Validation of an Internet-based Approach to Cognitive Screening in Multiple Sclerosis

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
Institute of Medical Science
University of Toronto

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2011

Abstract

Cognitive impairment affects approximately half of multiple sclerosis (MS) patients. The Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) has previously demonstrated validity for detecting cognitive impairment in MS, and is quick and easy to complete. The objective was to validate an internet version of the MSNQ. The following were completed at home over the internet for 82 MS patients: (a) patient self-report version of the MSNQ (P-MSNQ), (b) informant version of the MSNQ (I-MSNQ), and (c) Centre for Epidemiological Studies Depression Scale (CES-D). Thereafter, patients completed in-office neuropsychological testing using the Brief Repeatable Battery of Neuropsychological Tests (BRB-N). Both the P-MSNQ and I-MSNQ were highly correlated with depression. The best-cut off score on the I-MSNQ was a 26, which gave a sensitivity of 72% and 60% for detecting cognitive impairment on the BRB-N. Given the modest sensitivity and specificity values, the MSNQ is not recommended for neuropsychological screening purposes over the internet.
Acknowledgments

First, I would like to thank my supervisor Dr. Anthony Feinstein for all of his support and help guiding me along the way. You have been a truly inspirational mentor and have fuelled my interest to pursue knowledge in multiple sclerosis. Thanks for the faith you’ve always had in me and all of the opportunities you have provided me with. Second, my thesis committee, Dr. Brian Levine and Dr. Neil Rector, for all of their valuable contributions and investment into this project.

I would like to acknowledge the funding sources for this study: the Multiple Sclerosis Society of Canada and the Canadian Institutes of Health Research for studentship funding, and EMD Serono Canada.

To the patients and their families, thank you for your commitment to our research. I would also like to thank Nancy Kou and Kimia Honarmand for their time spent helping me collect and analyze data.

To my mom, dad, and brother, I love you and am forever grateful for your undying love and support.
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List of Abbreviations

7/24 - 7/24 Spatial Recall Test
10/36 – 10/36 Spatial Recall Test
ANART – American National Adult Reading Test
AUC – area under the curve
BRB-N – Brief Repeatable Battery of Neuropsychological Tests
CCST- California Card Sorting Task
CES-D – Centre for Epidemiological Studies Depression Scale
CFQ – Cognitive Failures Questionnaire
CIS – clinically isolated syndrome
COWAT- Controlled Oral Word Association Test
CVLT – California Verbal Learning test
CSI – Cognitive Stability Index
DKEFS – Delis-Kaplan Executive Function System
DSM – Diagnostic and Statistical Manual of Mental Disorders
EDSS – Expanded Disability Status Scale
fMRI – functional magnetic resonance imaging
FSBeS- Frontal Systems Behaviour Scale
ICC – intraclass correlation coefficient
I-MSNQ – Informant version of the Multiple Sclerosis Neuropsychological Questionnaire
MACFIMS – Minimal Assessment of Cognitive Function in Multiple Sclerosis
MMSE- Mini-Mental State Examination
MRI – magnetic resonance imaging
MS – multiple sclerosis
MSNQ – Multiple Sclerosis Neuropsychological Questionnaire
NABT- normal appearing brain tissue
NPV- negative predictive value
NSBMS – Neuropsychological Screening Battery for Multiple Sclerosis
PASAT – Paced Auditory Serial Addition Test
PDQ – Perceived Deficits Questionnaire
P-MSNQ – Patient version of the Multiple Sclerosis Neuropsychological Questionnaire
PPMS – primary progressive multiple sclerosis
PPV- positive predictive value
ROC – receiver operating characteristic
RRMS – relapsing-remitting multiple sclerosis
SDMT – Symbol Digit Modalities Test
SPMS – secondary progressive multiple sclerosis
SRT – Selective Reminding Test
SRT-CLTR – Selective Reminding Test Consistent Long Term Retrieval
SRT-LTS – Selective Reminding Test Long Term Storage
WCST – Wisconsin Card Sorting Task
SECTION 1: Introduction and Overview

Prior to reviewing the literature in detail, a brief overview of the study and the background section will be provided. The objective of this study was to develop a quick and easy way of screening for cognitive deficits in multiple sclerosis (MS) using the internet. In particular, this study aimed to validate an internet version of the already widely used and cited Multiple Sclerosis Neuropsychological Questionnaire (MSNQ). The rationale was the difficulty patients have in accessing a cognitive assessment, the internet version of which could help circumvent some of the factors limiting access. This thesis will begin with an overview of MS in general, in particular how it is diagnosed, putative causative factors, disease characteristics (i.e. the disease subtypes, symptoms), prognosis, and treatment. Cognition in MS will then be described. First, the cognitive difficulties patients typically experience, organized according to cognitive domain (e.g. memory, attention, processing speed). Related to this is the prevalence of these deficits, their association with disease-related factors (e.g. duration of MS, physical disability), whether or not these deficits progressively worsen with time, and what impact they have on such aspects as quality of life and functional ability. The relation between brain imaging and cognition in MS will then be described, followed by a discussion of the treatment of these cognitive deficits via the use of medication or cognitive rehabilitation.

The next section will focus on how cognition is measured in MS. First, a discussion of the potential factors influencing cognitive performance including confounding factors such as depressed mood, fatigue, visual and motor disturbances. This will be followed by a description of cognitive assessment techniques beginning with very brief instruments to more detailed neuropsychological test batteries. The focus will then shift to self-report measures of cognition and how these are poor indicators of actual cognitive performance, influenced by mood and poor insight, but faring somewhat better when measuring executive function specifically and as an index of cognitive change. The MSNQ was the chosen measure for this study so previous literature validating its use will be described.

The final section of the literature review will focus on the rationale for conducting this study. This will relate specifically to the reasons patients have difficulty accessing a cognitive assessment, and why the detection of these deficits, especially early on, is important. The
background section will finish with a description of how internet tests have been used in the previous literature to screen for different type of psychological disorders.

SECTION 2: Background

2.1) Overview of Multiple Sclerosis

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (brain, optic nerves and spinal cord). It is the most common cause of neurological disability in young and middle adulthood and is associated with reduced quality of life (Grima et al., 2000), while not necessarily shortening lifespan (Hirst et al., 2008). Approximately 1 million persons worldwide are affected by MS. Canada has one of the highest prevalences of MS in the world at 240 per 100000, translating into approximately 75000 affected (Beck et al., 2005). The etiology of MS is complex with genetic (Dyment, Ebers & Sadovnick, 2004) and environmental factors such as viral infection (Sospedra & Martin, 2005) and vitamin D (Ashcerio, Munger & Simon 2010) playing a role. The most common age of onset is between 20-40 years of age with the peak at 30 years. The female: male ratio for MS is 3:1, a figure which is rising possibly due to environmental factors such as dietary habits, outdoor activity, or changes in timing of childbearing years (Orton et al., 2006).

a) Diagnosis of MS

The diagnostic criteria for MS have changed over the last 30 years due to the integration of magnetic resonance imaging (MRI). Patients are now being diagnosed earlier, based on the presence of lesions on MRI rather than only overt neurological symptoms. The diagnosis of MS is based on the presence of two or more neurological attacks suggestive of demyelination (dissemination in time), and objective clinical evidence of two or more lesions evident on MRI (dissemination in space) (McDonald et al., 2001). Analysis of cerebrospinal fluid can also aid in diagnosis as it provides information about inflammation and immunological disturbance. In addition, visual evoked potentials can be used, especially when MRI criteria are not fulfilled.

b) Pathogenesis of MS
MS begins with an inflammatory event marked by the infiltration of immune cells into brain and spinal cord due to disruption of the blood-brain barrier (Kutzelnigg et al., 2005). These immune cells then go on to attack myelin. This destruction of myelin/demyelination leads to the formation of white matter lesions/plaques visible on MRI. Relapses are characterized by this inflammatory process leading to demyelination. During remission, there is a resolution of these inflammatory processes and subsequent remyelination.

In addition to the destructive immunological processes, axonal damage can occur either secondary to white matter damage, or as the primary event. It is likely that both happen in parallel (Trapp et al., 1998). The level of axonal loss is a primary determinant of permanent neurological disability in MS.

c) Disease subtypes

Before describing the subtypes of MS, it is important to define relapse, remission, and progression. A relapse (exacerbation or attack) is a period of one or more new neurological symptoms in which the causative lesions are likely to be inflammatory and demyelinating in nature. The subjective neurological symptoms and/or lesions must last at least 24 hours (McDonald et al., 2001). Relapses are associated with inflammatory processes in that they are acute, and involvement is multifocal and disseminated within the CNS. Progression is a steady worsening of symptoms and signs over a period of one year or longer. It is associated with degeneration, increasing axonal loss and disability.

There are three common forms of MS. These subtypes are relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS). Relapsing-remitting MS is characterized by periods of relapse and symptom exacerbations lasting up to 30 days with subsequent remission and little or no residual symptoms. The disease subtype affects approximately 80% of patients at initial diagnosis (Noseworthy et al., 2000). Fifty percent of patients with RRMS go on to develop SPMS characterized by disease progression interspersed with relapses, although there may be occasional minor remissions and plateaus. The median time for conversion from RRMS to SPMS is 19 years (Tremlett & Devonshire, 2006). The final subtype is PPMS, present in 15% of initial cases (Miller & Leary, 2007). This subtype is more prominent in males and patients who are older when they experience their first symptoms. In PPMS there is continuing disease progression from onset with occasional plateaus or temporary
minor improvements. A less common subtype (5% of cases) is progressive-relapsing MS where patients experience clear acute relapses but with periods in between characterized by continuing disease progression (Lublin & Reingold, 1996).

A clinically isolated syndrome (CIS) is defined as the first neurological episode suggestive of MS which has an acute or subacute onset followed by recovery. It most commonly presents as optic neuritis, brainstem or spinal cord syndromes. Thirty to seventy percent of CIS patients go on to develop clinically definite MS, more so those with brain lesions evident on MRI (Miller et al., 2005). There is also a benign form of the disease (benign MS) in which patients remain fully functional in all neurological symptoms 15 years after diagnosis of MS. The prevalence of benign MS is estimated to be 10-20% (Amato et al., 2006). MS also, however, has the potential to develop sub-clinically such that there are structural abnormalities on MRI suggestive of demyelination but no overt clinical symptoms (Gilbert & Sadler, 1983).

d) Symptoms

The common symptoms at disease onset are numbness/tingling (45%), weakness (20%), double vision and dizziness (13%), difficulty with co-ordination (13%), and optic neuritis (17%) (Marrie, 2007). During the course of the disease the following symptoms may be found: (a) Vision problems such as loss of vision, diplopia (double vision), and nystagmus (involuntary eye movements), (b) motor problems such as weakness, spasticity, ataxia, and tremors, (c) sensory problems such as numbness/tingling and pain (d) vestibular disturbances such as vertigo and imbalance. Other symptoms include cognitive difficulties, mood disorder (depression, anxiety, emotional lability), bladder and bowel disturbance, sexual disturbances, and fatigue.

e) The Expanded Disability Status Scale (EDSS)

The level of physical disability is used to assess disease progression and is commonly measured using the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). The EDSS is administered by a neurologist and scores range from 0 (normal) to 10 (death due to MS). It is graded according to the following eight functional systems: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral/cognitive, and other. An EDSS score of 4 indicates a moderately disabled patient who experiences limitation of ambulation, and is able to walk without aid or rest some 500 metres. An EDSS score of 6 indicates that assistance is required to
walk (i.e. cane, crutch, or brace) and a score of 7 represents confinement to a wheelchair. The EDSS is criticized for being weighted heavily towards pyramidal signs (ability to walk) and for not assessing cognition/ cerebral function well. It is used as a primary outcome measure in many MS clinical trials.

f) Prognosis

Predicting the future neurologically can be a challenge. The median time for progressing to an EDSS score of 6 (assistance required for walking) is 15 years from symptom onset irrespective of disease course (Weinshenker et al. 1991). The following factors have been significantly associated with poorer outcome: older age at onset, male sex, involvement of the cerebellum (e.g. balance disturbances), and insidious onset of a motor deficit as first symptom. The median time from disease onset to death is 30 years, i.e. life expectancy is only marginally affected by the disease (Hirst et al., 2008). The burden of MS thus is placed on the lifelong disability that accrues from the disease.

g) Treatment of MS

Treatment of MS takes several forms including controlling relapses when they occur, disease-modifying treatments to prevent further relapses, and chronic symptom management (e.g. for pain, fatigue, emotional disorder, cognitive dysfunction). Typically, corticosteroids such as methylprednisolone are used to treat acute relapses (Milligan, Newcombe & Compston, 1987). Disease-modifying agents work by suppressing the immune response and include the interferon-betas 1a (Avonex, Rebif) and 1b (Betaseron), glatiramer acetate (Copaxone), and natalizumab (Tysabri). All have been shown to reduce relapse rate, reduce the number of lesions on MRI, and slow disability progression (Jacobs et al., 1996, Panitch et al., 2002, Johnson et al., 2005, Polman et al., 2006). The effects of these disease-modifying agents on cognitive function will be discussed in section 2.8.

2.2) Cognitive impairment in MS

Cognitive impairment is recognized as one of the common sequelae in MS. The hallmark cognitive deficits in MS are in information processing speed, memory, attention, and executive function. Aphasia, apraxia, and visual agnosias, which are commonly seen in a dementia such as
Alzheimer’s disease, are rarely seen in MS. Approximately 22% of MS patients, however, will meet Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for dementia secondary to a medical condition (Benedict & Bobholz, 2006). This section will describe the common cognitive deficits in MS.

a) Memory

Prior to describing the memory deficits in MS, a description of the various memory systems is warranted. A primary distinction is between implicit (procedural or automatic) and explicit (declarative) memory. Explicit memory involves conscious effortful control whereas the former does not. Within explicit memory there is the division between short term or working memory, and long-term memory. Long-term memory can be further classified into episodic, which is memory for events and includes autobiographical memory, and semantic memory which encompasses prior knowledge and facts not linked to a particular time or place.

i) Implicit memory

Implicit memory is almost always intact in MS. This is typified by tasks of automatic memory (stimulus modality and frequency) (Grafman et al., 1991), priming and perceptual motor skill learning (Beatty, Goodkin, Monson, et al. 1989).

ii) Declarative (explicit) memory

Short-term/Working Memory

Short-term memory is a limited capacity, temporary memory store most commonly measured using the digit-span test in which subjects have to immediately repeat back a series of digits in the correct order that they were presented, with the number of digits to be remembered increasing sequentially per trial. MS patients generally do not demonstrate impairment on this task (Heaton et al., 1985; Rao, Leo, Bernardin et al., 1991). Short-term memory can be considered as operating as a complex system called working memory (Baddeley, 2010). According to the model of Baddeley (2010) working memory consists of the phonological loop for the temporary storage of verbal information, the visuospatial sketchpad for graphic information, and an episodic buffer. The episodic buffer acts as a passive store of multidimensional episodes or chunks combining visual, auditory as well as possibly smell and
taste information. It acts as a buffer where information from the other two systems can interact and as an interface with episodic long-term memory. These are all considered “slave” systems to the last component of working memory which is the executive component that manipulates the information held in the previously mentioned stores. Working memory is involved in complex cognitive processes such as language, comprehension, learning and reasoning. It facilitates the passage of information into long-term memory and is especially important when novel tasks are performed. For example, in the Paced Auditory Serial Addition Test (PASAT), numbers from one to ten are presented at a rate of once every three seconds (easy condition), or every two seconds (hard condition), with subjects asked to add each new number to the one immediately preceding it. It thus requires the rapid manipulation of information and is a classic test of working memory while straddling other cognitive domains such as information processing speed, and sustained, divided attention as well. It is one of the most often impaired tasks in MS patients (Rao, Leo, Bernardin et al., 1991) and used in common psychometric batteries such as the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) and the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) (described in section 2.10).

