerne la première catégorie, l'épidémiologie, la phénoménologie et les théories de l'étiologie sont décrites pour les syndromes de la dépression, du trouble bipolaire, de l'euphorie, des rires et des pleurs pathologiques, et de la psychose attribuable à la SEP. La partie consacrée à la cognition examine la prévalence et la nature de la dysfonction cognitive, et met l'accent sur les anomalies qui affectent les domaines multiples de la mémoire, de la vitesse du traitement de l'information et de la fonction exécutive. La détection, les antécédents naturels et les corrélations cérébrales sont aussi étudiés. Enfin, le traitement approprié à tous ces troubles est examiné, et l'on observe que la recherche traductionnelle fait défaut lorsqu'il s'agit de fournir des algorithmes pour guider les cliniciens. Les lignes directrices issues de la psychiatrie générale s'appliquent encore en grande partie, bien qu'elles ne soient peut-être pas toujours les plus efficaces pour les patients ayant des troubles neurologiques. L'importance de la future recherche qui s'attaquera à ce déséquilibre est soulignée, parce que les séquelles neuropsychiatriques ajoutent considérablement à la morbidité associée à la SEP.