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Cognitive Functioning in Multiple Sclerosis: An Investigation of the Utility of a Computerized Cognitive Testing System

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ABSTRACT

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The primary objective of this study was to assess cognitive functioning in participants with relapsing remitting multiple sclerosis (RRMS) using the MicroCog and to compare their performance to that of a demographically matched, healthy control group. It was hypothesized that as a group, participants with RRMS would have worse cognitive function than healthy controls on all Level 1, 2, and 3 Index scores of the MicroCog. Twenty-six participants with RRMS and twenty-nine sex and education matched healthy controls were administered the MicroCog (Standard Form) along with measures of depression and clinical status, and paper-pencil tests of processing speed (Symbol Digit Modalities Test; SDMT and Paced Auditory Serial Addition Test; PASAT). A series of ANCOVAs with depression as a covariate was performed to determine between group differences for each MicroCog Level 3 Index score (General Cognitive Proficiency (GCP) and General Cognitive Functioning (GCF)), Level 2 Index score (Information Processing Accuracy (IPA) and Information Processing Speed (IPS)), and Level 1 Index score (Attention/Mental Control, Memory, Reasoning/Calculation, Spatial Processing, and Reaction Time). Pearson's and point biserial *r* correlations were calculated in order to assess the degree to which Level 2 and 3 Index scores correlated with clinical and demographic factors (sex, disease duration, depression, and clinical status) and to correlate the MicroCog IPS index score with traditional measures of processing speed. Eight RRMS and two control participants met criteria for cognitive impairment on the MicroCog. ANCOVA results indicated there were significant differences between RRMS and control performance for two MicroCog scores (GCF and IPS). There were not significant differences for GCP, IPS, and all Level 1 scores. A post-hoc analysis performed for the same hypothesis with a group of age equivalent participants suggested a significant RRMS by depression interaction for Level 3 scores. RRMS was not predictive of Level 2 scores after controlling for depression in the age equivalent sample. Correlations for clinical and demographic factors with cognitive outcomes indicated significant relationships for clinical status and depression. There was not a significant relationship detected for disease duration or sex. MicroCog and processing speed measures were significantly related. Post-hoc analyses supported that the criterion validity of the MicroCog is comparable to other cognitive screening tools in RRMS. The results and limitations of our study are discussed, in addition to recommendations for future research.

Keywords: multiple sclerosis, cognitive impairment, computerized cognitive assessment

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Multiple Sclerosis (MS) is the most common non-traumatic neurological illness that affects young and middle-aged adults (Joy & Johnston, 2001; Rao, 1990; Rejdak, Jackson, & Giovannoni, 2010). The worldwide prevalence rate of MS is estimated to be approximately two million, with 300,000 to 350,000 individuals with MS in the United States (Fox, Bethoux, Goldman, & Cohen, 2006; Joy & Johnston, 2001; Kalb & Reitman, 2010; Noonan et al., 2010). Due to the debilitating nature of MS and its onset early in adulthood, the costs associated with MS and its treatment is high. A 1998 study estimated the national annual cost of MS in the United States as 6.8 billion dollars, with a total lifetime cost of $2.2 million per individual with MS (Whetten-Goldstein, Sloan, Goldstein, & Kulas, 1998). More recent estimates from the National Multiple Sclerosis Society estimated that health-care costs average nearly $70,000 a year per individual with MS (Krishnan, 2007).

Over the past several decades, research has described the cognitive deficits associated with MS. It is estimated that 40 to 65% of individuals with MS experience some form of cognitive impairment during the course of the disease (Rao, 1995; Amato, Zipoli, & Portaccio, 2006; Rao, Leo, Bernardin, & Unverzagt, 1991). Cognitive deficits can have detrimental impact on an physical health, as well as social, occupational, and psychological functioning in individuals with MS (Amato, Ponziani, Siracusa, & Sorbi, 2001; Glanz et al., 2010; Rao, 2004b; Rao, 1991b; Shevil & Finlayson, 2006). The purpose of this investigation is to explore the utility of the MicroCog, a computerized cognitive testing system in assessing cognitive function in MS populations.

Multiple Sclerosis

Multiple sclerosis is a chronic degenerative disorder of the central nervous system. Multiple sclerosis is an inflammatory demyelinating disease, distinguished by widespread white matter lesions throughout the brain and spinal cord that interrupt the conduction of nerve impulses and lead to reversible and irreversible neurologic morbidity. Some forms of MS are restricted to axonal dyemyelination, while others (particularly the more chronic, progressive forms) are linked to axonal damage, axonal degeneration and neuronal death (Fox et al., 2006; Goodin et al., 2002; Joy & Johnston, 2001; Rao, 1990). Lesions can occur in any white matter region of the central nervous system and commonly occur in the optic nerves, periventricular region, corpus callosum, brain stem white matter, cerebellum, and spinal cord (Lezak, Howieson, Bigler, & Tranel, 2012). Symptoms of MS include coordination abnormalities, visual difficulties, bladder dysfunction, bowel symptoms, sexual dysfunction, cognitive impairments, and fatigue. Patients experience various levels of disability, with some individuals being able to function normally for the majority of their illness while others progress rapidly towards severe disability (Joy & Johnston, 2001).

The symptoms of MS are heterogeneous, making diagnosis difficult. There is no specific laboratory test for MS and diagnosis is based on patient history, neurologic examination, and other clinical tests, such as evoked potentials or MRI of the brain and spine (Fox et al., 2006; Joy & Johnston, 2001; Rao, 1990). Onset of MS typically occurs between the ages of 15 to 50 years, with the mean age of onset around 30 years (Rao, 1990). A particularly devastating aspect of MS is its tendency to present with little or no warning (the first symptoms are typically quite mild) as individuals are beginning to establish their family and careers. Life expectancy is reduced by approximately 10-15 years with around half of patients living 30 years or more after disease

diagnosis. Multiple sclerosis is more common in women (about two-thirds of those diagnosed), in individuals from a North European heritage, and in individuals who live in high latitudes during childhood (Joy & Johnston, 2001).