**Long-term memory**

Long-term memory tasks require more than a brief limited capacity (i.e. working memory). Both verbal (list learning) and visual long-term memory are impaired in MS (Rao, Leo, Bernardin et al., 1991; Beatty et al., 1989). A few studies have employed a selective reminding procedure whereby both MS and healthy controls were equated on initial acquisition of information. This is done by having subjects repeat verbal and or visual material until they approach or reach 100% accuracy in reproducing it across two subsequent trials. Though requiring more trials to reach this criterion, given adequate learning of the information, MS patients demonstrate the same level of recall and recognition as healthy controls, suggesting that the primary deficit in MS is in the acquisition of information (DeLuca, Barbieri-Berger, & Johnson, 1994; DeLuca, Gaudino, Diamond et al., 1998; Demaree, Gaudino, DeLuca, et al., 2000). In a separate study, Chiaravolloti and colleagues (2003) showed that patients who required more learning trials to reach the perfect learning criteria performed significantly worse on recall measures. That is, they do not benefit from repetition in isolation but may require more intensive memory strategies such as increased organization in cognitive rehabilitation interventions. Both difficulty processing rapidly presented information (i.e. impaired information processing speed) as well as deficient
working memory contribute to the long-term memory deficits in MS (Archibald & Fisk, 2000; DeLuca, Barbieri-Berger, & Johnson, 1994).

MS patients generally perform better on measures of recognition and cued recall versus free recall, i.e. those requiring less effort. In addition, patients are less likely to use novel strategies such as semantic encoding (Arnett et al., 1997) or visual imagery techniques (Canellopoulou & Richardson, 1998), which can also be attributed to poor executive functioning. MS patients also demonstrate impaired prospective memory or failure to remember to do something at a specific time in the future (Bravin et al., 2000). In this study, patients were able to remember when to perform a specific task, but more often failed to remember what is was they were supposed to do (i.e. the content of the memory), suggesting that inadequate initial learning of the information is the reason for these prospective memory deficits.

**Autobiographical Memory**

Using an autobiographical memory interview, MS patients were significantly impaired on the recall of semantic memories (generic memories, e.g. “which high school did you attend?”) from all time periods (childhood, early adulthood, recent adulthood), but not on the recall of specific autobiographical events occurring at a particular time and place (Paul et al., 1997). In a later study of patients with very advanced disease (mean EDSS of 8.5), deficits in the memory of specific autobiographic events were evident (Kenealy et al., 2002). Furthermore this followed a temporal gradient with more recent events being affected, typical of some dementing conditions. Thus, autobiographical memory appears affected in MS, especially in patients with more advanced disease.

**Semantic memory**

Semantic memory has been reported as intact in MS (Rao, Leo, Bernardin et al., 1991; Klonoff et al., 1991). Some studies, however, have noted abnormalities for example on memory for famous faces and events (Paul et al., 1997; Beatty et al., 1988, Beatty et al., 1989) perhaps suggesting deficient retrieval mechanisms.

**b) Information processing speed**
The demyelination that is inherent to MS can have several consequences that influence processing speed. First, although partially demyelinated axons may be able to transmit single or low frequency signals, this is not the case with high frequency signals (McDonald & Sears, 1970). In addition, when there are two successive electrical impulses the second one is unable to transverse the axon due an increased refractory period of transmission. This refractory period changes from approximately 1ms in myelinated to 4ms in demyelinated axons (Achiron et al., 2007). Cognitive tests involving speeded responses require information transfer between separate brain regions. Therefore, damage to interconnecting white matter tracts can help explain the information processing deficits characteristic of this disease.

The most commonly used tests of information processing speed in MS are the PASAT and the Symbol Digit Modalities Test (SDMT), where patients demonstrate marked impairment. The PASAT has faced many criticisms. Firstly, performance is not self-paced but rather stimuli are presented at a quick fixed rate, inducing anxiety in many patients. Second, it easily lends itself to strategies created by the patient in order to make the task more manageable, albeit against the instructions (Fisk & Archibald, 2001). For example, patients sometimes adopt a chunking strategy where they skip items intermittently (e.g. add a pair of numbers, skip the next number, and then add the next numbers) so that they don’t have to perform two tasks at once. Third, the PASAT is associated with significant practice effects (Bever et al., 1995). Finally, the PASAT is also a task of working memory, requires more executive functions, and is heavily reliant on intact mathematical ability. This is problematic because tests of information processing speed should measure the speed of execution of few elementary cognitive operations, not complex cognitive abilities and strategies (Forn et al., 2009). These tasks should also not be simple enough such that they only measure the speed of pure sensorimotor operations (Rypma et al., 2006). The SDMT meets these criteria and is increasingly being preferred as the test of choice in MS. In this task, a key of nine different symbols matched to nine numbers is given at the top of the page. Below there are a series of symbols and subjects are asked to say the number that goes with the symbol as quickly as they can within 90 seconds. The SDMT has been suggested as the most sensitive measure of cognitive dysfunction in MS (Parmenter et al., 2007; Strober et al., 2009), and has been shown to correlate with brain imaging indices such as brain lesion volume (Stankiewicz et al., 2009; Lazeron et al., 2005), cerebral atrophy (Christodoulou et al., 2003), diffusion tensor imaging indices of normal appearing brain tissue (Warlop et al., 2009), and
retinal nerve fiber layer thickness (Toledo et al., 2008). It is also quick and easy to administer, and does not induce the same amount of anxiety and fatigue as the PASAT.

There is a slowing in all stages of information processing speed in MS (Kujala et al. 1994), namely automatic (not requiring conscious effort) and controlled processing of stimuli requiring attention and working memory. The deficits in information processing speed in MS are well detected using computerized methods of assessment (e.g. Wilken et al., 2003; Achiron et al., 2007; Lazeron et al., 2006; Younes et al., 2007). Patients consistently demonstrate significantly slower response times, furthermore greater decrements are observed as processing demands/task complexity increases. Studies suggest, however, that given enough time to complete a task, MS patients can perform just as well as controls (Demaree et al., 1999).

c) Attention

MS patients often demonstrate deficits in focused/selective and divided attention. Focused attention is defined as mental processes focused to one source or kind of information to the exclusion of others (Zomeren & Brouwer, 1994) and is typified by tasks in which irrelevant stimuli (“distracters”) must be ignored. One commonly used paradigm for measuring focused attention is the Stroop colour-word test, where MS patients show marked impairment (Kujala et al., 1995). Divided attention is defined as the division or sharing of mental processing capacity between two or more sources of information or two or more mental operations (Zomeren & Brouwer, 1994). This is commonly measured using computerized methods where MS patients exhibit greater decrements in performance than controls when moving from single-task to dual-task conditions (McCarthy et al., 2005).

d) Executive function and verbal fluency

Executive functioning refers to a collection of related abilities comprising abstract reasoning, conceptual flexibility, planning and organization of behaviour. MS patients have consistently been demonstrated to perform poorly on the Wisconsin Card Sorting Task (WCST) (Rao, Leo, Bernardin et al., 1991) a classic test of executive function. Comparing performance on the WCST to the California Card Sorting Test (CSST), though patients generated fewer categories than controls on both tasks they only had a greater number of perseverative errors on the WCST and not on the CCST (Beatty & Monson, 1996). This is likely because the scoring procedure of
the WCST makes it difficult to disentangle perseverative errors from the inability to create categories. As such, these authors concluded that difficulty forming concepts rather than perseveration appears to underlie the problem-solving deficits in MS. The CCST has recently been modified to Delis-Kaplan Executive Function System (DKEFS) sorting task and is part of the MACFIMS battery (described in section 2.10).

Poor planning ability has also been demonstrated in MS (Arnett et al., 1997; Foong et al., 1997). Furthermore, executive functioning deficits likely contribute to impairment on other tests of cognitive ability. For example, these deficits have been shown to correlate strongly with the use of semantic encoding to aid in memory recall (Arnett et al., 1997). Verbal fluency tasks have been shown to be sensitive to frontal function, though not wholly subserved by it (Basso et al., 1996). MS patients have difficulty generating responses on this task (Rao, Leo, Bernardin et al., 1991).

e) Language

Aphasia is rarely seen in MS, though a minority of patients demonstrate difficulties with language. Approximately nine percent of patients are impaired on the Boston Naming Task (Rao, Leo, Bernardin et al., 1991). Generally, phonemic cuing facilitates retrieval during this task, suggesting intact semantic knowledge (Lezak, Howieson & Loring, 2004). Verbal fluency, also a measure of executive function, is often disrupted in MS with patients performing worse on phonemic fluency versus semantic fluency.

f) Visuospatial functioning

Approximately a quarter of MS patients demonstrate visuo-perceptual deficits. A study of 49 MS patients found that colour discrimination, perception of the Muller-Lyer illusion, and object recognition were most commonly affected though there was large inter-individual variety (Vleugels et al., 2000). MS patients also demonstrate problems in facial recognition (Beatty et al., 1989; Rao, Leo, Bernardin et al., 1991), and identifying visuospatial location, for example in the Judgement of Line Orientation Task (Rao, Leo, Bernardin et al., 1991), a test which included in the MACFIMS battery (described in section 2.10).

2.3) Prevalence of cognitive deficits in MS
The most commonly cited prevalence estimate of cognitive dysfunction is 43%, based on the work by Rao and colleagues (1991). This study sampled from a community-based population of 100 MS patients with different disease subtypes (39 RRMS) and 100 age, education, and gender-matched controls. All subjects completed a lengthy cognitive battery comprised of 31 tests and assessing a wide range of cognitive abilities. Performance below the 5th percentile of the healthy control group defined impairment on any one test. MS patients failed a significantly higher number of tests (mean=4.6, sd=4.9) than healthy controls (mean =1.1, sd=1.8). Using a cut-off of 4 or more failed tests, 48% of patients were cognitively impaired. By subtracting the false positive rate in healthy controls (5%), these authors arrived at the 43% prevalence rate of cognitive impairment. Patients were most frequently impaired on measures of (with frequency of impairment given in parentheses): verbal memory (22-31%), visual memory (31%), working memory / PASAT (22-25%), verbal fluency (22%), and visuospatial skills (12-19%). Performance on measures of short-term memory (Digit Span), semantic memory (President’s test), and language (Boston Naming Test) was relatively intact.

Subsequent studies adopting similar cut-offs have reported prevalence estimates of cognitive impairment ranging from 34-60% (e.g. Olazaran et al., 2009; Nocentini et al., 2006; Benedict et al., 2006). This prevalence, however, has been shown to vary based on sampling characteristics. Duquin and colleagues (2008) calculated the prevalence of cognitive impairment in three groups of MS patients. Fifty-seven of these MS patients were research volunteers who received financial compensation for participating, 106 were clinic patients referred for routine monitoring of cognition, and 128 were clinically complex cases referred for specific clinical problems such as repeated complaints of impairment, workplace failure, differential diagnosis, or psychiatric comorbidity. The prevalence estimates were as follows: 46% for research volunteers, 59.4% for clinic patients, and 65.6% for clinically complex cases. They also noted that research volunteers were significantly younger, and that more patients in the clinically complex group had progressive MS. They concluded that sampling characteristics and recruitment context are important in determining prevalence estimates of cognitive impairment.

Another important factor is how cognitive impairment is defined. The largest study to date included 550 RRMS patients about to undergo treatment with Rebif (Patti et al., 2009). Using the BRB-N (this consists of the Selective Reminding Test, 10/36 Spatial Recall Test, PASAT, SDMT, and the Controlled Oral Word Association Test (COWAT) and is described in section
2.10 and the Methods section), these authors reported a prevalence of cognitive impairment of 18%, less than half that first described by Rao and colleagues (1991). In this study, the authors adopted a more liberal threshold for defining cognitive impairment. Here, impairment was defined as performances 1 SD below the healthy control group on 3 or more tests of the BRB-N. In a subsequent commentary Benedict (2009) noted that by adopting a more standard definition of cognitive impairment in this sample, namely 1.5 SD below the mean on 2 or more tests of the BRB-N, the prevalence estimate increased to 45%.

2.4) Relation to disease-related variables

The relation between cognitive dysfunction and MS subtype is equivocal, with some studies demonstrating that patients with progressive MS demonstrate greater cognitive deficits than those with RRMS (e.g. Heaton et al., 1985; Huijbreghts et al., 2004; Gaudino et al., 2001), while others have not found this (e.g. Beatty, Goodkin, Hertsgaard, et al. 1990; Rao, Leo, Bernardin et al., 1991). In one particular study comparing performance between the three subtypes of MS, patients with RRMS performed better than those with PPMS and SPMS on the PASAT and SDMT (Huijbregts et al., 2006). The relations between cognition and disease duration (Heaton et al., 1985; Rao, Leo, Bernardin et al., 1991), as well as between cognition and physical disability (Beatty, Goodkin, Hertsgaard, et al. 1990; Patti et al., 2009), are similarly equivocal.

2.5) Progression of cognitive deficits

Cognitive deficits present at baseline tend to progressively worsen with time, though rarely in the span of a few years (Jennekens-Schinkel et al., 1990; Amato et al., 1995). This is in comparison to other dementing disorders where cognitive decline can be more rapid. Kujala and colleagues (1997) monitored the cognitive performance of two clinically and demographically similar MS groups, 20 who were cognitively preserved, and 22 with mild cognitive deterioration, also 34 healthy controls, over a period of 3 years. Cognition generally remained intact in the cognitively preserved group at follow-up. However, 77% of patients with mild deterioration demonstrated further and more severe cognitive deficits at follow-up. In a longer 10-year study of 50 subjects with MS and 70 healthy controls (Amato et al., 2001), the percentage of patients who were impaired increased from 26% to 56%. In addition, patients who were initially mildly impaired were now considered moderately impaired. Previously detected deficits in verbal memory, abstract reasoning, and linguistic processes were still present at follow-up, at which time deficits
in attention/short-term spatial memory also emerged. Thus, with more long-term follow-up (i.e. a
decade) cognitive deterioration becomes increasingly evident.

The effect of aging on cognitive performance does not differ between MS patients and healthy
individuals. Bodling, Denney, and Lynch (2009) tested 245 MS patients and 188 healthy controls
on the Stroop task. All subjects were divided into five age cohorts. MS patients in each age
group were significantly slower than the healthy controls. Both groups also demonstrated a
similar pattern of deteriorating performance with age. There was, however, no group by age
interaction, suggesting that the effect of age on processing speed is similar for MS patients and
healthy individuals.

2.6) Impact of cognitive deficits

Numerous studies have documented the negative impact of cognitive dysfunction on patients
with MS. Perhaps the single biggest cognitive handicap is in vocational status with patients less
likely to be employed, even after controlling for physical disability (Rao, Leo, Bernardin et al.,
1991; Honarmand et al., 2010). Patients with cognitive dysfunction also engage in fewer social
activities and require greater assistance performing activities of daily living (Rao, Leo, Ellington
et al., 1991, Amato et al., 1995). Cognitive impairment adversely affects rehabilitation outcome
(Langdon & Thompson, 1999), adherence to disease-modifying therapies (Bruce et al., 2010),
and the ability to drive a car (Schultheis et al., 2010). Subsequently, patients with cognitive
impairment also report poorer quality of life (Benito-Leon, Morales & Rivera-Navarro, 2002).

2.7) Brain imaging correlates of cognitive dysfunction

a) Structural MRI

i) Lesions and atrophy

Cognitive impairment in MS has been shown to correlate with different indices of brain
pathology as revealed by MRI. Global markers of impaired cognition have been linked to total
hyper- and hypo-intense lesion volume (Rovaris et al., 1998; Lazeron et al., 2005; Sperling et al.,
2001; Rao et al., 1989). This relation pertains particularly to lesions disrupting cortical-cortical
connections (Lezak, Howieson & Loring, 2004). For example, robust relations have been found
between damage to the corpus callosum, comprised of white matter fibers responsible for
interhemispheric transfer, and several related cognitive functions such as processing speed, rapid problem solving, and dichotic listening tasks (Rao et al., 1989; Pelletier et al., 1993). Brain atrophy, however, has emerged as a more powerful predictor of cognitive impairment than lesion volume (Benedict et al., 2004). This is related to the more ominous significance of atrophy. Whereas lesions are due to inflammatory processes and demyelination, atrophy represents mostly axonal loss. In particular third ventricle width, related to atrophy of the thalamus, has been shown to explain significant variance in neuropsychological outcomes, more so than brain parenchymal fraction (Benedict et al., 2004) and neocortical gray matter volume (Benedict et al., 2006) suggesting the importance of central atrophy. Cortical lesions/ demyelination (Roosendaal et al., 2009) and cortical atrophy (Calabrese et al., 2009), however, are increasingly being recognized as a substrate for cognitive deficits in MS.

Decline in cognitive function has been shown to correlate with increasing brain MRI lesion load (Hohol et al., 1997), as well as increasing brain atrophy (Summers et al., 2008).

ii) Normal-appearing brain tissue (NABT)

Looking beyond lesions and atrophy, significant associations have emerged with indices of normal-appearing brain tissue (NABT) such as diffusion tensor and magnetization transfer imaging (Filippi et al., 2000; Rovaris et al., 2002; Dineen et al., 2009; Warlop et al., 2009; Akbar et al, 2010). In particular, the study by Dineen and colleagues (2009) found that reduced structural integrity of the white matter tracts involved in connecting cognitively important processing regions was related to impairment in those functions (e.g. in working memory, visual memory). Normal-appearing brain tissue damage could be related to Wallerian degeneration of axons traversing lesions, retrograde degeneration of neurons secondary to axonal damage, acute edema associated with inflammation, gliosis, or cortical demyelination.

b) Functional MRI

Reasons for the only modest correlation between MRI parameters such as lesions, atrophy and damage to NABT could be due to the neuronal plasticity and functional reorganization present at least in the early stages of the disease. This has been shown in studies utilizing functional MRI (fMRI). The gist of these research findings is that MS patients show not only increased activation of the same areas as healthy subjects while performing a cognitive task, but recruitment of
ancillary regions as well (Bonzano et al., 2009; Penner et al., 2003; Bobholz et al., 2006; Forn et al., 2006; Cader et al., 2006). This pattern of response has been viewed as compensatory, the brain having to work harder – and less efficiently – in managing cognitive demands. How this occurs could be via the use of redundant neural pathways, or axonal sprouting that can compensate for the destruction of axon. In addition, the cholinergic system likely plays a mediating role (Parry et al., 2003, Cader, Palace & Matthews., 2009). This functional plasticity, however, has an upper limit upon which these compensatory mechanisms fail, likely because structural damage is too great.

An interesting finding is that MS patients with greater intellectual reserve (greater predicted premorbid verbal IQ and education) are able to withstand greater brain atrophy before demonstrating the same level of cognitive deterioration as patients with less intellectual reserve (Sumowski et al., 2010). In this study, patients with higher intellectual reserve showed greater cognitive efficiency during the fMRI performance of a working memory task. This was marked by less recruitment of prefrontal regions, and less deactivation of the default mode network, when completing this task.

2.8) Treatment of cognitive deficits

a) Medication

i) disease-modifying treatments

Disease-modifying treatments may be associated with cognitive gains. Pliskin and colleagues (1996) found greater improvements in visual memory in 30 patients treated with interferon beta-1b compared to placebo. In another larger study of 149 patients, interferon beta-1b was associated with greater improvement in the PASAT at three and five year follow-up (Kappos et al., 2009). The results with Interferon beta-1a have similarly been promising. Fisher and colleagues (2000) tested 166 subjects treated with Interferon beta-1a on a detailed cognitive battery probing the following domains: (a) information processing, learning, and memory, (b) visuospatial properties and executive functioning, and (c) verbal abilities and attention span. These authors found improvement in the treated group on the first two domains, but not the third, over a span of two years. They also reported slower worsening on the PASAT in treated patients. Glatiramer acetate has not been shown to improve cognition (Weinstein et al., 2009), though this
deserves a second look because neither the placebo nor treated group demonstrated cognitive deficits at baseline, which does not fit with the typical picture of MS where approximately 43% of patients demonstrate impairment (Rao, Leo, Bernardin et al., 1991).

ii) Cholinergic drugs

Cholinesterase inhibitors have been used to treat memory, especially in Alzheimer’s disease. In an open-trial study of donepezil in 17 MS patients (Greene et al., 2000), improvements were noted in attention, memory, executive functioning, as well as different aspects of behaviour. In a double-blind placebo controlled trial of 69 patients, Krupp and colleagues (2004) found improvements with donepezil on performance of the Selective Reminding Test (SRT), a measure of verbal memory, as well as self-reported memory. These same authors were not able to replicate these findings in a more recent larger study of 120 subjects (Krupp et al., 2010). This study utilized the same design as the previous study and only noted a trend in blinded clinician reported rating of cognitive change. Thus, initial randomized-controlled trials have shown promising results on donepezil but this has failed replication in a larger study. Rivastigmine, another cholinesterase inhibitor, has also not been able to show cognitive benefits in MS (Shaygannejad et al., 2008).

iii) Amantadine

Medications for fatigue, such as amantadine may ameliorate cognition in MS. In 45 patients given either amantadine, pemoline, or placebo, only the amantidine treated group showed improvement on SDMT (Geisler et al., 1996). This is in contrast to a later study that did not report beneficial effects of amantidine compared to placebo in 24 patients (Sailer et al., 2000).

iv) Amphetamines

Amphetamines may provide some promise. In an exploratory dose finding study of 19 patients, Benedict and colleagues (2008) found improvements with l-amphetamine sulfate on SDMT and PASAT performance. In a second larger study of 151 patients l-amphetamine sulfate was not able to confirm improvement on the SDMT, though there was improvement on verbal and visual memory as measured by the California Verbal Learning Test (CVLT) and Brief Visuospatial Memory Test (Morrow et al., 2009).
b) Cognitive Rehabilitation

Cognitive rehabilitation can take the form of remediation/retraining of specific deficits or use of compensatory strategies to maximize the abilities that the patient retains. Evaluating the success of cognitive rehabilitation programs remains a challenge in MS. This is due to test-retest practice effects, heterogeneity of samples (e.g. with respect to disease severity), and use of non-standardized training procedures. Furthermore, changes in fatigue, depression, also the use of medications may induce changes in cognitive performance. In one of the first studies of cognitive rehabilitation in MS, Jonsson and colleagues (1993) randomized 40 patients with mild or moderate cognitive dysfunction to either cognitive treatment, comprised of both remediation and compensation, or to non-specific mental stimulation. The notable finding was that treating cognitive impairment led, in some patients, to less depression, but no benefits on cognition.

Plohmann and colleagues (2008) found that specific computerized retraining of attention deficits (e.g. in selective, divided, or sustained attention) resulted in improvements in those areas specifically trained. Other studies have failed to demonstrate beneficial effects of cognitive rehabilitation. Lincoln and colleagues (2002) reported no change in subjectively reported cognitive impairment, mood, or quality of life after an individualized intervention of attention, memory, and executive function in a large sample of 240 patients. More disappointingly, in the well-designed double-blind randomized control trial of Solari and colleagues (2004), no differences were found between specific computerized retraining of attention and memory deficits and the control condition which has comprised of training of visuo-constructional and visuo-motor coordination.

In the last two years, cognitive rehabilitation studies in MS have painted a more optimistic picture. Vogt and colleagues (2009) implemented computer-based working memory training and noted benefits in working memory and mental speed. Furthermore, these beneficial effects did not vary according to training schedule (high versus low intensity). Shatil and colleagues (2010) found that personalized cognitive training using a home-based computer assisted program, with data sent via the internet, resulted in good adherence as well as improved memory and processing speed. Other recent studies have similarly found benefits of cognitive rehabilitation using intensive cognitive computer-assisted rehabilitation of attention, information processing, and executive functions (Mattioli et al., 2010), an executive function intervention program (Fink
et al., 2010), and computerized retraining of divided attention and executive function deficits (Flavia et al., 2010).

In a related manner, it has been shown that patients who pre-morbidly lead more intellectually enriched lives, for example engaging in more pre-morbid cognitive leisure activity (e.g. reading books, playing cards) are able to withstand greater brain atrophy before showing cognitive impairment (Sumowski, Wylie, Chiaravolotti, et al., 2010; Sumowski, Wylie, Gonnella, et al., 2010), suggesting the utility of cognitive exercise to slow neuropsychological decline. Findings from fMRI studies have shed some light on the possible mechanisms by which cognitive rehabilitation can exert its positive effects. Two recent studies have demonstrated that post-training brain activation patterns differ from those pre-treatment (Penner et al., 2006; Fillipi et al., 2010). More specifically, there is additional recruitment of areas involved in the cognitive domains specifically trained (e.g. complex attention). Thus, functional plasticity can be enhanced by neuropsychological intervention. In addition, the amount of brain atrophy has been shown to correlate with treatment efficacy. Hildebrandt and colleagues (2007) compared cognitive training treatment outcomes between patients with high and low brain atrophy. They found that only patients with low brain atrophy showed improvements on the PASAT, though both groups improved on the CVLT. Fink and colleagues (2010) showed that baseline brain volume was correlated with improvement on a test of response shifting after an executive function intervention program. Thus, in patients with pronounced brain atrophy, cognitive rehabilitation may not be as effective as structural damage may be too great to allow for functional reorganization.

2.9) Potential confounds of cognitive performance

a) Depression

When assessing cognition in MS, neuropsychological test performance may be influenced by confounds such as mood, fatigue, and motor/sensory deficits. Depression has been shown to exacerbate cognitive difficulties, especially with regards to the central executive component of working memory (Feinstein, 2006). Arnett et al. (1999a) compared performance between three groups of subjects, namely MS patients with depression, MS patients without depression, and healthy controls, on a series of cognitive capacity demanding and non-demanding tasks. Patients with depression performed more poorly than both groups on the capacity-demanding tasks,
suggesting that depression reduces the amount of attentional resources to complete cognitively intensive tasks. In a follow-up report by the same authors (Arnett et al., 1999b), MS patients with depression performed more poorly on a task of working memory capacity, but not on a short-term memory task that did not involve working memory, compared to MS patients without depression and healthy controls. A third study (Demaree, Gaudino & Deluca, 2003) compared cognitive performance between patients with severe depression, those with mild depression, and healthy controls. These authors found that severely depressed patients were more impaired on a test of verbal memory (SRT) and working memory (PASAT). In summary, depression exerts negative effects on cognitive ability primarily through its deleterious effects on working memory.

b) Fatigue

The relationship between fatigue and effect on cognitive performance has not been clearly established. Subjective fatigue is commonly reported in patients but this does not necessarily coincide with a decline in cognitive performance. For example, neuropsychological test performance did not change after completing a workday, although subjective reports of cognitive fatigue did (Beatty et al., 2003). A different result was supported by Krupp and colleagues (2000). Here 45 MS patients and 14 healthy controls were given a 4 hour neuropsychological test battery, followed by a continuous effortful cognitive task (mental arithmetic problems), and then a repeat neuropsychological test battery. The groups did not differ cognitively at baseline, but whereas controls showed improvement, MS patients showed declines on measures of verbal memory and conceptual planning after performance of the continuous effort task. These results suggest that fatigue does exert negative effects on cognition, and that patients experience this subjectively, but perhaps the level of demands placed by the intervening tasks is the mediating variable for a decline in cognitive performance.

c) Visual/ motor disturbances

Mild visual disturbances have been shown to affect performance on visual-based tests of attention such as the SDMT (Bruce, Bruce & Arnett, 2007). Similarly, oral motor speed has been shown to influence performance on tasks requiring rapid oral responses such as the PASAT, COWAT and SDMT (Arnett et al., 2008). Thus, appropriate screening for these deficits is warranted in cognitive assessment batteries given the effect they can have on test performance.
2.10) Detecting cognitive impairment in MS

a) Mini-Mental State Examination (MMSE)

The Mini-Mental State Examination (MMSE) is a brief screening instrument for global cognitive impairment used primarily in dementia. It is administered and scored in a neurologist’s office in 5 to 10 minutes. Its use in patients with MS has been evaluated and it has been shown to have poor sensitivity. This is not unexpected given the subtlety of cognitive deficits in MS. Beatty and Goodkin (1990) found that only 3 out of the 85 MS patients (4%) scored below the commonly used cut-off of 24. With this cut-off score in mind, the mean MMSE for patients was 28.4 (SD=2.4) suggesting its use would result in an unacceptable number of false negatives. The low sensitivity of the MMSE (20-25%) for MS has been reported in other studies as well (Rao, Leo, Bernardin et al., 1991; Franklin et al., 1988), not warranting its clinical use.

b) Brief Screening Batteries – NSBMS and BRB-N

The Neuropsychological Screening Battery for MS (NSBMS) was developed by selecting the most sensitive measures from a lengthier (seven hour) and more comprehensive neuropsychological battery in the study of Rao and colleagues (1991) (study previously described in section 2.3). The tests of the NSBMS include (with abbreviations and cognitive domain placed in parentheses): the Selective Reminding Test (SRT; verbal memory), 7/24 Spatial Recall Test (7/24; visual memory), Controlled Oral Word Association Test (COWAT, verbal fluency), and Paced Auditory Serial Addition Test (PASAT; working memory, sustained attention). Defining cognitive impairment as performance below the 5th percentile of the normal control group on two or more of these four tests, the NSBMS demonstrated a sensitivity of 71% and specificity of 94% for detecting impairment on the detailed neuropsychological test battery. The NSBMS takes approximately 20-30 minutes to administer.