The clinical course of MS is variable and is characterized by relapses or flare-ups (episodic acute periods of worsening or inflammation), gradual progressive deterioration of neurologic function, or combinations of both. Four clinical courses or types of MS have been described based on disease course, including: relapsing-remitting, secondary progressive, primary–progressive and progressive-relapsing. Relapsing-remitting MS (RRMS) occurs in about 85% of patents and is defined as "clearly defined disease relapses with full recovery or with sequelae and residual deficits upon recovery" (Fox et al., 2006; Lublin & Reingold, 1996). During relapses, acute symptoms will develop over several days, typically become most severe after 1 to 2 weeks, and then gradually resolve. After 10-20 years into the RRMS course, the disease typically progresses and develops into secondary progressive MS. In secondary progressive MS, neurological symptoms gradually worsen and patients experience occasional relapses, minor remissions, and plateaus. Many patients with RRMS transition into secondary progressive MS later in the disease course. A third clinical course is primary-progressive MS which is defined as "disease progression from onset with occasional plateaus and temporary minor improvements allowed" (Lublin & Reingold, 1996). About 15% of patients present with primary progressive MS, which is characterized by gradual worsening of neurological symptoms (Fox et al., 2006). Finally, progressive-relapsing MS and is a "progressive disease, with clear acute relapses, with or without full recovery with periods between relapses characterized by continuing progression" (Lublin & Reingold, 1996). Progressive-relapsing MS occurs in about 5% of patients (Fox et al., 2006).

Currently there is no cure for MS, but there is increased optimism for new treatments as research advances have begun to elucidate the underlying mechanisms of the disease. Treatment is aimed at slowing the progression of pathology and emphasis is placed on early detection and intervention to maximize treatment effects. Managing the disease can be quite complex depending on the needs and symptoms of the individual patient, but typically involves the use of disease modifying agents (immunomodulating medications), treatment of acute exacerbations with corticosteroids, medications used to treat the various symptoms of MS (e.g. fatigue, depression, etc.), physical and occupational rehabilitation, and psychosocial support (Fox et al., 2006; Kalb & Reitman, 2010; Rao, 1990).

Cognitive Impairments in Multiple Sclerosis

Cognitive impairment as a common feature of multiple sclerosis (Prakash, Snook, Lewis, Motl, & Kramer, 2008; Rao et al., 1991c) and can adversely affect the individual's ability to function normally in their daily life. Participants with MS who were cognitively intact were compared to those with cognitive impairment, and individuals with cognitive impairment were less likely to be employed, engaged in fewer leisure and social activities, were more likely to have psychiatric disorders (e.g. depression, anxiety), and have greater difficulty performing household tasks (Rao, 1991b). Cognitive impairment has significant negative impact on driving performance even in MS participants with minimal to no physical impairment (Schultheis, Garay, Millis, & DeLuca, 2002). Cognitive impairment can occur regardless of MS type and can occur in early stages of the disease, even before full criteria for MS is met (Achiron & Barak, 2003; Camp et al., 1999; De Sonneville et al., 2001; Deloire et al., 2011; Deloire et al., 2005; Foley, Benedict, Gromisch, & DeLuca, 2012; Glantz et al., 2010; Huijbregts, Kalkers, de Sonneville, de Groot, & Polman, 2006; Rao, 1991c)). There is evidence for unique cognitive

deficit profiles depending on MS course type. Patients with progressive forms of MS have significantly worse cognitive function than patients with RRMS for memory, working memory, and attention (Huijbregts et al., 2006).

Specific cognitive deficits can vary between patients in regards to type and severity (Lezak et al., 2012). A number of cognitive domains have been found to be impaired in cross-sectional and longitudinal studies, including attention, memory, processing speed, executive function, and language.

Cognitive impairments may vary over time depending on disease course. For example, a longitudinal study investigated the progression of cognitive impairment (at intervals of four and ten years) in 50 MS participants compared to 70 healthy controls matched for sex, age, and education level (Amato et al., 2001). The number of participants who had cognitive impairments (i.e., MS participants whose scores fell below the fifth percentile of the study's control group) increased over time. Thirteen out of 50 MS participants had impairments on three or more subtests at year one and 25 participants had impairments three or more subtests at year ten. Across the study period the cognitive deficits were most common for verbal memory and abstract reasoning. Compared to four years, after ten years the type of deficits expanded to include impairments in linguistic functioning, attention, and short term memory (Amato et al., 2001). A second longitudinal study compared 22 RRMS participants' neuropsychological performance at year one to their performance approximately 18-years later (Strober, Rao, Jar-Chi, Fischer, & Rudick, 2014). Nine participants (41%) were cognitively impaired (i.e., had two or more test scores that fell 1.5 standard deviations or more below the normative mean) at study entry. The number of participants with cognitive impairment increased to 13 (59%) at 18-year follow-up, an approximately 44% increase. At study entry, information processing speed, word

list learning, and memory were impaired and continued to deteriorate over time. Attention, working memory, and visuospatial abilities also were impaired at 18-year follow up.

Neuroradiological and pathological studies help elucidate some of the anatomical correlates and patterns in cognitive impairment in MS. A review of MRI studies by DeLuca, Yates, Beale, and Morrow (2015) found a relationship between cognitive impairment and T_2 white matter lesion volume. No significant relationship between white matter lesion distribution and cognitive impairment has been consistently identified. The exception is the corpus callosum, where MS participants with a higher lesion volume in the corpus callosum are more likely to be cognitively impaired. Both white matter and gray matter damage have been implicated in MS pathogenesis, and damage to the hippocampus, thalamus, nucleus accumbens, and basal ganglia are thought to play a role in cognitive impairment. Deluca et al. postulated that, based on results of post-mortem studies, damage along white matter tracts that connect areas of cortical and deep gray matter structures may be the best way to illustrate cognitive impairment in MS (i.e., white matter and gray matter forming circuits that are involved in a specific type of cognitive functioning, such as memory formation). Detailed information regarding specific domains of cognitive impairments is below.

Memory. A 2008 meta-analysis found memory impairments were the most frequent cognitive impairment in MS participants (Prakash et al., 2008). Immediate verbal memory is the most extensively studied domain of impairment with an effect size of $g=-0.59$ ($p<.05$) based on 75 studies. The second most studied domain is verbal delayed recall memory with an effect size $g=-0.77$ ($p<.05$) based on 44 studies. Visual immediate and delayed recall and verbal recognition memory deficits were also prominent. There are efforts to delineate whether deficits in memory are more likely due to poor initial learning as opposed to retrieval deficits, and there is evidence

emerging for the former argument (DeLuca, Leavitt, Chiaravalloti, & Wylie, 2013; Lafosse, Mitchell, Corboy, & Filley, 2013). Brissart, Morele, Baumann, & Debouverie (2012) used scores of verbal episodic memory tests for 426 participants with MS and found a high prevalence of memory impairment in MS. A pattern emerged where deficits in information retrieval were more common in the early stages of MS and then there was an increase in memory deficits as the disease progresses.