The NSBMS has been modified to the Brief Repeatable Battery of Neuropsychological Tests (BRB-N). This was done by adding the SDMT as a measure of information processing speed. In addition, the 7/24 has been changed to the more difficult 10/36 Spatial Recall Test given the previous version’s ceiling effects. The BRB-N has become the most widely used neuropsychological battery for MS. It was developed primarily for serial use in clinical trials in order to monitor cognitive changes as there are 15 alternate, equivalent versions. Bever and
colleagues (1995) administered the BRB-N to 19 patients every 2 months for 4 months. They found significant variability for all tests, i.e. that they were all sensitive to cognitive change, though strong practice effects were demonstrated with the PASAT. A criticism of the BRB-N, however, is the lack of adequate normative data available in order to define cognitive impairment.

c) Intermediate cognitive battery - MACFIMS

A more extensive battery, requiring 90 minutes to administer, is the Minimal Assessment of Cognitive Function in MS (MACFIMS; Benedict et al., 2002). It was developed by an expert panel of neuropsychologists and tests were selected according to specific criteria including: (i) standardized stimulus materials and administration, (ii) availability of normative data, (iii) less ceiling and floor effects, (iv) adequate reliability data, (v) able to discriminate between MS patients and healthy controls, (vi) alternate forms to control for practice effects, (vii) easily administered, and (viii) not confounded by sensory and motor function. The MACFIMS assesses cognition in the following domains (with the test names added in parentheses): (a) processing speed/working memory (PASAT, SDMT), (b) learning and memory (California Verbal Learning Test-II, Brief Visuospatial Memory Test-Revised), (c) executive function (D-KEFS Sorting Test), (d) visual perception/spatial processing (Judgement of Line Orientation Test), and (e) Language/Other (COWAT). Cognitive impairment is typically defined as performance 1.5 SD below the healthy control group on two or more of the 11 test measures. In its validation study, all tests of the MACFIMS were able to discriminate between MS patients and healthy controls, also between RRMS and SPMS (Benedict et al., 2006). In addition, most tests, especially those of verbal memory and executive function, were able to distinguish between employed and unemployed patients.

d) Self-reports of cognition

The use of subjective reports of cognitive difficulties has also been evaluated in MS. The accuracy of these measures has generally been found to be poor, being heavily influenced by behavioural variables such as depression, disinhibition, and poor insight. Metacognition, or ability to assess one’s own cognitive ability, will be described in MS first according to the influence of mood, poor insight, and fatigue.
i) Influence of behavioural variables

*Mood*

Depression creates a negative and pessimistic view of oneself, leading to an exaggeration of cognitive problems. Bruce and Arnett (2004) found that patients in the “moderately” depressed range gave the most accurate self-appraisals of cognition. In contrast, patients with mild depression overestimated their memory difficulties, whereas patients with more severe depression underestimated these problems. The authors explain this by stating that once depression becomes moderate, the attention and memory deficits become more severe and “catch up” to previously engrained negative appraisals. Lovera and colleagues (2006) compared the Perceived Deficits Questionnaire (PDQ) to performance on the PASAT, CVLT and mood measured using the Beck Depression Inventory-Amended. The PDQ is part of the Multiple Sclerosis Quality of Life Inventory consisting of 20-items listing perceived cognitive problems (e.g. I lose my train of thought when I am speaking) that are rated according to their frequency. In this study, the authors only found significant correlations between the PDQ and mood, i.e. none of the cognitive measures. In patients who scored 0.5 SD or more below the mean on either the PASAT or CVLT, a more extensive neuropsychological battery was administered and here also no correlations between the PDQ and cognition were demonstrated.

Work by Bruce and colleagues (2010) has demonstrated a close relationship between subjective appraisals of memory and many different indices of psychopathology including depression, anxiety, neuroticism, and normative dissociation which is a disruption of an individual’s usually integrated cognitive processes such as consciousness, and identity. Their data reveal that MS patients misattribute aspects of their psychological distress to memory deficits. In summary, the literature has been consistent in reporting the influence of mood, in particular depression, on self-reports of cognition in MS.

*Poor Insight*

The reduced awareness in patients with greater executive dysfunction and more severe disease (e.g. greater physical disability) has been noted as an influence of subjective reports of cognition. Metamemory, or the ability to assess one’s own memory, was evaluated in the study by Beatty and Monson (1991). These authors found that more severely disabled MS patients did not report
significantly greater difficulty in remembering events that occur in everyday life compared to healthy controls. This was despite performing significantly worse on objective memory measures. This result highlighted the patients’ poor insight into their memory deficits and their tendency to overestimate their memory abilities. Marrie and colleagues (2005) reported that subjective cognitive complaints do correspond to objective cognitive impairment but that this relationship is non-linear. In this study, patients with mild cognitive impairment reported greater cognitive complaints than patients who were unimpaired or patients with severe impairment. The patients with mild deficits were younger and perhaps hypersensitive to their deficits whereas the older, more impaired patients didn’t view themselves as having any deficits at all, once again attributed to reduced awareness and insight.

Fatigue

Mental fatigue has also been shown to influence subjective reports of cognition. Bol and colleagues (2010) studied the effect of physical and mental fatigue on cognitive complaints and on actual cognitive performance. They measured cognitive complaints using the cognitive failures questionnaire (CFQ). It consists of 25 items of daily cognitive mistakes, with higher scores indicating more cognitive complaints. These authors found that anxiety and depression, measured by the Hospital Anxiety and Depression Scale, and mental but not physical fatigue, were able to explain 9% and 39% of the variance in CFQ scores respectively. Fatigue only influenced patient’s subjective cognitive reports and not their actual neuropsychological test performance. These authors concluded that fatigue, depression, and anxiety contribute to patient’s self-reports of cognition, but the large overlap between symptoms of mental fatigue and cognitive dysfunction affect the interpretation of these results.

ii) Self-reports of executive function

Results relating self-reported cognition to executive functioning specifically (i.e. not just memory) have provided slightly more support for the validity of self-report measures. Basso and colleagues (2008) measured subjective complaints of impairment using the Frontal Systems Behaviour Scale (FSBeS), which provides patient-reported indices of apathy, disinhibition, and executive functioning. They found that FSBeS ratings emerged as a significant independent predictor of neuropsychological deficit and poor adaptive function. Adaptive function was measured by disability status, ability to manage activities of daily living, and the extent to which
work and home environments have to be modified consequent to symptoms of MS. Smith and Arnett (2010) found that self-reports of executive dysfunction correlated better with objective indices of cognitive performance than informant reports. This could be because the executive deficits may reveal themselves more subtly than signs of memory impairment and thus are not as readily observed by informants. They also found that self-report accuracy varied with education, with more educated patients being more accurate in their accounts.

iii) Self-report measures as an index of cognitive change

It could be that self-report measures are better suited for monitoring cognitive changes rather than overall performance level. Christodoulou and colleagues (2005) found that self-report and neuropsychological measures did not correlate with each other either at baseline or after treatment with donepezil. They did, however, find that change in overall neuropsychological performance was associated with change in self-reported cognition. This suggests that patients are more attuned to changes in their cognitive performance rather than their overall level of cognitive functioning. In part this may be mediated by changes in other behavioural variables. Kinsinger, Lattie, and Mohr (2010) found that patients whose fatigue and depression improved after behavioural therapy reported fewer cognitive complaints post-treatment, although objectively their neuropsychological performance did not alter. Furthermore, improvement in fatigue and depression resulted in greater accuracy in cognitive self-reports at follow-up.

iv) Multiple Sclerosis Neuropsychological Questionnaire (MSNQ)

The Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) is a brief 15-item self-report measure of perceived cognitive difficulties. Two versions of the questionnaire are used, one for the patient (P-MSNQ), and one for an informant (I-MSNQ) who is well acquainted with the patient, to complete. Sample items from the MSNQ are shown in Table 1.

Table 1. Sample items from the informant version of the Multiple Sclerosis Neuropsychological Questionnaire. Each item is rated according to how often these problems occur and how severe they are from 0 (never, does not occur) to 4 (very often, very disruptive).

1. Does he/she get easily distracted?
2. Is he/she slow to solve problems?
3. Does he/she forget appointments?
4. Does he/she have to be reminded to do tasks?
5. Does he/she have difficulty keeping track of two things at once?
6. Does he/she have difficulty controlling his/her impulses?
Validation studies of the MSNQ

Four studies to date have tested the validity of the MSNQ as a screening instrument for cognitive impairment. A summary of the findings from these studies is shown in Table 2. In the original study, 50 MS patients completed a detailed neuropsychological battery (Benedict et al., 2003). The P-MSNQ was found to correlate with depression, but not with cognitive test performance. The opposite result was found with the I-MSNQ, which was found to correlate with cognitive test performance, but not with depression. As a result, only the I-MSNQ was used to generate a cut-off score that would maximally discriminate between patients with and without cognitive impairment. A cut-off score of 27 was able to classify correctly 94% of patients, with a sensitivity and specificity of 0.83 and 0.97 respectfully. These data were collected from mostly RRMS patients with short duration of illness, and normal or mildly impaired cognitive function. In addition, sample size was modest. With these shortcomings in mind, the same authors undertook a second study (Benedict et al., 2004). The MSNQ was given to 85 MS patients and 40 demographically matched normal controls. All subjects underwent detailed neuropsychological testing with the MACFIMS in addition to completing the MSNQ. This time, the P-MSNQ and the I-MSNQ both correlated significantly with cognitive test performance and depression. But whereas the I-MSNQ was correlated more strongly with cognitive test performance, the opposite was true for the P-MSNQ which was more robustly associated with depression. With a cut-off score of 24, the P-MSNQ turned out to be correct 68% of the time. If one removed depressed patients from these data, the percentage correctly classified rose to 74%. Figures for the I-MSNQ were lower than first reported, but still remained impressive, i.e. a decline from 94% to 85% in those correctly classified. This time, the best cut-off on the I-MSNQ was 22, with a sensitivity of 87% and specificity of 84%.

A third study attempted to replicate these findings (O’Brien et al., 2007). This sample was comprised of 48 patients with more severe disease (i.e. greater EDSS, more patients with progressive MS, and more cognitive impairment) but less education than in the previous two reports. The results revealed that the P-MSNQ was correlated with depression and 2 out of 10 cognitive tests. The I-MSNQ did not correlate with depression, but with seven out of ten cognitive tests. Evaluating the ability of the MSNQ to discriminate between patients with and
Table 2. Comparison of sample characteristics and results between previous MSNQ studies and this study

<table>
<thead>
<tr>
<th></th>
<th>Benedict et al., 2003</th>
<th>Benedict et al., 2004</th>
<th>O'Brian et al., 2007</th>
<th>Vanotti et al., 2008</th>
<th>Final Sample, Akbar et al., 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size</td>
<td>50</td>
<td>85</td>
<td>48</td>
<td>125</td>
<td>82</td>
</tr>
<tr>
<td>Age, mean (sd)</td>
<td>42.6(7.2)</td>
<td>42.4 (9.3)</td>
<td>45.1 (8.9)</td>
<td>42.3 (10.5)</td>
<td>44.5(8.9)</td>
</tr>
<tr>
<td>Education(Years), mean (sd)</td>
<td>15.0(2.3)</td>
<td>14.8 (2.3)</td>
<td>14.7 (2.1)</td>
<td>13.7 (3.4)</td>
<td>15(2.2)</td>
</tr>
<tr>
<td>Gender (% Female)</td>
<td>66%</td>
<td>80%</td>
<td>80%</td>
<td>67%</td>
<td>78%</td>
</tr>
<tr>
<td>Disease Type (% RRMS)</td>
<td>80%</td>
<td>80%</td>
<td>70%</td>
<td>86%</td>
<td>68%</td>
</tr>
<tr>
<td>Percent Cognitively Impaired</td>
<td>24%</td>
<td>35%</td>
<td>45%</td>
<td>29%</td>
<td>35%</td>
</tr>
<tr>
<td>P_MSNQ Total Score, mean (sd)</td>
<td>22.5 (10.2)</td>
<td>27.4 (11.9)</td>
<td>23.4 (11.2)</td>
<td>18.1 (11.7)</td>
<td>32.1(10.0)</td>
</tr>
<tr>
<td>I_MSNQ Total Score, mean (sd)</td>
<td>18.4 (11.1)</td>
<td>21.3 (12.9)</td>
<td>19.4 (12.7)</td>
<td>17.2 (12.6)</td>
<td>26.7(11.5)</td>
</tr>
<tr>
<td>Number of years informant has known patient, mean (sd)</td>
<td>25.2(13.4)</td>
<td>23.3(13.1)</td>
<td>22.5 (10.5)</td>
<td>21.1(13.1)</td>
<td>22.7(12.3)</td>
</tr>
<tr>
<td>Significant Correlations with the P-MSNQ</td>
<td>Depression - BDI and CES-D</td>
<td>Depression- CES-D</td>
<td>Depression - BDI</td>
<td>Depression - BDI-FS</td>
<td>Depression - CES-D</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cognition - 5/8 tests</td>
<td>Cognition 2/10 tests</td>
<td>Cognition - 1/5 tests</td>
<td>Cognition - 1/5 tests</td>
<td></td>
</tr>
<tr>
<td>Significant Correlations with the I-MSNQ</td>
<td>Depression- CES-D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cognition - 6/6 tests</td>
<td>Cognition - 8/8 tests</td>
<td>Cognition 7/10 tests</td>
<td>Cognition - 5/5 tests</td>
<td>Cognition - 5/5 tests</td>
</tr>
<tr>
<td>Best I-MSNQ cut-off for cognitive impairment</td>
<td>27</td>
<td>22</td>
<td>10</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>83%</td>
<td>87%</td>
<td>94%</td>
<td>91%</td>
<td>72%</td>
</tr>
<tr>
<td>Specificity</td>
<td>97%</td>
<td>84%</td>
<td>55%</td>
<td>80%</td>
<td>60%</td>
</tr>
</tbody>
</table>

CES-D –for Epidemiological Studies Depression Scale
BDI – Beck Depression Inventory
BDI-FS – Beck Depression Inventory Fast-Screen
without cognitive impairment, the authors were not able to replicate previous findings. The best cut-off score for the I-MSNQ was a 10, significantly lower than the previously reported optimal cut-offs, with a sensitivity and specificity of 94% and 55%, respectively, and with 74% of patients correctly classified. A final study attempted to validate the MSNQ in an Argentinean population of 125 patients by comparing it to performance on the Spanish version of the BRB-N (Vanotti et al., 2009). This sample, like the first two studies, was mostly characterized by patients with RRMS (86%), shorter disease duration, and lower prevalence of cognitive impairment. Here, the P-MSNQ correlated with depression and the SRT. The I-MSNQ was correlated with all five tests of the BRB-N, but not depression. The best cut-off score for cognitive impairment was a 26 on the I-MSNQ, correctly classifying 92% of patients, with a sensitivity and specificity of 91% and 80% respectively.