Several studies have found MS participants perform significantly worse than healthy controls for working memory. A meta-analysis found working memory impairment (effect size $g=0.51$, $p<.05$) based on 85 studies (Prakash et al., 2008). Participants with MS performed worse on more challenging working memory tests (e.g. PASAT, Digit Span Backward) rather than simple tests of working memory (e.g. Digit Span Forward). The PASAT is one of the most specific (Rao et al., 1991c) and widely used measures of working memory used in MS populations (Fischer, Rudick, Cutter, & Reingold, 1999). One study of 215 participants with MS found slow processing speed was more common than deficits in working memory (DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004).

Attention. Like other domains, the severity of impairment in attention is heterogeneous across studies (McCarthy, Beaumont, Thompson, & Peacock, 2005; Paul, Beatty, Schneider, Blanco, & Hames, 1998). Studies also vary in their definition of types of attention studied (e.g. controlled, simple, focused, divided, etc.). It appears that MS participants have impairments in divided attention and alternating attention (Chiaravalloti & DeLuca, 2008; Lezak et al., 2012; Rao et al., 1991c) whereas simple attention is more likely to remain intact. Prakash et al. (2008) found impaired sustained and selective focused attention in MS participants.

Processing speed. Many individuals with MS report feeling mentally slow and have difficulty thinking quickly or keeping up with the pace of normal conversation (Lezak et al., 2012). Information processing and response time deficits are consistently reported deficits in MS populations (Covey, Zivadinov, Shucard, & Shucard, 2011; Jennekens-Schinkel, Sanders, Lanser, & Van der Velde, 1988; McCarthy et al., 2005; Paul et al., 1998). Studies have found information processing speed is slower early in the disease course, while working memory deficits increase as the disease progresses to SPMS (Archibald & Fisk, 2000; DeLuca et al., 2004). Some authors have argued that processing speed deficits might account for performance deficits in other cognitive domains (e.g., executive functioning) (Chiaravalloti, Stojanovic-Radic, & DeLuca, 2013; Owens, Denney, & Lynch, 2013).

Executive function. Executive functioning deficits are commonly identified in participants in MS (Chiaravalloti & DeLuca, 2008; Lezak et al., 2012; Rao, 2004a), but, like other cognitive domains, there is inconsistency in assessment tools and operational definitions of executive dysfunction making across study comparisons difficult (Denney, Hughes, Owens, & Lynch, 2012). Drew, Tippett, Starkey, & Isler (2008) assessed executive function in 95 MS participants using the Delis-Kaplan Executive Function System (DKEFS). The majority of MS participants (63%) scored more than one standard deviation below the mean on at least one measure. Sixteen of the participants had widespread difficulties in executive function however, there was little consistency in which type executive function (e.g. reasoning, decision making, inhibition of responses) was impaired. Impairments also occur on timed tasks of executive function (e.g., Stroop Test) suggesting that response time might, at least in part, may contribute to the observed impairments in executive function (Macniven et al., 2008). Prakash et al., also

found impaired executive functioning in MS participants (effect size g=0.51, p<.05) based on 29 studies (2008).

Language. Lezak et al. (2012) noted that language abilities typically remain unaffected in MS participants except when rapid and efficient retrieval is needed, such as in verbal fluency tasks. Tests of verbal fluency, comprehension, verbal expression, and verbal discourse (g=-0.28, p<.05) are often impaired (Prakash et. al, 2008). Other studies find impairments in naming and verbal and category fluency (Friend et al., 1999).

Visuospatial. Few studies assess visuospatial impairments in MS. Prakash et al. (2008) found MS groups were more impaired for visuoconstruction compared to controls. Similarly, Rao et al. (1991c) found that MS participants performed significantly worse than controls on tests of visual-spatial function (i.e., Benton Judgment of Line Orientation and Facial Recognition).

Clinical Correlates of Cognitive Status in Multiple Sclerosis

Efforts to develop methods to predict, measure, and track change over time in cognitive impairments in MS have focused on the relationships between cognitive deficits with demographic or disease characteristics. There are inconsistencies in literature concerning the association between cognitive impairment and clinical or demographic variables, including longer disease duration, older age, physical disability, fatigue, sex, and education (Achiron & Barak, 2003; Achiron et al., 2005; Amato et al., 2001; Bagert, Camplair, & Bourdette, 2002; Brassington & Marsh, 1998; Chiaravalloti & DeLuca, 2008; Glanz et al., 2007; Johnson, Gudrun, DeLuca, Leo, & Benjamin, 1997; Krupp & Elkins, 2000; Lynch, Parmenter, & Denney, 2005; Prakash et al., 2008; Rao et al., 1991c; Reuter et al., 2010; Thornton & Raz, 1997; Zakzanis, 2000). To illustrate, review of four large studies of correlates of cognitive impairment

in MS (Rao et al., 1991c, Amato et al., 2001, Prakash et al., 2008; Borghl et al., 2013) indicated mixed results when assessing the relationship between demographic (e.g. age, female sex) and clinical variables (e.g. longer disease duration, physical disability) with cognitive impairments. Rao et al., found that physical disability (weakly) predicted cognitive impairment, whereas longer disease duration and MS course did not predict cognitive impairment. Amato et al. found that older age, physical disability, and a progressive disease course correlated with severity of cognitive decline over time. Prakash et al., found that participants over 40 years old were more likely to have cognitive impairments compared to younger individuals and studies that included only females found higher rates of cognitive impairment compared to studies that enrolled both males and females. Further there was no effect for physical disability or disease course, however these effects may be domain specific such that clinical factors only predict performance on some measures such as learning and memory. Borghl et al. (2013) identified factors associated with cognitive impairment in a large sample of participants with RRMS (n=267) compared to healthy controls (n=279). Results indicated that female sex, lower education, anxiety, and lower intelligence were not predictive of cognitive impairment. When controlling for covariance between these factors, the final model found longer duration of illness, physical disability, and a lower vocabulary scale predicted cognitive impairment.

A covariate not discussed above that has received increased attention in research focused on cognition in MS is depression. Depression is common in patients with MS (Lezak et al., 2012) and is associated with impaired working memory, processing speed, memory, abstract reasoning, and executive functioning (Chiaravalloti & DeLuca, 2008). A recent review of the effects of depression (Feinstein, Magalhaes, Richard, Audet, & Moore, 2014) found a higher prevalence of depression in MS relative to the general population. Participants with severe

depression were found to have greater difficulties with working memory, executive functioning, and information processing speed than participants with fewer depression symptoms. Also, structural brain changes in MS have been associated with depression symptoms (in addition to genetic, immunological, and psychosocial factors of MS). For example, atrophy in areas like the dominant anterior temporal areas and dominant medial inferior frontal regions have been associated with worse depression in MS. Feinstein et al. describe that diffusion tensor imaging studies found lower fractional anisotropy in normal appearing white matter and higher mean diffusivity in normal appearing gray matter in these same areas for participants with more severe depression. Other studies found abnormalities in pathways (i.e., ventrolateral prefrontal cortex and the amygdala) involved in mood regulation in MS participants with depression.

Summary of Cognitive Impairments

Participants with MS are more likely than healthy controls to have cognitive deficits in multiple cognitive domains (i.e. memory, attention, processing speed, executive functioning, visuospatial, and language). Participants with MS tend to perform worse than healthy controls for verbal recall and verbal immediate memory, as well as working memory and complex attention. Slow processing speed is also common and may affect performance on tests of executive function. The domains and severity of the cognitive impairment in MS are heterogeneous and vary widely between and within individual patients. Cognitive impairment can occur at any time during the course of MS, including in the very early stage of the disease. There are no consistent clinical and demographic factors found to be associated with cognitive function in MS but there is empirical support for female sex, age, education, physical disability, disease duration, course type, and depression as possible correlates.

Neuropsychology Assessment

Research has supported the importance of early recognition and subsequent monitoring of cognitive deficits in MS. Identification of cognitive deficits may allow for disease modifying medications to be introduced sooner so disease progression can be delayed and cognitive functioning preserved (Achiron & Barak, 2003; Bagert et al., 2002; Lensch et al., 2006; Patti et al., 2009). Certain disease modifying medications, such as interferon β-1a, may prevent physical and cognitive deterioration in individuals with RRMS (Fischer et al., 2000). Recent investigations have assessed the use of acetylcholinesterase inhibitors to target the prevention of cognitive decline in MS (Christodoulou, MacAllister, McLinskey, & Krupp, 2008; Krupp et al., 2011). Awareness of cognitive deficits might also aid in decision making surrounding psychosocial issues, such as driving, employment, and levels of independence, and approaches towards rehabilitation (Chiaravalloti & DeLuca, 2008; Lezak et al., 2012; Rao, 1991b; Schultheis et al., 2002).

Neuropsychological instruments are considered the gold standard for measuring a patient's cognitive functioning and change in cognition over time (Achiron & Barak, 2003; Calabrese, 2006; Joy & Johnston, 2001; Lensch et al., 2006; Patti et al., 2009; Rao, 1995; Rudick et al., 1996; Wallin, Wilken, & Kane, 2006). While a comprehensive neuropsychological examination of patients with MS would be ideal (Lezak et al., 2012), it is often unrealistic to refer each patient for a full battery of neuropsychological tests due to patient fatigue and financial costs. Therefore, there is a need for a brief, reliable cognitive instrument that could be used in outpatient settings to screen for and identify MS patients at risk for cognitive impairment (Foley et al., 2012; Lensch et al., 2006; Rao et al., 1991c). Cognitive impairments on such tests

may also be used to identify individuals in which comprehensive neuropsychological testing is warranted.

Current brief cognitive tests are available are predominantly in paper-pencil form and include the Brief Repeatable Battery of Neuropsychological Tests (BRB-N), the Mini Mental Status Exam (MMSE), and the Paced Auditory Serial Addition Test (PASAT). The BRB-N has good specificity in detecting cognitive impairments in MS participants (Scherer, 2007) and is a cost effective, widely used measure (Boringa, et al., 2001), but does not include normative data (Rao, 1991a). The PASAT is included as part of a widely used clinical outcome measure in MS, the Multiple Sclerosis Functional Composite (MSFC) task (Fischer, Jak, Kniker, Rudick, & Cutter, 2001). The PASAT has good specificity but has been criticized for its moderate sensitivity (Rogers & Panegyres, 2007; Scherer, 2007). The PASAT measures only processing speed and attention, and can result in significant frustration for individuals who take the test due to test difficulty (Tombaugh, 2006). Given that deficits in mental processing speed are common in MS, a measure of mental processing speed that does not frustrate patients is needed. Although convenient and cost efficient, the MMSE has low sensitivity in detecting cognitive impairment in MS (28-36%) and is not generally recommended as a screening tool in this population (Rao et al., 1991c; Rogers & Panegyres, 2007; Scherer, 2007). Although these instruments are useful to clinicians, there continues to be a need for a time and cost efficient tests that tap a wide variety of cognitive domains, has good psychometric properties, is easy to administer, and can be used to identify or screen for cognitive impairments in an outpatient setting (Foley et al., 2012).

Computerized cognitive assessment. The use of a computerized cognitive test is a seemingly ideal way to improve screening for cognitive impairment in MS. There are several advantages to computerized neuropsychological assessment compared to paper and pencil tests.

Computerized assessments allow for more accurate measurement of time-sensitive tasks. Administrators have the ability to integrate and automate interpretive algorithms (e.g. statistically reliable change) (Bauer, et al., 2012). Administration is standardized, and therefore administration error is reduced (Elwood, 2001). Other advantages include the ability to administer multiple tests simultaneously, speed of scoring, ease of data handling and analysis, and more precise quantification of reaction times (Powell et al., 2004). Few computerized cognitive batteries have been investigated in participants with MS (Lapshin, O'Connor, Lanctôt, & Feinstein, 2012).

MicroCog

The MicroCog is a computerized testing system that assesses neurocognitive functioning in adults. There are 18 subtests which are combined into summary scores for nine interrelated cognitive areas including Level 1 (Attention, Memory, Spatial Processing, Reasoning/Calculation, Reaction Time), Level 2 (Information Processing Accuracy, Information Processing Speed), and Level 3 (General Cognitive Functioning and General Cognitive Proficiency). Due to its ease of administration and evidence for its capability to detect a wide range of cognitive deficits in other clinical populations, it is a good candidate for use as a screening tool for cognitive impairment in MS (Powell et al., 2004). The MicroCog is one of the first commercially marketed computerized test batteries (Elwood, 2001) and used as a clinical tool and outcome measure with a variety of populations, including: adult participants with epilepsy, military veterans, cardiac surgery participants, physicians referred for competency evaluations, National Football League players, and United States Air Force pilots (Holliday & Costello, 1997; Korinek, Thompson, McRae, & Korinek, 2009; Willeumier, Taylor, & Amen, 2012). In a 2008 review of computerized cognitive batteries for detecting cognitive changes in