**Psychometric properties of the MSNQ**

In the study by Benedict and colleagues (2004), thirty-four MS patients completed the MSNQ again a week later and the results revealed good test-retest reliability with correlations of 0.90 and 0.93 for the P-MSNQ and I-MSNQ respectively. Vanotti and colleagues (2008) evaluated the test-retest reliability after one week in a subset of patients (n=23) and found this to be high for both the P-MSNQ (r=.95) and I-MSNQ (r=.94). Inter-rater reliability of the I-MSNQ (2 different informants) was also measured and found to be moderate (ICC=.56). Benedict et al. (2008) evaluated the test-retest reliability of the P-MSNQ, administered at monthly intervals for 6 months. They found it to be high, with correlations ranging from 0.86 to 0.90, replicating previous findings.

The P-MSNQ is now being used as an outcome variable in clinical trials. The largest study to date utilizing the P-MSNQ evaluated its test-retest reliability at 4-week intervals for 48 weeks (Morrow et al., 2010). The sample comprised of 660 patients with MS undergoing treatment with natalizumab. This study took place in 21 countries and utilized 14 different language versions of the scale. Correlations between 4-weekly P-MSNQ scores were high, ranging from 0.82-95, with a correlation of 0.72 between baseline and week 48. Furthermore, these correlations did not differ by region/country, showing that the MSNQ was reliable in different languages/countries. These authors therefore recommended the use of the MSNQ for monitoring change in cognition over time.
Three studies have conducted internal reliability analyses of the MSNQ and have reported high Cronbach’s alpha coefficients (Benedict et al., 2004, 2005; Vanotti et al., 2008). These values have ranged from 0.90 to 0.93 for the P-MSNQ and 0.93 to 0.94 for the I-MSNQ.

**Patient-informant discrepancies in MSNQ scores**

Carone and colleagues (2005) investigated patient/informant discrepancies in MSNQ ratings. Patients were classified as over-estimators or under-estimators based on informant ratings. Over-estimators, or patients rating themselves as more cognitively intact than their informants, were characterized by greater degrees of cognitive impairment, euphoric behavioural disinhibition, unemployment, and lower conscientiousness based on the NEO Five-Factor model of personality. Under-estimators, or patients rating themselves as more cognitively impaired than their informants, were once again characterized by greater and more severe depression. These authors thus suggest that MSNQ discrepancy scores can be used as a marker of frontal-executive dysfunction and/or depressed mood.

**Summary of the MSNQ**

An emerging literature therefore points to the effectiveness of the informant but not the patient MSNQ as a screening instrument for cognitive impairment in MS. The MSNQ demonstrates high test-retest, adequate internal consistency, and adequate inter-rater reliability. The interpretation of MSNQ scores should not only take into account patient depression but poor insight as well, especially in patients with greater cognitive decline (e.g. patients with progressive MS). Overall the informant MSNQ is less influenced by these factors.

**2.11) Obtaining a cognitive assessment**

Many MS patients experience difficulty obtaining a cognitive assessment for a variety of reasons. This is especially discouraging given the negative impact of these deficits and the importance of early detection. These factors will be discussed in the following section.

**a) Limited access to a neurologist**

The role of the neurologist is central to the management of MS. However, between a quarter to a third of MS patients are not able to see a neurologist on a yearly basis (Minden et al., 2008).
These patients are more likely to be poor, live in rural areas, belong to minority groups, have an illness of longer duration (i.e. more than 15 years), have difficulty walking, require wheelchair/scooter, and be confined to a bed. Given that referrals for neuropsychological testing frequently originate from a neurologist, these data indicate a potential source of bias in terms of those patients referred for cognitive testing. The importance of socioeconomic status should also be noted. Out of 92 low-income minorities surveyed, 32% have never been seen by an MS specialist (Shabas & Heffner, 2005) and 25% were never offered disease modifying treatment by their physician. The reasons for MS subjects of lower socioeconomic status to receive disease modifying treatment may reflect many factors such as less education, less access to information, and less knowledge of their disease. These same factors could hinder their ability to seek and receive a cognitive assessment.

b) Paucity of neuropsychologists in Canada

A review identified approximately 230 neuropsychologists in Canada, only a minority of whom are involved in MS research (Hayman-Abello, Hayman-Abello & Rourke, 2003). While the percentage of neuropsychologists who undertake regular clinical assessments of MS patients in this country is not known, the cognitive batteries mentioned earlier require expertise to administer and are therefore not part of a routine clinical appointment.

c) Funding

In Canada the cost of a neuropsychological assessment is not provincially funded, apart from in Alberta. The cost of a private neuropsychological assessment may be beyond the financial means of a patient group with a high unemployment rate. This obstacle differentially affects the less well-off in our society.

d) Neurological predictors of impairment

Cognitive deficits are not part of the diagnostic criteria for MS (McDonald et al., 2001). Readily discernible language abnormalities and visual agnosias are rare in MS. As such, cognitive deficits are not commonly detected by a neurologist during routine clinical examination. Indeed it has been shown that clinical neurologists will miss significant cognitive dysfunction in as many as 50% of patients they examine (Peyser et al., 1980). In addition to the subtlety of these
deficits, cognitive performance is only weakly correlated with disease duration and physical disability and thus these indices cannot be used to predict who will or will not be cognitively impaired.

2.12) The importance of detection

The early detection of cognitive deficits in MS may be helpful for many reasons. First, these deficits can occur early on in the disease (Amato et al., 1995; Feinstein, Youl & Ron, 1992) at times predating the appearance of lesions on MRI (Glanz et al., 2007). Secondly, once cognitive deficits appear they are likely to worsen with time (Amato et al., 2001). Furthermore, the cognitive benefits of disease modifying medication may be larger when this treatment is applied earlier (Kappos et al., 2009).

The failure to detect cognitive impairment can also lead to several negative consequences. First, there may be unrealistic expectations for employment on the part of family and employers. Second, recognizing cognitive problems can also help family members and caregivers adjust to the disease. Without knowledge of objective cognitive difficulty, they may interpret a patient’s forgetfulness, or slowness to complete tasks as signs of a lack of motivation, or an unreasonable attempt to seek attention or sympathy.

2.13) Use of the internet for assessing cognition

Cognitive screening batteries that are administered over the internet have been developed for use in patients with Alzheimer’s disease (Dougherty et al., 2010), traumatic brain injury (Erlanger et al., 2002), and schizophrenia (Medalia, Lim & Erlanger, 2005), with one reported study in MS (Younes et al., 2007). These authors conducted a three-way comparison of performance on a computerized battery called the Cognitive Stability Index (CSI), the PASAT, and a formal neuropsychological battery in 41 MS patients with various disease subtypes. The CSI consists of tests of attention, processing speed, visual memory and reaction time. Both the CSI and PASAT had the same specificity (86%), but the CSI was three times as sensitive as the PASAT in detecting overall cognitive impairment on the neuropsychological battery (83% compared to 28%). Overall, the CSI appears to offer some promise as a tool for assessing cognition over the internet. It must, however, be administered in the presence of an examiner and requires approximately 30 minutes to administer. The use of self-report or informant-based internet
screening questionnaires for cognitive impairment in MS or any other neurological/psychiatric disease has not been reported in the literature.

SECTION 3: Aim, Rationale and Hypothesis

Aim of study: To validate an internet version of the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ).

Rationale

To summarize, many patients do not receive a cognitive assessment for a multitude of reasons including: (a) limited access to a neurologist, (b) small number of neuropsychologists, (c) cost, and (d) difficulty in detecting cognitive deficits during routine neurological examination. Making an internet version of the MSNQ available to MS patients would to some degree address some of these limitations although it is important to remember that the MSNQ is only a screening instrument, albeit one with good sensitivity and specificity. The MSNQ was chosen over other cognitive screening instruments because of this previously demonstrated validity, also it’s quick and easy administration, requiring only a few minutes to complete. Furthermore, it does not require the presence of an examiner, which other computerized test batteries such as the CSI (described in section 2.13) do.

Hypothesis

The internet-based MSNQ will be an effective screening instrument for cognitive impairment in MS. It will demonstrate acceptable sensitivity and specificity for detecting overall cognitive impairment on a battery of neuropsychological tests. The P-MSNQ will be better correlated with depressed mood, whereas the I-MSNQ will be better correlated with objective neuropsychological test performance.

SECTION 4: Methods

1) Patients

a) Inclusion criteria
The inclusion criteria included: a confirmed diagnosis of MS (based on revised McDonald criteria, Polman et al., 2005), age below 65, no co-morbid neurological disease or any concurrent physical disease potentially affecting the nervous system, no history of learning disability, and no neuropsychological testing within the last year in order to minimize practice effect. A present or past history of depression or anxiety did not exclude patients from participation. In addition, informants must have known patients for longer than a year in order to complete the I-MSNQ.

b) Exclusion criteria

Patients were excluded because of the following reasons: (a) severe visual problems that would affect testing, defined as a visual acuity greater than or equal to 20/40 (see section 2.9) (n=2), (b) taking longer than 45 minutes to complete the online MSNQ (n=2), and (c) refusal to complete the cognitive tests. In this case, one patient refused to complete the PASAT.

2) Recruitment

a) Sunnybrook MS clinic

Recruitment took place primarily at a MS clinic at Sunnybrook Health Sciences Centre. This was done one of two ways. First, using the clinic’s database of patients, those meeting inclusion criteria were contacted via telephone. They were asked if they would be interested in taking part in the study either on the same day or on a different day as their next appointment. Second, during their routine clinical visit, patients were asked by their treating psychiatrist if they would be interested in participating. All subjects were reimbursed for travelling and parking costs and were given feedback on their cognitive test results upon request.

b) MS Society of Canada advertisements

Patients were also recruited by advertisements/ flyers given out at a seminar done by the MS Society of Canada on MS and cognition. This advertisement was also posted on the MS Society of Canada’s e-newsletter.

3) Healthy controls

Healthy subjects were needed to derive normative data for the neuropsychological tests. They were recruited from: (a) family members and friends of the MS patients, and (b)
advertisement/flyers posted in the MS Society of Canada’s e-newsletter and throughout Sunnybrook hospital. They too were reimbursed for transportation and parking costs. These individuals carefully screened for the absence of neurological or psychiatric disease. Three subjects were excluded for meeting cut-offs for clinically significant depression and/or anxiety (score greater than or equal to 8 on either subscale; Honarmand & Feinstein, 2009) assessed using the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983), leaving the final sample at 35. They were matched to the MS group on age, years of education, gender, and premorbid IQ.

4) Order of testing

In formulating the methodology there was uncertainty as to whether the MSNQ should precede or succeed neuropsychological testing. The advantage to completing the neuropsychological testing first was that initial contact could be established with the patient. The internet instructions could also be explained in person, and the patient sent home to complete the MSNQ within a week. To this end, the first 44 subjects followed this order of testing. Two subjects did not complete the MSNQ after testing despite being contacted several times, thus leaving the final sample at 42.

The advantage to asking the patients to do the MSNQ first was that it more clearly reflected the real world reality of how the MSNQ would be used over the internet. The potential drawback to this approach was that the patient would be required to complete the MSNQ before making face-to-face contact with the researchers. Given the greater real world applicability of this approach a larger sample (i.e. n=82) were tested in this manner. These subjects, after initially consenting to participate in the study, were immediately given instructions on the phone or by email on how to complete the MSNQ. They were told that they must have the MSNQ completed prior to coming in for cognitive testing.

Data will be presented for both testing situations.

5) Data collected

a) Demographic and neurological data
Demographic (age, education) and neurological data (EDSS, duration of MS, disease course, and use of any disease-modifying drugs) were collected prior to neuropsychological testing. The EDSS scores were obtained by reviewing patient files and requesting this information from each patient’s neurologist. They were obtained within a month of the cognitive testing.

b) Visual acuity

Visual acuity was measured using the Snellen near vision eye chart. This was held at a distance of 14 inches away from the patient. Patients were asked to read the letters on the chart with both eyes, using their own corrective lenses if needed. Patients were given the visual acuity measurement that corresponded to the line prior to their first letter misidentification. Screening for mild visual disturbances is warranted given that this can negatively affect performance on tests of visual attention (e.g. on the SDMT, Bruce, Bruce & Arnett, 2007). A visual acuity of greater than 20/40 is the recommended threshold and was used in this study.

c) Cognition

i) Website / Online MSNQ

A confidential, password protected website was established for this study (www.mscognition.com). Each patient was provided with a unique study ID and password for login. The online assessment comprised of both the patient MSNQ (P-MSNQ) and the informant MSNQ (I-MSNQ). Patients and their informants were asked to complete their sections separately. The website was designed so that each questionnaire had to be completed before going on to the next one. This was done to ensure completeness of data. The time to complete each questionnaire was measurable based on internet data revealing the time at which subjects answered their first and last questions.

ii) Neuropsychological Testing

All subjects had a neuropsychological assessment with the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) (Rao, 1991). This consists of: (a) the Selective Reminding Test (SRT) (Buschke & Fuld, 1974), (b) the 10/36 Spatial Recall Test (10/36) (Rao et al., 1984), (c) the Symbol Digit Modalities Test (SDMT) oral administration (Smith, 1982), (d) the Paced Auditory Serial Attention Test (PASAT) (Gronwall, 1977) and (e) the Controlled Oral Word
Association Test (COWAT) (Benton & Hamsher, 1976). In addition, an estimate of premorbid IQ was obtained with the American National Adult Reading Test (ANART) (Grober & Sliwinski, 1991). Each of these tests will be described.

a) The Selective Reminding Test (SRT) measures verbal memory. Subjects are read a list of 12 words and asked to say as many of the words as they can remember. The examiner then reads the words that they missed and asks the subject to recall the entire list again, including words from their last attempt. This is done for 6 trials. There is also a delayed recall, where subjects are asked to recall the entire list again after 20 minutes. Three measures are obtained from the SRT: (a) long term storage (SRT-LTS), words that are recalled on two subsequent trials (i.e. without having to be reminded), (b) consistent long term retrieval (SRT-CLTR), words in LTS that are recalled on all subsequent trials, and (c) delayed recall. The BRB-N uses CLTR as the outcome measure for the SRT.

b) The 10/36 Spatial Recall Test (10/36) measures visuospatial learning. Subjects are shown a 6 X 6 checkerboard design with 10 dots placed in varying locations for 10 seconds. They are then asked to reproduce this design using 10 chips and their own checkerboard. This is done for 3 trials. The total number of correctly placed chips across the 3 trials is recorded and this is used as the outcome measure for the BRB-N. Like the SRT, there is also a delayed recall after 20 minutes.

c) The Symbol Digit Modalities Test (SDMT) is a measure of information processing speed. Only the oral version of the test is administered, as the written version would introduce motor confounds. Patients are asked to say the number that goes with the symbol according to a symbol-digit pairing key shown on the top of the page. The total number of correct substitutions after 90 seconds is recorded.

d) The Paced Auditory Serial Addition Test (PASAT) is a measure of information processing speed, working memory, and sustained attention. The examiner plays a tape in which numbers (from 1-10) are presented at a rate of once every three seconds in the first trial (easy condition), and once every two seconds in the second trial (hard condition). Subjects are asked to add each new number to the one immediately preceding it. The total number of correct items out of 60 for each trial is recorded. Performance at the two second presentation rate is used at the outcome measure for the BRB-N.
e) The Controlled Oral Word Association Test (COWAT) is a measure of verbal fluency. Subjects are asked to say as many words as they can that begin with a certain letter in one minute. For the BRB-N, these letters are F, O, and J. The COWAT is scored according to the total number of admissible responses across the 3 trials.

f) An estimate of premorbid verbal IQ was obtained using the American version of the National Adult Reading Test (ANART)(Schwartz & Saffran, 1987). In this task, subjects are required to read a list of irregular words. The total number of correctly pronounced words is used to generate a verbal IQ score. Predicted IQ from the ANART has been shown to correlate well with various IQ measures using the Wechsler Adult Intelligence Scale (WAIS) (Grober & Sliwinski, 1991).