older adults, compared to other computerized cognitive tests the MicroCog had equal to or better normative data, comprehensiveness of cognitive domains covered/depth of coverage within domains, reliability, and validity (Wild, Howieson, Webbe, Seelye, & Kaye, 2008). The MicroCog is a particularly well suited computerized assessment battery to be used in patients with MS. A particular strength of the MicroCog is the test's focus on and precise measurement of processing speed, a common symptom in many forms of neuropathological disease processes including MS (Lezak et al., 2012). This focus gives incremental utility to the MicroCog over paper-and-pencil neuropsychological tests and other computerized assessment batteries where accuracy is the sole focus, and allows more detailed interpretations of performance deficits. For example, interpretation guidelines for the MicroCog indicate that the Alphabet subtest, a test that follows a continuous-performance paradigm, helps the examiner to determine whether impaired performance is indicative of impaired information processing speed as opposed to impulsivity. Global scores of processing speed and accuracy allow evaluators to determine a patient's overall, across subtest, performance pattern (e.g. slow and accurate versus fast and inaccurate) and whether the differences between the scores are statistically significantly relative to the normative population. Given these features of the MicroCog, it is a promising candidate for use with patients with MS.

The MicroCog is used as a screening test or a diagnostic tool as part of a general neurological examination. There are two forms of the MicroCog available, a long form which takes about one hour to administer and consists of 18 subtests, and a short form which takes about 30 minutes to administer and contains 12 subtests. The MicroCog can be administered on almost any laptop or desk top computer (PsychCorp, 2012). The test is designed to assess normal and neurologically impaired or elderly individuals as it allows for breaks during test

administration and uses minimal keys on the computer (limited to the numeric keypad (0-9), "Backspace" and "Enter" keys, and the letter "P") (Powell et al., 2004).

MicroCog scoring and interpretation. Figure 1 gives a description of the scores and interpretation derived from the MicroCog. At the most basic level are the individual subtest scores. The individual scores provided by each subtest are variable, and yield age and education adjusted scores. These individual subtest scores are computed and are converted to scaled scores (M=10, SD±3) with higher scores corresponding with better performance. Percentile ranks, qualitative descriptions (i.e. Below Average-Above Average), and 95% confidence intervals are also provided. Along with scores from individual subtest scores are three higher levels of score interpretation. Level 1 includes scores for five cognitive domains including: Attention/Mental Control, Memory, Reasoning/Calculation, Spatial Processing, and Reaction Time. Table 1 displays the various subtests within each of these cognitive domains.

Level 2 provides scores for overall information processing speed (IPS) and information processing accuracy (IPA). Level 3 provides Global Cognitive Function (GCF) and Global Cognitive Proficiency (GCP) scores. For Levels 1-3, the sums of corresponding subtest standards scores are converted to a scale with a mean of 100 and standard deviation of 15, with higher scores indicative of better performance.

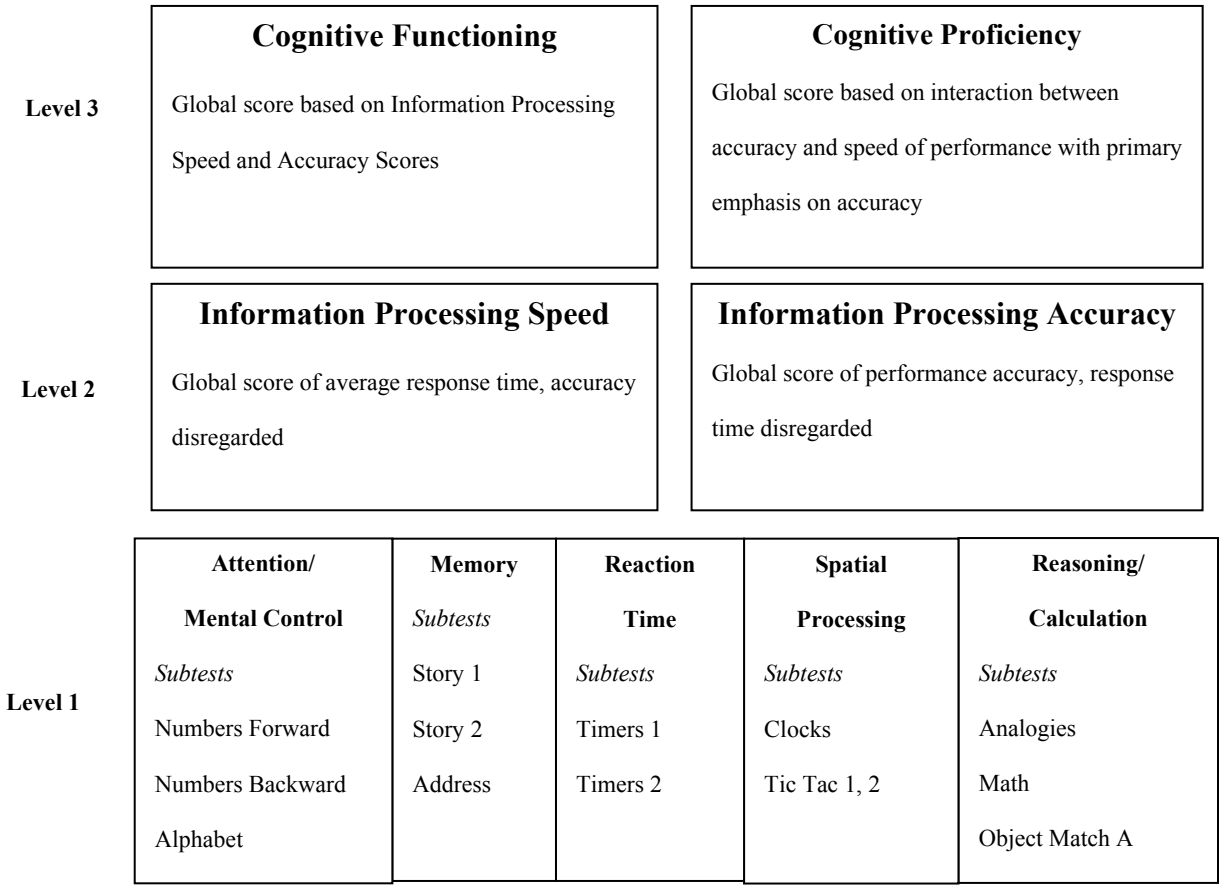

Figure 1. Levels of MicroCog index scores.

MicroCog psychometrics. The MicroCog was normed on a sample of adults aged 18-89 years that was representative of the US population (based on the 1988 census) in terms of age, race, and education. The sample contained 810 adults, 90 for each age grouping. The MicroCog has virtually no ceiling effects and thus can be used to test a wide range of individuals, including highly educated individuals (Elwood, 2001). The MicroCog subtests (Table 1) compare favorably with comprehensive neuropsychological test batteries (Elwood, 2001).