Overall cognitive impairment was defined by convention as a performance of 1.5 standard deviations below the healthy control group scores on two or more of five BRB-N variables. To summarize, these variables are the SRT consistent long-term retrieval (SRT-CLTR) score, the 10/36 total recall score, the total number of correct responses on the SDMT, the total number of correct responses at the 2 second presentation rate of the PASAT, and the total correct words named on the COWAT. This criteria for defining cognitive impairment is found in the BRB-N manual (Rao, 1991).

d) Depression

Depression was measured online with the Centre for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977). The CES-D is a 20-item self-report measure of depressive symptomatology. Each item is rated according to frequency of occurrence during the past week from 0 (never or rarely) to 3 (most or all of the time). The CES-D assesses four factors: (a) depressed affect, (b) positive affect (these items are reverse scored), (c) somatic complaints, and (d) interpersonal relationships. The CES-D has been validated as a screen for depression (Radloff, 1977) and been used in large samples of MS patients, with demonstrable good psychometric properties (Verdier-Taillefer et al., 2001). A cut-off score of greater than or equal to 16 is the generally accepted threshold for clinically significant depression (Radloff, 1977). In a sample of 47 MS patients who were about to begin disease-modifying treatment, this cut-off correctly classified 74.5% of patients who were found to have major depression based on DSM diagnosis (Pandya, Metz & Patten, 2005).
5) Test-retest reliability

A randomly selected subset of patients with their same informants (n=23) were asked to complete the online assessment again after a mean duration of 61 (sd=43) days in order to evaluate test-retest reliability. No patient experienced clinical relapses in the interim time between the two administrations.

6) Data analysis

Data were first checked for normalcy of distributions. Pearson correlations were then computed between the internet MSNQ, the internet CES-D, and each of the BRB-N variables. Significance was set at p<.05. Thereafter, the sample was divided into those subjects with and without cognitive impairment based on the results of the BRB-N. This was used as the “gold standard” for defining cognitive impairment. Sensitivity and specificity values were then calculated for every possible cut-off score of the MSNQ. Sensitivity is defined as the true positive rate or the probability that a patient with cognitive impairment obtains a positive test result, i.e. scores above the MSNQ threshold. Specificity is defined as the true negative rate, or the probability that a patient with no cognitive impairment obtains a negative test result, i.e. scores below the MSNQ threshold. The sensitivity and specificity of possible threshold scores on the MSNQ were calculated in order to determine the optimal cut-off score which gave the highest sensitivity and specificity values. Positive Predictive Value (PPV) and Negative Predictive Value (NPV) were also calculated. Positive Predictive Value is defined as the probability of true cognitive dysfunction given a positive test result, and NPV is defined as the probability of no cognitive impairment given a negative test result.

A receiver operator characteristic (ROC) curve analysis was also performed. The ROC curve plots the true positive rate/ sensitivity as a function of the false positive rate (1-specificity) for varying threshold scores. The area under the curve (AUC) represents the overall ability of the instrument (MSNQ) to distinguish between patients with and without cognitive impairment. This value ranges from 0 to 1, with higher values representing greater discriminability.

Given the effect that depression can have on the accurate reporting of cognitive difficulties, the MSNQ may only be valid if applied to patients without clinically significant depression.
To address this, a separate analysis was run for patients with and without depression using a cut-off score of greater than or equal to 16 on the CES-D (Radloff, 1997; Pandya, Metz, & Patten, 2005).

A linear regression was also undertaken to evaluate the relative amount of variance in MSNQ scores explained by depression and cognitive test performance. The test-retest reliability of the MSNQ was assessed using an intraclass correlation coefficient (ICC). The ICC estimates the reliability within a subject by comparing the within- and between- subject variance. Cronbach’s alpha coefficients were also obtained to provide measures of internal consistency of the P-MSNQ and the I-MSNQ.

7) Ethics

This study received ethics approval from the Research Ethics Board at Sunnybrook Health Sciences Centre, affiliated with the University of Toronto. All patients gave their written and informed consent to participate in the study.

The primary purpose of this study was to investigate whether or not use of the MSNQ over the internet would be an accurate way of detecting cognitive impairment. As such, feedback was not given to patients on the results of their MSNQ scores (i.e. if their scores indicate possible cognitive impairment). However, if this study was successful and the website were to be launched, ethical considerations would have to made regarding the provision of feedback to patients over the internet. On the plus side the importance of giving patients access to an assessment they may never have received was highlighted. In addition, the benefits of having patients and close informants made familiar with all aspects of the disease needs to be stressed. Finally, it would also be important not to over-interpret the MSNQ results, i.e. it is not a substitute for detailed neuropsychological testing. Rather it is a screen and should best be viewed as an instrument identifying those patients who could benefit from further testing or assistance. On the negative side it was felt important that the website not identify potential cognitive problems and leave it at that. Therefore, in the event of the MSNQ being used over the internet it was envisaged that the website would be programmed to identify those patients whose score fell in the impaired MSNQ range and instruct them to contact their neurologist or family doctor as appropriate.
SECTION 5: Results

1) MSNQ completed before neuropsychological testing (n=82)

a) Demographic and illness data

Demographic comparisons (age, gender, education, ANART verbal IQ) between MS patients and controls are shown in Table 3 and did not reveal any significant differences. Disease-related variables for the MS patients are also shown in Table 3.

b) MSNQ

i) Informant characteristics

The mean number of years informants knew the patient was 22.7 (sd=12.3). Fifty-nine (72%) informants saw patients daily, 16 (19.5%) four to six times a week, and 7 (8.5%) one to three times a week. Forty-seven (57.3%) informants were spouses, 5 (6.1%) were domestic partners, 11 (13.4%) were friends, 11 (13.4%) were parents, 5 (6.1%) were children and 3 (3.7%) were other family members.

ii) MSNQ score distributions

Scores on both the P-MSNQ and I-MSNQ were normally distributed according to the Kolmogorov-Smirnov test (P-MSNQ, z=.645, p=.799; I-MSNQ, z=.727, p=.666).

The mean P-MSNQ score was 32.1 (sd=10.0), and mean I-MSNQ score was 26.7 (sd=11.5). The mean P-MSNQ score was significantly higher than the mean I-MSNQ score (t(81)=5.0, p<.001).

iii) Time to complete the MSNQ

It took patients and informants on average 3.7 (sd=2.8) and 7.0 (sd=7.5) minutes respectively to complete the MSNQ. Informants took significantly longer than patients to complete the MSNQ (Mann-Whitney U=1376.5, p<.001). The distribution of time it took to complete the P-MSNQ and I-MSNQ are shown in Figures 1 and 2 respectively. Neither were normally distributed (P-MSNQ time, z=1.594, p=.012; I-MSNQ time, z=2.067, p<.001).
Table 3. Demographic and disease-related variables for MS patients (n=82) and healthy control subjects (n=35)

<table>
<thead>
<tr>
<th></th>
<th>MS patients (n=82)</th>
<th>Healthy Control Subjects (n=35)</th>
<th>t-test or $X^2$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD)</strong></td>
<td>44.5 (8.9)</td>
<td>40.5 (12.1)</td>
<td>$t = -1.78$</td>
<td>.080</td>
</tr>
<tr>
<td><strong>Gender (F/M)</strong></td>
<td>64 / 18</td>
<td>26 / 9</td>
<td>$X^2 = .196$</td>
<td>.658</td>
</tr>
<tr>
<td><strong>Years of Education</strong></td>
<td>15.0 (2.2)</td>
<td>15.9 (2.0)</td>
<td>$t = 1.90$</td>
<td>.060</td>
</tr>
<tr>
<td><strong>ANART verbal IQ</strong></td>
<td>113.2 (8.0)</td>
<td>112.0 (9.4)</td>
<td>$t = -.704$</td>
<td>.483</td>
</tr>
<tr>
<td><strong>Time since diagnosis (months)</strong></td>
<td>114.5 (89.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Disease Course</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsing-Remitting</td>
<td>56 (68%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary Progressive</td>
<td>17 (21%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Progressive</td>
<td>7 (9%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive Relapsing</td>
<td>2 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>On disease-modifying treatment (Y / N)</strong></td>
<td>34 / 48 (41%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EDSS</strong></td>
<td>2.9 (2.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Figure 1.** Distribution of time it took for patients to complete the P-MSNQ

![Graph showing distribution of time it took for patients to complete the P-MSNQ](image)

**Figure 2.** Distribution of time it took for informants to complete the I-MSNQ

![Graph showing distribution of time it took for informants to complete the I-MSNQ](image)
c) Neuropsychological data

The scores on all cognition measures for patients and healthy controls are shown in Table 4. MS patients performed more poorly than controls on all cognitive measures except the 10/36. Twenty-nine (35.4%) patients were deemed cognitively impaired as defined earlier (see Methods Section 5).

Table 4. Comparison between MS patients (n=82) and healthy control subjects (n=35) on test scores of the BRB-N

<table>
<thead>
<tr>
<th></th>
<th>MS patients (n=82)</th>
<th>Healthy Control Subjects (n=35)</th>
<th>t-test</th>
<th>p-value</th>
<th>% of MS patients impaired (&gt;1.5 SD below the mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRT - LTS, mean (SD)</td>
<td>39.0 (14.2)</td>
<td>53.5 (8.3)</td>
<td>6.9</td>
<td>&lt;.001**</td>
<td>50%</td>
</tr>
<tr>
<td>SRT - CLTR</td>
<td>27.2 (14.5)</td>
<td>44.6 (12.4)</td>
<td>6.2</td>
<td>&lt;.001**</td>
<td>45%</td>
</tr>
<tr>
<td>SRT - Delay</td>
<td>6.9 (2.5)</td>
<td>10.1 (1.9)</td>
<td>6.7</td>
<td>&lt;.001**</td>
<td>60%</td>
</tr>
<tr>
<td>10/36 - Total</td>
<td>19.3 (5.7)</td>
<td>21.4 (5.4)</td>
<td>1.8</td>
<td>.07</td>
<td>17%</td>
</tr>
<tr>
<td>10/36 - Delay</td>
<td>6.5 (2.5)</td>
<td>7.4 (2.2)</td>
<td>1.8</td>
<td>.07</td>
<td>27%</td>
</tr>
<tr>
<td>SDMT - Total</td>
<td>45.2 (12.3)</td>
<td>57.5 (13.0)</td>
<td>4.9</td>
<td>&lt;.001**</td>
<td>27%</td>
</tr>
<tr>
<td>PASAT - 3 seconds number correct</td>
<td>40.6 (13.1)</td>
<td>48.5 (9.7)</td>
<td>3.6</td>
<td>.001**</td>
<td>27%</td>
</tr>
<tr>
<td>PASAT - 2 seconds number correct</td>
<td>30.5 (10.8)</td>
<td>37.2 (10.0)</td>
<td>3.1</td>
<td>.003*</td>
<td>22%</td>
</tr>
<tr>
<td>COWAT - Total Correct</td>
<td>30.0 (10.2)</td>
<td>35.1 (9.4)</td>
<td>2.6</td>
<td>.01*</td>
<td>20%</td>
</tr>
</tbody>
</table>

* = p<.01, ** = p <.001
d) Depression

The mean patient CES-D score was 23.5 (sd=13.3). The number of patients who met criteria for clinically significant depression (CES-D score greater than or equal to 16) was 63%.

e) Correlations

i) MSNQ and neuropsychological test performance

Correlations between the MSNQ, cognitive variables, and depression are shown in Table 5. The P-MSNQ was significantly correlated with the SRT Delay, and both presentation rates of the PASAT. The I-MSNQ was significantly correlated with all nine measures of the BRB-N as well as ANART predicted verbal IQ.

ii) MSNQ and depression

As seen in Table 5, both the P-MSNQ and I-MSNQ were highly correlated with depression although this correlation was more robust for patients (r=.62, p<.01, and r=.44, p<.01, respectively).

f) Sensitivity and Specificity Analysis

The sensitivity and specificity percentages for possible cut-off scores on the I-MSNQ and P-MSNQ are shown in Tables 6 and 7 respectively. From this it can be seen that the cut-off score that gave the optimal sensitivity (72.4%) and specificity (60.4%) for detecting overall cognitive impairment on the BRB-N was 26 on the I-MSNQ, with 64.6% of patients correctly classified overall. Calculation of sensitivity, specificity, PPV, and NPV using this cut-off is shown in Table 8. The PPV was 50%, thus given a positive MSNQ result, there was a 50% chance that actual cognitive impairment was present. The NPV was 80%, thus given a negative MSNQ score 80% of the time no cognitive impairment existed. The ROC area under the curve (AUC) was 0.707 for the I-MSNQ (Figure 3) and 0.566 for the P-MSNQ (Figure 4), the former being statistically significant (p=.002 and p=.327 respectively).
Table 5. Pearson correlation coefficients between internet MSNQ, depression and cognitive test scores (n=82)

<table>
<thead>
<tr>
<th></th>
<th>P-MSNQ</th>
<th>I-MSNQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>CES-D</td>
<td>.62**</td>
<td>.44**</td>
</tr>
<tr>
<td>SRT - LTS</td>
<td>-.19</td>
<td>-.28**</td>
</tr>
<tr>
<td>SRT - CLTR</td>
<td>-.20</td>
<td>-.30**</td>
</tr>
<tr>
<td>SRT - Delay</td>
<td>-.23*</td>
<td>-.34**</td>
</tr>
<tr>
<td>10/36 Total</td>
<td>-.13</td>
<td>-.24*</td>
</tr>
<tr>
<td>10/36 Delay</td>
<td>-.19</td>
<td>-.23*</td>
</tr>
<tr>
<td>SDMT - Total Correct</td>
<td>-.10</td>
<td>-.27*</td>
</tr>
<tr>
<td>PASAT - 3 seconds</td>
<td>-.27*</td>
<td>-.42**</td>
</tr>
<tr>
<td>PASAT - 2 seconds</td>
<td>-.27*</td>
<td>-.29**</td>
</tr>
<tr>
<td>COWAT</td>
<td>-.16</td>
<td>-.34**</td>
</tr>
<tr>
<td>ANART Verbal IQ</td>
<td>-.13</td>
<td>-.31**</td>
</tr>
</tbody>
</table>