Table 1

MicroCog Level 1 Index scores and descriptions

MicroCog Index	Subtests	Description of task
Attention/ Mental Control	Numbers Forward	Based off Digit Span Forward paradigm, simple attention
	Numbers Reversed	Based off Digit Span Backward paradigm, mental control/working memory
	Alphabet	Adapted from continuous performance paradigm, sustained focused attention with letters
	Wordlist 1	Adapted from continuous performance paradigm, sustained focused attention with words
	Wordlist 2	Incidental learning of words from Wordlist 1
Memory	Story 1 and 2	Verbal memory, immediate and delayed recall
	Address	
Reasoning/ Calculation	Analogies	Modeled after Millers Analogies Test; inductive reasoning
	Object Match	Modeled after Visual Verbal Test; Concept formation and cognitive flexibility
	Math Calculations	Mental calculations; Basic arithmetic operations; modeled from WAIS-III Arithmetic subtest
Spatial Processing	Tic Tac Subtest	Short term recall of location of stimuli on a gridlike matrix
	Clocks	Visuoperceptual analysis of clock faces
Reaction Time	Timers 1 and 2	Simple reaction time in auditory and visual modalities; time elapsing between stimuli and response

Reliability of the MicroCog. Table 2 provides a summary of the reliability of the MicroCog by level of interpretation (subtests and Levels 1-3) for the normative age group of 18 to 44 years. There is limited research on the reliability and validity of the MicroCog in clinical populations.

Table 2

MicroCog Reliability Summary

Reliability Coefficients [a,1]	SE_M [1]	Decision Consistency Reliability [b,1]
Average reliability coefficient	Average SE_M	Average Stability Coefficient
Subtest (total score): 0.74	Subtest (total score): 1.47	Subtest (total score): 0.84
Level 1: 0.87	Level 1: 5.29	Level 1: 0.85
Level 2: 0.93	Level 2: 3.79	Level 2: 0.86
Level 3: 0.95	Level 3: 3.35	Level 3: 0.91
Reliability Coefficient Range:	SE_M Range:	Stability Coefficient Range
Subtest (total score): 0.58-0.98	Subtest (total score): 0.42-1.94	Subtest (total score): 0.73-0.96
Level 1: 0.83-0.94	Level 1: 3.67-6.18	Level 1: 0.73-0.96
Level 2: 0.92-0.95	Level 2: 3.35-4.24	Level 2: 0.78-0.94
Level 3: 0.95-0.95	Level 3: 335-3.35	Level 3: 0.90-0.92

Note. a = single administration, split half internal consistency; b= test-retest stability, consistency of classification from test to retest, ages 18-44 only; c=intercorrelations of the subtests and index scores; 1=MicroCog Manual. SE_M = standard error of measurement; Subtest scores included total scores for Numbers Forward, Numbers Reversed, Alphabet, Wordlist 1&2, Story 1&2 Immediate & Delayed Recall, Clocks, Tic Tac, Analogies, Math, Object Match A&B; Level 1 Index includes Attention/Mental Control, Memory, Spatial Processing, Reasoning/Calculation, Reaction Time; Level 2 Index includes Information Processing Speed & Information Processing Accuracy; Level 3 Index includes General Cognitive Proficiency & General Cognitive Functioning.

Table 2 shows the split half internal consistency reliability coefficients for most tests except those where this was not possible due to presentation format and/or task requirements. The average subtest reliability coefficients range from 0.58 to 0.98, with a mean of 0.76. Average reliability coefficients for index total score and response time ranged from 0.78 to 0.95 (Powell et al., 2004).

Test-retest reliability was measured by testing participants twice (Time 2 at seven months) and finding how consistently the participants were classified as Below average, Low Average, Average, and Above Average at both the subtest and index score levels. The agreement from test to retest were very stable and showed little practice effects (Powell et al., 2004). In 2006, Raymond et. al published reliable changes indices and regression based equations to allow for administrators to account for practice effects when tests are repeated at two weeks and three months in healthy individuals over the age of 50.

Validity of the MicroCog. Data from validity studies of subtest and Level 1 index scores support the validity of the MicroCog. For example, Memory subtests correlated at 0.66. Validity for Level 2 Index scores are as follows: For Information Processing Accuracy, of the 10 subtests total scores that could be analyzed, 9 factor loadings were above 0.50. For Information Processing Speed, of the 8 subtest response times in the analysis, 7 factor loadings were above 0.50. Another factor analytic study of the MicroCog in a sample of participants suffering from substance abuse confirmed a two factor model of the MicroCog the authors identified as the Information Processing Accuracy and Information Processing Speed scores (Level 2 Indices) (Lopez, Sumerall, & Ryan, 2002). For both factors, factor loadings from the corresponding subtest scores were 0.50 or above for 16 out of the 20 subtests.

Criterion validity studies provide evidence for how well the MicroCog accurately classifies participants as a healthy control or as a member of their respective clinical group. The MicroCog developers and Elwood (2001) summarized a series of studies comparing the performance of clinical groups to nonclinical groups. Clinical groups included dementia (diagnosed as probable Alzheimer's, or multiinfarct or vascular dementia), lobectomy, lupus, schizophrenia, mixed psychiatric/neurologic groups. Altogether, using Level 1 Index scores as discriminant variables, the correct classification rates for clinical groups (besides Major Depression) ranged from 65% (lupus) to 92% (dementia). One such study (Green, Green, Harrison, & Kutner, 1994) included 52 patients with mild cognitive impairment (47 diagnosed with probable Alzheimer's disease and five diagnosed with multi-infarct or vascular dementia). The mean scores for all index scores of the non-impaired controls were in the Average range. The mean scores for the clinical group ranged from 70.7 to 84.9 (one to two deviations from the normative mean). The authors calculated that with a 10% prevalence rate of dementia, the sensitivity and specificity would yield a PPP of .70 and an NPP of .98. In a study of Gulf War veterans, the MicroCog correctly classified 27 out of 31 veterans with mild to no cognitive impairment based on standardized neuropsychological tests (Holliday & Costello, 1997).