* = p<.05, ** = p<.01
Table 6. Probability of internet informant MSNQ (I-MSNQ) predicting cognitive impairment on the BRB-N

<table>
<thead>
<tr>
<th>Threshold score greater than or equal to</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>100</td>
<td>18.9</td>
</tr>
<tr>
<td>14</td>
<td>96.6</td>
<td>20.8</td>
</tr>
<tr>
<td>15</td>
<td>96.6</td>
<td>26.4</td>
</tr>
<tr>
<td>16</td>
<td>96.6</td>
<td>28.3</td>
</tr>
<tr>
<td>18</td>
<td>93.1</td>
<td>30.2</td>
</tr>
<tr>
<td>19</td>
<td>86.2</td>
<td>32.1</td>
</tr>
<tr>
<td>20</td>
<td>86.2</td>
<td>35.8</td>
</tr>
<tr>
<td>21</td>
<td>82.8</td>
<td>43.4</td>
</tr>
<tr>
<td>22</td>
<td>75.9</td>
<td>45.3</td>
</tr>
<tr>
<td>23</td>
<td>75.9</td>
<td>49.1</td>
</tr>
<tr>
<td>24</td>
<td>75.9</td>
<td>52.8</td>
</tr>
<tr>
<td>25</td>
<td>75.9</td>
<td>54.7</td>
</tr>
<tr>
<td>26</td>
<td>72.4</td>
<td>60.4</td>
</tr>
<tr>
<td>27</td>
<td>65.5</td>
<td>60.4</td>
</tr>
<tr>
<td>28</td>
<td>62.1</td>
<td>64.2</td>
</tr>
<tr>
<td>29</td>
<td>62.1</td>
<td>66</td>
</tr>
<tr>
<td>30</td>
<td>58.6</td>
<td>67.9</td>
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<tr>
<td>31</td>
<td>55.2</td>
<td>75.5</td>
</tr>
<tr>
<td>32</td>
<td>51.7</td>
<td>77.4</td>
</tr>
<tr>
<td>33</td>
<td>51.7</td>
<td>79.2</td>
</tr>
</tbody>
</table>
Table 7. Probability of internet patient MSNQ (P-MSNQ) predicting cognitive impairment on the BRB-N

<table>
<thead>
<tr>
<th>Threshold score greater than or equal to</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>100</td>
<td>1.9</td>
</tr>
<tr>
<td>14</td>
<td>97</td>
<td>1.9</td>
</tr>
<tr>
<td>15</td>
<td>97</td>
<td>3.8</td>
</tr>
<tr>
<td>16</td>
<td>97</td>
<td>5.7</td>
</tr>
<tr>
<td>17</td>
<td>97</td>
<td>7.5</td>
</tr>
<tr>
<td>19</td>
<td>93</td>
<td>11.3</td>
</tr>
<tr>
<td>20</td>
<td>93</td>
<td>15.1</td>
</tr>
<tr>
<td>21</td>
<td>89.7</td>
<td>17</td>
</tr>
<tr>
<td>22</td>
<td>79.3</td>
<td>17</td>
</tr>
<tr>
<td>23</td>
<td>75.9</td>
<td>17</td>
</tr>
<tr>
<td>24</td>
<td>75.9</td>
<td>18.9</td>
</tr>
<tr>
<td>25</td>
<td>72.4</td>
<td>24.5</td>
</tr>
<tr>
<td>26</td>
<td>72.4</td>
<td>30.2</td>
</tr>
<tr>
<td>27</td>
<td>69</td>
<td>34</td>
</tr>
<tr>
<td>28</td>
<td>69</td>
<td>41.5</td>
</tr>
<tr>
<td>29</td>
<td>65.5</td>
<td>41.5</td>
</tr>
<tr>
<td>30</td>
<td>62.1</td>
<td>43.4</td>
</tr>
<tr>
<td>31</td>
<td>62.1</td>
<td>47.2</td>
</tr>
<tr>
<td>32</td>
<td>62.1</td>
<td>49.1</td>
</tr>
<tr>
<td>33</td>
<td>51.7</td>
<td>50.9</td>
</tr>
<tr>
<td>34</td>
<td>51.7</td>
<td>54.7</td>
</tr>
</tbody>
</table>
Table 8. Sensitivity and specificity table for the I-MSNQ in detecting overall cognitive impairment on the BRB-N for MS patients (n=82)

<table>
<thead>
<tr>
<th></th>
<th>Cognitive impairment</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BRB-N failed</td>
<td>BRB-N passed</td>
</tr>
<tr>
<td>I-MSNQ &gt;=26</td>
<td>21(^a)</td>
<td>21</td>
</tr>
<tr>
<td>I-MSNQ &lt; 26</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>53</td>
</tr>
</tbody>
</table>

\(^a\) - each cell represents number of patients

Sensitivity = 21/29 X 100 = 72%

Specificity = 32/53 X 100 = 60%

Positive Predictive Value = 21/42 X 100 = 50%

Negative Predictive Value = 32/40 X 100 = 80%

Percent Correctly Classified = (21+32) / 82 X 100 = 65%
Figure 3. ROC curve for the internet informant MSNQ (I-MSNQ) predicting cognitive impairment on the BRB-N (n=82)
Figure 4. ROC curve for the internet patient MSNQ (P-MSNQ) predicting cognitive impairment on the BRB-N (n=82)
Altering the threshold for global cognitive impairment on the BRB-N (i.e. scores of 1.5 SD below the healthy control group on 2 out of 9 as opposed to 2 out of 5 cognitive measures) yielded a higher prevalence of global dysfunction (i.e. 61%). However, this did not substantially alter the sensitivity and specificity results of the I-MSNQ. Here, the optimal cut-off on the I-MSNQ was a 25, with a sensitivity of 70% and specificity of 66%.

g) Confining analysis to patients without depression

Because of the reported influence of depression on self-reports of cognition, confining the analysis to patients without depression could improve the accuracy of the MSNQ in detecting cognitive impairment. When patients who scored greater than or equal to 16 on the CES-D were removed the sample size was reduced to 31. The prevalence of cognitive impairment in this group was lower at 16%. The I-MSNQ once again discriminated patients with cognitive impairment better than the P-MSNQ. The best cut-off on the I-MSNQ was 21, with sensitivity of 80%, specificity of 62%, and 65% of patients correctly classified.

h) Relationship of the MSNQ to demographic and disease-related variables

Correlations between MSNQ scores and demographic and disease-related variables are shown in Table 9. The only significant correlation was between P-MSNQ and EDSS, which was negative. MSNQ scores did not differ based on gender (P-MSNQ, t(80)=1.64, p=.105; I-MSNQ, t(80)=1.42, p=.160) or use of disease-modifying drugs (P-MSNQ, t(80)=-1.09, p=.279; I-MSNQ, t(80)=-.907, p=.367). MSNQ scores also did not differ according to disease course which was coded according to the categories of RRMS, PPMS, SPMS, and Progressive Relapsing MS (one-way ANOVA, P-MSNQ, F (3,79) =2.1, p=.087; I-MSNQ, F(3,79)=1.1, p=.349).

i) Linear Regression

A hierarchical linear regression was employed investigating the relative contribution of mood and cognition to patient and informant MSNQ reports. Only those variables that were significant in the correlation analysis were entered into the regression. Correlations between significant variables were sought and if found to be high (defined as r>.7) the least significant variable was excluded. For the P-MSNQ, the 2-second PASAT was excluded as it correlated highly with 3-second PASAT score. Similarly, for the I-MSNQ, the following variables were excluded because
Table 9. Pearson correlation coefficients between internet MSNQ, demographic and disease-related variables (n=82)

<table>
<thead>
<tr>
<th></th>
<th>P-MSNQ</th>
<th>I-MSNQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-.043</td>
<td>-.193</td>
</tr>
<tr>
<td>Education</td>
<td>.050</td>
<td>-.009</td>
</tr>
<tr>
<td>Time since diagnosis</td>
<td>-.178</td>
<td>-.109</td>
</tr>
<tr>
<td>(months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since MS symptom</td>
<td>-.151</td>
<td>-.167</td>
</tr>
<tr>
<td>onset (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDSS score</td>
<td>-.305**</td>
<td>-.139</td>
</tr>
</tbody>
</table>

* = p<.05, ** = p<.01

of significant correlation with other indices: SRT-LTS, SRT-CLTR, 10/36 Delayed Recall, and 2-second PASAT.

**P-MSNQ**

Depression, followed by the cognitive variables, were entered into the linear regression model to determine whether cognition could explain significant additional variance beyond that of mood in P-MSNQ scores. CES-D score was able to explain 38.2% of the variance in P-MSNQ scores ($R^2=.382$, Adjusted $R^2=.374$, $\Delta F=49.5$, $p<.001$). Adding the significant cognitive variables (SRT-Delay, PASAT-3 seconds) raised the variance percentage to 40.4%, a change which was not statistically significant ($\Delta R^2=.02$ $\Delta F=1.43$, $p=.246$). The final model was overall statistically significant ($F(3, 78)=17.62$, $p<.001$), with only CES-D score ($b=.584$, $t(78)=6.51$, $p<.001$), but no cognitive variables emerging as significant predictors of P-MSNQ scores (SRT-Delay, $b=-.044$, $t(78)=-.412$, $p=.681$; PASAT-3, $b=-.123$, $t(78)=-1.153$, $p=.252$).

**I-MSNQ**
Depression was entered first into the regression analysis. CES-D was able to explain 19.1% of the variance ($R^2=.191$, Adjusted $R^2=.181$, $\Delta F=18.9$, $p<.001$). Adding the significant cognitive variables (SRT-Delay, 10/36 Total, SDMT Total, PASAT-3 seconds, COWAT) raised the variance percentage to 32.3%, a change which was statistically significant ($\Delta R^2=.131$, $\Delta F=2.90$, $p=.019$). The final model was overall statistically significant ($F(6,75)=5.95$, $p<.001$). Depression ($b=.339$, $t(75)=3.377$, $p=.001$) and PASAT-3 seconds ($b=-.264$, $t(74)=-1.951$, $p=.055$) were the only significant predictors in this final model.

j) Test-retest reliability and Cronbach’s alpha results

Test-retest reliability values were significant for both the P-MSNQ (ICC=.815, $p<.001$) and I-MSNQ (ICC=.767, $p<.001$). Scores between times 1 and 2 did not differ significantly for the P-MSNQ or the I-MSNQ ($t(22)=-1.10$, $p=.285$ and $t(22)=1.32$, $p=.200$ respectively). Cronbach’s alpha coefficients were also high for both the P-MSNQ (.911) and I-MSNQ (.933).

2) MSNQ completed after neuropsychological testing ($n=42$)

As mentioned previously, the first 42 patients completed cognitive testing with the BRB-N before completing the online assessment at home. The data presented thus far have been confined to the 82 patients who completed the online assessment at home before the in-office BRB-N testing. This section will compare these two data sets.

a) Comparison of sample characteristics

Table 10 shows a comparison of demographic, disease-related, and cognitive variables between the two groups of patients, showing no significant differences on any of these factors.

b) Comparison of correlation coefficients

The correlations between the online MSNQ and cognitive test performance for the first 42 patients are shown in Table 11. Here neither version of the MSNQ correlated with any cognitive measures. This is in contrast to the data from the 82 patients already presented where significant correlations were evident between the MSNQ and several cognitive measures (Table 5). The Fisher transformation allows the conversion of correlation coefficients to z-scores so that the
Table 10. Comparisons between demographic, cognitive, and disease-related variables between patients who completed the MSNQ after (n=42) or before (n=82) the BRB-N

<table>
<thead>
<tr>
<th>Variable</th>
<th>MSNQ after BRB-N (n=42)</th>
<th>MSNQ before BRB-N (n=82)</th>
<th>t-test / X²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD)</strong></td>
<td>45.1(8.3)</td>
<td>44.5(8.9)</td>
<td>0.35</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Education (years)</strong></td>
<td>14.8(2.3)</td>
<td>15.0(2.2)</td>
<td>-0.74</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Gender (M/F)</strong></td>
<td>11/31</td>
<td>18/64</td>
<td>0.2</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>VIQ</strong></td>
<td>112.7(6.9)</td>
<td>113.2(8.0)</td>
<td>-0.43</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>Online P-MSNQ Total</strong></td>
<td>34.4(10.2)</td>
<td>32.1(10.0)</td>
<td>1.39</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Online I-MSNQ Total</strong></td>
<td>29.6(12.5)</td>
<td>26.7(11.5)</td>
<td>1.19</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Informant - number of years known</strong></td>
<td>23.1(12.3)</td>
<td>22.7(12.3)</td>
<td>0.15</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Online CES-D Total</strong></td>
<td>26.0(13.2)</td>
<td>23.2(13.3)</td>
<td>1.13</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Cognitive Impairment on the BRB-N (Y/N)</strong></td>
<td>18/24</td>
<td>29/53</td>
<td>0.83</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Months Since Diagnosis</strong></td>
<td>113.3(98.0)</td>
<td>114.5(89.1)</td>
<td>-0.17</td>
<td>0.87</td>
</tr>
<tr>
<td><strong>Disease Course</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Relapsing Remitting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>56</td>
<td>0.36</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Secondary Progressive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Progressive Relapsing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary Progressive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EDSS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.1 (2.5)</td>
<td>2.9 (2.5)</td>
<td>0.48</td>
<td>0.64</td>
</tr>
</tbody>
</table>
Table 11. Pearson correlation coefficients between the MSNQ and cognitive test performance in patients who completed the MSNQ after the BRB-N (n=42)

<table>
<thead>
<tr>
<th></th>
<th>P-MSNQ</th>
<th>I-MSNQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>CES-D</td>
<td>0.60**</td>
<td>0.41**</td>
</tr>
<tr>
<td>SRT - LTS</td>
<td>0.18</td>
<td>0.13</td>
</tr>
<tr>
<td>SRT - CLTR</td>
<td>0.14</td>
<td>0.14</td>
</tr>
<tr>
<td>SRT - Delay</td>
<td>0.08</td>
<td>0.09</td>
</tr>
<tr>
<td>10/36 Total</td>
<td>0.09</td>
<td>-0.19</td>
</tr>
<tr>
<td>10/36 Delay</td>
<td>0.09</td>
<td>-0.15</td>
</tr>
<tr>
<td>SDMT - Total Correct</td>
<td>0.05</td>
<td>0.04</td>
</tr>
<tr>
<td>PASAT - 3 seconds</td>
<td>0.05</td>
<td>-0.06</td>
</tr>
<tr>
<td>PASAT - 2 seconds</td>
<td>0.32</td>
<td>0.19</td>
</tr>
<tr>
<td>COWAT</td>
<td>0.14</td>
<td>0.11</td>
</tr>
<tr>
<td>ANART Verbal IQ</td>
<td>0.01</td>
<td>-0.04</td>
</tr>
</tbody>
</table>

* = p<.05, ** = p<.01

sampling distribution is normal (Fisher, 1921). A z-score of the differences between correlation coefficients of two independent samples can then be calculated (Field, 2009). This data is shown in Table 12. The differences in z-scores were significant for the following correlations: (a) P-MSNQ and PASAT, (b) I-MSNQ and SRT, (c) I-MSNQ and PASAT, and (d) I-MSNQ and COWAT, with patients who completed the MSNQ prior to cognitive testing demonstrating higher correlations.
Table 12. z-score differences in correlation coefficients between patients who completed the MSNQ after (n=42) or before (n=82) the BRB-N

<table>
<thead>
<tr>
<th></th>
<th>P-MSNQ</th>
<th>I-MSNQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>CES-D</td>
<td>0.25</td>
<td>0</td>
</tr>
<tr>
<td>SRT - LTS</td>
<td>-1.81</td>
<td>-2.15*</td>
</tr>
<tr>
<td>SRT - CLTR</td>
<td>-1.71</td>
<td>-2.20*</td>
</tr>
<tr>
<td>SRT - Delay</td>
<td>-1.51</td>
<td>-2.22*</td>
</tr>
<tr>
<td>10/36 Total</td>
<td>-1.24</td>
<td>-0.11</td>
</tr>
<tr>
<td>10/36 Delay</td>
<td>-1.40</td>
<td>-0.59</td>
</tr>
<tr>
<td>SDMT - Total Correct</td>
<td>-0.72</td>
<td>-1.41</td>
</tr>
<tr>
<td>PASAT - 3 seconds</td>
<td>-1.68</td>
<td>-1.74</td>
</tr>
<tr>
<td>PASAT - 2 seconds</td>
<td>-3.07**</td>
<td>-2.13*</td>
</tr>
<tr>
<td>COWAT</td>
<td>-1.60</td>
<td>-2.27*</td>
</tr>
<tr>
<td>ANART Verbal IQ</td>
<td>-0.83</td>
<td>-1.38</td>
</tr>
</tbody>
</table>

* - p <.05, ** - p<.01

c) Sensitivity and specificity analysis

Using the same criteria for cognitive impairment on the BRB-N (1.5 SD below the healthy control group on 2 or more of the 5 variables), 18 (45%) of patients were cognitively impaired. The optimal cut-off score on the I-MSNQ was 27 with a sensitivity of 50% and specificity of 38% for detecting cognitive impairment on the BRB-N (Table 13). From the ROC analysis, the AUC was not significant for both the P-MSNQ (AUC=.542, p=.647), nor the I-MSNQ (AUC=.446, p=.550).
Table 13. Probability of internet informant MSNQ predicting cognitive impairment in patients who completed the MSNQ after the BRB-N (n=42)

<table>
<thead>
<tr>
<th>Threshold score greater than or equal to</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>100</td>
<td>8.3</td>
</tr>
<tr>
<td>13</td>
<td>94.4</td>
<td>12.5</td>
</tr>
<tr>
<td>15</td>
<td>88.9</td>
<td>12.5</td>
</tr>
<tr>
<td>16</td>
<td>88.9</td>
<td>16.7</td>
</tr>
<tr>
<td>17</td>
<td>77.8</td>
<td>16.7</td>
</tr>
<tr>
<td>19</td>
<td>72.2</td>
<td>16.7</td>
</tr>
<tr>
<td>21</td>
<td>66.7</td>
<td>16.7</td>
</tr>
<tr>
<td>22</td>
<td>61.1</td>
<td>16.7</td>
</tr>
<tr>
<td>23</td>
<td>55.6</td>
<td>20.8</td>
</tr>
<tr>
<td>24</td>
<td>55.6</td>
<td>29.2</td>
</tr>
<tr>
<td>26</td>
<td>50</td>
<td>33.3</td>
</tr>
<tr>
<td>27</td>
<td>50</td>
<td>37.5</td>
</tr>
<tr>
<td>28</td>
<td>38.9</td>
<td>37.5</td>
</tr>
<tr>
<td>29</td>
<td>38.9</td>
<td>45.8</td>
</tr>
<tr>
<td>31</td>
<td>38.9</td>
<td>54.2</td>
</tr>
<tr>
<td>33</td>
<td>33.3</td>
<td>58.3</td>
</tr>
<tr>
<td>34</td>
<td>33.3</td>
<td>62.5</td>
</tr>
<tr>
<td>36</td>
<td>33.3</td>
<td>66.7</td>
</tr>
<tr>
<td>37</td>
<td>33.3</td>
<td>70.8</td>
</tr>
<tr>
<td>40</td>
<td>27.8</td>
<td>75</td>
</tr>
<tr>
<td>44</td>
<td>22.2</td>
<td>83.3</td>
</tr>
<tr>
<td>45</td>
<td>11.1</td>
<td>87.5</td>
</tr>
</tbody>
</table>
SECTION 6: Discussion

The aim of this study was to validate an internet version of the MSNQ. If successful, this could be used to provide patients with greater access to a cognitive assessment. It is important to emphasize that the MSNQ should not be viewed as a substitute for more detailed neuropsychological testing. Rather, it is a helpful screening instrument and which, in the absence of a neuropsychological service, can also become a useful fallback tool potentially providing a marker of overall cognitive functioning. Overall, this study showed that the I-MSNQ when used over the internet has modest sensitivity and weaker specificity.

This study sample was representative of the MS population in general, with an appropriate percentage of patients with RRMS (68%) and progressive forms of MS. This sample also had overall relatively mild physical disability (mean EDSS=2.9). A comparison of this sample and those of previous MSNQ studies is shown in Table 2. The demographic and disease characteristics, percentage of patients who were cognitively impaired, and length of time informants knew the patient were similar to these other studies.

This study’s finding of modest sensitivity and weaker specificity overlaps in part with most, but not all of the small MSNQ literature to date. In the original study with a sample of 50 subjects, sensitivity and specificity values of 83% and 97% respectively were reported (Benedict et al., 2003). A replication study in 85 subjects found a sensitivity of 87% and specificity of 84% (Benedict et al., 2004). A third study, with an Argentinean population reported similar results (Vanotti et al., 2008), unlike a fourth report (O’Brien et al., 2007) which noted an excellent sensitivity (94%), but a specificity of 55% which is markedly lower than that in this study. Thus, of four published reports, one failed to adequately validate the scale (O’Brien et al., 2007). This study may therefore be viewed as a second failed attempt suggesting additional data are necessary before any firm conclusions about the robustness of the MSNQ can be reached. The published literature also varies on what is the optimal cut-off score for the I-MSNQ. These have ranged from 10 to 27 possibly reflecting small sample sizes and varying sample characteristics.

Having pointed out differences in the sensitivity and specificity between this study and those in the published literature, there were also areas in which data converged. First, the P-MSNQ correlated more closely with self-reported depression whereas the I-MSNQ was more closely linked with objective evidence of cognitive impairment. This indicates that MS patients are often
not the best judges of their own cognition, an observation that replicates previous findings pertaining to metacognition in MS (outlined in section 2.10). This could possibly be due to depressed mood or poor insight. P-MSNQ scores were significantly higher than I-MSNQ scores in this study, thus it is likely that depression was playing a larger role in patient reports although this is difficult to disentangle. Furthermore, this study found high test-retest reliability and was able to replicate the robust Cronbach’s alpha results.

This study’s finding of a correlation between informant MSNQ ratings and patient depression, though less robust, was also found in one of the other four MSNQ studies (Benedict et al., 2004). This may relate to the high prevalence of depressed patients in this sample, with 63% meeting the cut-off on the CES-D for clinically significant depression. In this regard it should be remembered that rates of depression in MS are high with more than 50% of a large community sample (n=696) found to be depressed using the CES-D (Verdier-Taillefer et al., 2001). Another study of 1374 MS patients reported a more modest albeit still elevated figure of 42%, also using the CES-D (Chwastiak et al., 2002). Be that as it may, in the present study, even when patients with major depression were excluded from the sample, the sensitivity and specificity of the I-MSNQ did not change dramatically.

The quality of the informant reports can also be questioned in relation to mood. Depression in the informants was not measured in this study. Significant caregiver distress has been reported in MS (Knight et al., 1997), which may affect depression levels in informants. Thus, depression in the informants themselves may have been biasing their MSNQ ratings, seeing their family member/friend’s cognition in a more negative light.

The linear regression analysis showed that cognitive variables (SRT-Delay and PASAT-3) were not able to add significantly to depression in explaining the variance in P-MSNQ scores. This is in contrast to Benedict et al. (2008) who found that both depression, measured by the BDI-FS, and information processing speed, measured by the SDMT, were able to account for significant variance in P-MSNQ self-report scores. Cognition, however, emerged as a significant predictor, alongside depression, of informant MSNQ scores raising the variance percentage from 19 to 33%.

The neuropsychological assessment or gold standard for defining cognitive impairment was valid as all tests of the BRB-N except one (10/36 Spatial Recall Test) were able to discriminate
between MS patients and healthy controls. The prevalence of cognitive dysfunction in this study as elicited by the BRB-N approximated the 40% figure cited for samples of community living MS patients with predominantly relapsing-remitting disease (Rao, Leo, Bernardin et al., 1991). This figure was also derived from the BRB-N which in itself is a screening tool. Using a more comprehensive cognitive battery such as the MACFIMS (described in section 2.10) may theoretically have given a different result with the MSNQ although here it is important to note that even when the threshold of the BRB-N was altered, with a concomitant increase in the percentage of cognitive impairment found, no substantial changes in I-MSNQ sensitivity and specificity were found.

The internet MSNQ in this study had strong test-retest reliability and internal reliability (Cronbach’s alpha). This supports the robustness of the MSNQ as a cognitive measure. Our sensitivity and specificity results, however, suggest that there is a drawback to the internet administration route. Studies that have compared internet to paper-and-pencil versions of questionnaires have consistently reported that the internet is a valid means of collecting data. This, however, is in the context of questionnaires relating to personality (Buchanan & Smith, 1999), depression (Lin et al., 2007), including a 7-item version of the CES-D (Herrero & Meneses, 2006), and anxiety disorders (Farvolden et al., 2003). No studies have looked at self-report measures of cognitive functioning. One trend that has been noted is that the internet results in greater self-disclosure. For example, patients report higher self-reported rumination, or responses related to feeling depressed over the internet (Davis, 1999). Increased self-disclosure over the internet may result in patients therefore reporting greater subjective cognitive failures as this study’s findings suggest.

Another issue related to internet administration is that patients may have corroborated with their informants in answering the questions, even though instructions were very clear that this should not take place. The use of a high stakes cognitive tests in unproctored situations, as in at home internet testing can lead to inflated scores compared to administration in proctored situations (e.g. Carstairs & Myors, 2009). This may reflect subjects not following instructions and asking others around them for assistance of even answers. Thus, there was no way of ensuring that patients and informants answered their questions independently.
It is also possible that patients were less attentive when completing the internet questionnaire as they could respond at their own leisure, perhaps taking a break between questions or being distracted by interruptions. There was large variability in the time subjects took to complete the MSNQ as shown in Figures 1 and 2. Of note, informants took significantly longer than patients to complete the same number of questions which does not fit with the typical picture of cognitive dysfunction in MS, namely one characterized by psychomotor slowing and delayed information processing speed. In the most extreme example of this, two informants had to be excluded as their response times exceeded 45 minutes, a situation not encountered with patients. The reasons why some informants possibly took breaks during completion of the questionnaires are not known. The degree to which they were properly engaged with the process, therefore may be in doubt, but this can only be indirectly inferred. Other considerations of internet administration include the different visual layout of the questionnaire compared to the paper version, especially on different computer screens, which may have influenced responses. Difficulty reading the computer screen may have also posed a problem for some patients, though the option of large font was incorporated into the website for patients and informants to choose. Patient’s visual acuity was also tested when they completed the neuropsychological testing.

An interesting finding from this study was the negative correlation between MSNQ scores and physical disability as measured by the EDSS. This is a surprising finding given that greater disease severity is generally associated with more impaired cognition (Heaton et al., 1985; Huijbregts et al., 2004; Patti et al., 2009). There may be two explanations for this. First, patients in the early stages of the disease may be hypersensitive to their disease in general, misperceive cognitive deficits and report them. This was found in a study by Marrie and colleagues (2005) where patients with changes in cognition, not severe enough to meet criteria for impairment, reported many subjective difficulties. Second, patients with more severe disease (i.e. higher EDSS) may have reduced awareness and insight and thus see themselves as less cognitively impaired than they actually are. This has consistently been described in the metacognition literature (see section 2.10, Beatty & Monson., 1991; Marrie et al., 2005). In a study of the MSNQ (Carone et al., 2005), patients who overestimated their cognitive ability were characterized by greater cognitive impairment and euphoric behavioural disinhibition, both indicative of more severe disease.

Comment on reversing of test order
Higher correlations between the online MSNQ and cognitive test performance were found in patients who were given the online MSNQ before (n=82) versus after (n=42) the cognitive testing. It is important to note that these two groups did not differ on any demographic or disease-related variables, nor on cognitive test performance (see Table 10). There may be a couple of reasons for these interesting results. First, many patients find neuropsychological testing to be difficult and may have been discouraged after having performed worse than expected. This may have led them to become more noticeable of cognitive difficulties in everyday life and subsequently give themselves higher MSNQ ratings. The poorer correlations suggest that these ratings were more inaccurate, with perhaps more false positive errors. Of note, however, is that MSNQ scores did not differ between the two groups making this explanation difficult. In addition, this may have influenced patient ratings on the MSNQ but should not have influenced the accuracy of the informant ratings. Having made this point, it is possible that some patients do in fact speak to their family members and friends (i.e. the informants) about how they thought they performed in turn influencing informants’ perceptions.

**Limitation of study**

A limitation of this study was that patients who first completed the MSNQ were not asked to repeat the test when they came in for neuropsychological testing. A comparison of these two results would in theory have allowed the influence of test site (home versus office) to be compared. Such an approach, however, has its own drawback. Recall bias, or remembering previous responses, could have influenced the results of the repeat MSNQ. These same arguments both for and against, apply to the informant ratings as well.

**Conclusions**

In conclusion, internet administration of the MSNQ is not a valid means of screening for cognitive impairment in MS. Though the I-MSNQ demonstrated significant correlations with cognitive test performance, a sensitivity of 70% and specificity of 66% does not warrant its widespread clinical use over the internet. What this study demonstrated is the important role of depression in influencing patient’s cognitive complaints and the poor correlation between these
complaints and objective neuropsychological testing. This has consistently been demonstrated in the literature to date (reviewed in section 2.10).

This study also demonstrated that administration of a previously established questionnaire at home over the internet may not yield the same results as a traditional paper-and-pencil version administered in a doctor’s office. That is, the two versions are not necessarily equivalent. It is likely that the internet introduces potential confounds (e.g. distracters, failure to follow instructions, etc.) that negatively influence the accuracy of self-report measures. The likelihood of these same confounders affecting a different set of internet-based tests, i.e. formal neuropsychological indices (e.g. Younes et al., 2007) remains high and suggests that if internet testing is to achieve greater validity it will need to be more structured and supervised. From the resource issues identified earlier this will continue to present a challenge. Given the central role played by the internet in contemporary society future efforts in this area can be expected.
References


131. Marrie RA. Overview of MS for the non-clinician. Presented at the World Congress on Treatment and Research in Multiple Sclerosis. 2007.