There is good convergent validity for the MicroCog. For example, for Level 1 Index scores, the Attention/Mental Control Index score correlated with the Wechsler Memory Scale-Revised Attention/Concentration Index (WMS-R-AC) at 0.57, the Memory Index score correlated with the WMS-R-Delayed Recall at 0.46, the Reasoning/Calculation Index Score correlated with the Shipley Institute of Living Scale Abstraction T-Score at 0.56, and Spatial Processing correlated with Dementia Rating Scale-Construction subtest at 0.37. The IPA Index score correlated at 0.54 with the Full Scale Intelligence Quotient of the Wechsler Adult

Intelligence Scale-Revised (WAIS-R). The IPS correlated with the Performance Intelligence Quotient of the Wechsler Adult Intelligence Scale-Revised at 0.31. Other authors have found similar findings in studies with older adults (Green et al., 1994; Helmes & Miller, 2006; Johnson & Rust, 2003) and individuals with brain injuries (O'Keefe, 1997).

Study Objectives and Hypotheses

The MicroCog is a reliable, valid measure of cognitive functioning and has been used in a variety of patient populations. This, along with its ease of administration, makes the MicroCog a good candidate instrument for use as an outpatient screening tool for cognitive impairment, including mental processing speed, in participants with RRMS. There is no research that uses the MicroCog to assess cognitive function in RRMS populations.

Objectives

The primary objective of this study is to use the MicroCog to assess cognitive function in clinically definite RRMS sample compared to matched healthy controls.

Hypothesis 1

RRMS participants will have worse cognitive function compared to controls.

Primary Outcome: RRMS participants will have worse cognitive function compared to controls on all MicroCog Level 2 and 3 Index Scores.

Secondary Outcome: RRMS participants will have worse cognitive function on Level 1 Index scores compared to controls.

Hypothesis 2

Clinical variables (clinical status, symptoms of depression, disease duration) will be associated with worse cognitive performance on MicroCog Level 2 and 3 index scores. That is more impaired clinical status, higher severity of depression symptoms, and longer disease

duration will be associated with cognitive impairments. Sex will not be associated with worse cognitive performance on the MicroCog.

Hypothesis 3

The MicroCog Information Processing Speed (Level 2) Index score will be associated with a paper-and-pencil tests of processing speed commonly used in assessment of participants with RRMS, the Symbol Digit Modalities Test and the Paced Auditory Serial Addition Test.

Methods

Twenty-eight participants between the ages of 18-65 diagnosed with RRMS as defined by McDonald criteria (Polman, et al., 2011) were recruited and screened by a Board Certified Neurologist (John F. Foley, MD) from the Rocky Mountain Neurological MS Clinic in Salt Lake City, Utah. RRMS participant recruitment took place within the neurology clinic. Twenty-nine controls were recruited within the clinic (i.e. family members/friends of participants and researchers, office staff). Study inclusion criteria were diagnosis of RRMS, age 18 to 65 years, and English speaking. Study exclusion criteria included: non-English speaking, visual deficits, hearing deficits, dense dominant limb paralysis (that would interfere with test administration), history of drug or alcohol abuse, prior cognitive impairment or developmental disabilities (e.g., traumatic brain injury, stroke resulting in cognitive deficits, Parkinson's disease, Huntington's disease, Alzheimer's disease). Two of the 28 RRMS recruited were not included in the final analyses because after data collection it was confirmed through their medical chart that the participant had a medical or substance use condition that could confound results, including brain aneurysm and drug/ alcohol abuse with history of multiple concussions.

Demographic and Medical Variables

Demographic and medical history was collected and included sex, age, date of birth, and years of education. Medical history included comorbid medical disorders (cardiovascular disease, diabetes, etc.), medications, prior neurologic disease (e.g. traumatic brain injury), and radiology reports from prior magnetic resonance imaging (MRI) scans. Medical history specific to RRMS (including disease duration and type of MS) was also collected. Disease duration was defined as date of symptom onset to date of data collection. This was reported by the participant and also confirmed through their medical chart. In the event the participant's report was discrepant from their medical chart, the medical chart date was used. In the event no information on symptom onset was in their medical chart, the participant's report was used. Only the year of symptom onset was taken into account, not month or date.

Depression

This study utilized the Beck Depression Inventory–II (BDI-II; Beck, Steer, & Brown, 1996) as a measure of depression symptoms. This instrument consists of 21 statements describing somatic and cognitive-affective symptoms of depression. Scores range from 0 to 63 with higher scores reflecting more severe depressive symptoms. A review of the psychometric properties of the BDI revealed a mean coefficient alpha for internal consistency of 0.86 in psychiatric populations. The review also revealed high correlation coefficients with the Hamilton Rating Scale for Depression (HRSD) (r=0.72) and clinical ratings (r=0.73). One week test-retest reliability is high (r=0.93) (Beck, Steer, & Carbin, 1988). The BDI-II is the most commonly used depression scale in MS associated depression (Arnett et al., 2005). Sacco et al. (2016) indicated the BDI-II has good internal consistency and good convergent and divergent validity with MS patients.

Clinical Status Measure – Multiple Sclerosis Functional Composite

The National Multiple Sclerosis Society's Multiple Sclerosis Functional Composite (MSFC) task was used as a measure of clinical status (Fischer et al., 2001). The MSFC was developed as part of a task force as an outcome measure that has good correlation with biologically relevant clinical dimensions, good reliability, and an ability to show change over time (Cutter et al., 1999). The MSFC includes a the timed 25-foot walk (T25FW) to measure leg function, the timed nine-hole peg test (9HPT) to measure upper extremity function, and the 3-second version of the PASAT to measure neuropsychological function. The MFSC has high intrarater and interrater reliability (0.97 and 0.96 respectively over four administrations) with both RRMS and SPMS participants (Cohen, et al., 2000; Fischer et al., 1999). The MFSC correlates with quality of life measures including subtests of the Multiple Sclerosis Quality of Life Inventory (MSQLI) (Sickness Impact Profile (r=-0.62); Medical Outcomes Study 36-Item Short-Form Health Survey (r=0.41)) (Miller, Rudick, Cutter, Baier, & Fischer, 2000).

For the current study raw scores on the three component subtests were converted into z-scores based on the means of the healthy control group. The average of a participant's three z-scores is the participant's overall MSFC z-score.

Processing Speed

The Symbol Digit Modalities Test, a paper-pencil test of processing speed and attention, was administered (Smith, 1973). The SDMT presents a series of nine abstract symbols, each of which is paired with a single digit in a key at the top of a sheet of paper. The remainder of the paper has a pseudo-randomized sequence of the nine symbols and the subject is required to scan the key and respond with the digit associated with each symbol as quickly as possible. The outcome variable for the SDMT is the total number of items correct within 90 seconds.

Administration procedures were followed as put forth by the SDMT manual. Standard scores were derived based on the age and education corrected normative data in the SDMT manual.

The SDMT has test-retest correlations ranged from 0.82 to 0.95 when administered monthly over a five month period in a sample of participants with clinically definite MS and controls (Benedict et al., 2008). The SDMT has been found to correlate strongly with magnetic resonance imaging (MRI) measures of disease burden in MS (Benedict et al., 2004; Christodoulou et al., 2003).

Effort

In order to ensure that participants are trying their best on the cognitive tests, Reliable Digit Span (RDS) was used to assess effort (Greiffenstein, Baker, & Gola, 1994). RDS was calculated for each participant by summing the longest string of digits repeated without error over two trials for both forward and backward conditions on MicroCog subtests Numbers Forward and Numbers Backward subtests. An RDS of 7 or less qualified as possible poor effort (Lezak et al., 2012).

MicroCog

The MicroCog was administered on a desktop computer by the study investigator (S.M.). Standardized instructions were followed as put forth by the MicroCog manual. Participants were monitored during testing and behavioral observations (e.g. whether able to sustain attention to test without encouragement) were made during administration to aid in determining whether the MicroCog is well suited to be taken without ongoing assistance from the examiner. Participants were administered the 18 subtest standard form of the instrument, with an administration time of 60 minutes. The subtest descriptions are below.

MicroCog subtest descriptions. The subtests from the MicroCog standard form are shown below along with the description of each task (Powell et al., 2004).

1. Timers 1: Participants presses the Enter key in response to auditory signals, visual signals, and visual signals preceded by auditory signal (5 of each type of signal).
2. Address: On the screen a name and address are presented. Participants are told to memorize address for questions later on in the test.
3. Clocks: For each trial participants are shown a clock face with an hour and minute hand. The participant must choose from 5 digital choices which is the correct time on the stimulus clock.
4. Story 1-Immediate Recall: A story will be presented and participants must immediately recall the story as demonstrated by recognition of details of the story in 6 multiple choice questions.
5. Math: Eight math problems are answered using the numeric keypad and include addition, multiplication, and division problems. The participant may not use paper.
6. Tic Tac 1: A 3x3 block matrix is presented. Three to five blocks within the matrix contain a colored square. After the stimulus is removed from the screen, the participant must reproduce the pattern using the numeric keypad.
7. Analogies: The participant answers multiple choice questions on verbal analogies.
8. Numbers Forward: The participant is shown a series of single digits, up to 9 digits. After the digits are off the screen, the participant enters in the digits (in order) on the numeric keypad.
9. Story 2-Immediate Recall: Same description as Story 1 but with different content.

10. Wordlist 1: The participant is asked to press Enter when a word appears from an instructed category (e.g. Look for words that are items on clothing). There are four categories total.
11. Wordlist 2: The participant is asked to press Enter when a word appears that was from one of the four categories in Wordlist 1.
12. Numbers Reversed: The participant is shown a series of single digits, up to 9 digits. After the digits are off the screen, the participant enters in the digits (in reverse order) on the numeric keypad.
13. Address: The participant is asked to choose the name and address previously presented in the test.
14. Object Match: The participant is shown a set of four stimuli (figures) and asked to choose the number of the figure that does not match the other figures.
15. Story 1 Delayed Recall: The participant is asked multiple choice questions based on Story 1 content.
16. Alphabet: The participant is shown a series of letters. The subject is asked to pick out letters in alphabetical order by pressing Enter whenever the next letter in the alphabet appears.
17. Tic Tac 2: Same description as Tic Tac 1 with different stimuli.
18. Story 2 Delayed Recall: The participant is asked multiple choice questions based on Story 2 content.
19. Timers 2: Same description as Timers 1.

Statistics

Statistical analyses were conducted using IBM SPSS Statistics Version 23. Given the high number of planned statistical analyses and the low sample size, a Bonferroni correction was calculated. Alpha level p=0.001 was utilized for all results interpretation.

Descriptive statistics for demographic, medical, psychological, cognitive data (i.e. MicroCog scores) and physical function were conducted. Continuous data were analyzed using independent samples t-tests and categorical data were analyzed using Chi-square analysis.

Hypothesis 1 (Group differences in Level 1, 2, and 3 MicroCog performance)

Primary outcome: An analysis of covariance (ANCOVA) test was calculated to determine if there was significant difference between the RRMS and control group performances for all Level 2 and 3 MicroCog scores. Depression was included as a covariate in the analysis.

Secondary outcome: An analysis of covariance (ANCOVA) test was calculated to determine if there were significant performance differences between RRMS and control groups for all Level 1 MicroCog scores. Depression was a covariate in the analysis.

Hypotheses 2 (Covariates of MicroCog performance)

Pearson's correlation was calculated to assess the relationships between MicroCog scores (Level 2 and 3) clinical variables (MSFC score, disease duration, and depression). A point biserial r was be calculated to assess the relationship between MicroCog scores and sex.

Hypothesis 3 (Correlation between MicroCog and traditional processing speed measure)

Pearson's correlation was calculated to assess the relationships between SDMT and PASAT performance and MicroCog Information Processing Speed (IPS) index score.

Results

Demographic and Medical Variables

Descriptive statistics for demographic and clinical variables are reported in Table 3. For the RRMS group the mean age was 48.96 (SD=11.23) and the mean number of years of education was 14.65 (SD=2.76). Approximately 76% of the RRMS group was female. For the control group the mean age was 35.9 (SD=11.79), mean years of education was 16.07 (SD=2.2), and 72% of the sample were female. There were no differences between the RRMS and control groups for female sex (t(53)=-2.11, p=.04) or education ($\chi^2(1)=0.15$, p=0.70). There was a significant difference between RRMS and control group for age with the RRMS group being older (t(53)=4.19, p=0.00). Radiological findings for each RRMS participant are listed in Table 4. There were some participants whose most recent radiology study did not include discussion of white matter lesion distribution. In these cases (identified in the table) the research coordinator from Rocky Mountain Neurological MS Clinic reviewed the participant's prior radiology studies and provided a summary statement of the participant's distribution of white matter lesions. All brain imaging indicated some degree of white matter disease was present. Three participants with RRMS had generalized atrophy. Five participants had widespread white matter disease. Some imaging reports indicated white matter lesions in specific brain structures including periventricular white matter (*n*=8; specific areas included infratentorial and supratentorial regions, left hemisphere, frontal horn of the right and left lateral ventricle), corpus callosum or pericallosal areas (*n*=4; specific areas included left brachium pontes, and frontal, parietal, posterior temporal and occipital lobes), bilateral basal ganglia (*n*=1), brainstem and cerebellum (*n*=1), left subcortical frontal lobe (*n*=1), left temporo- or temporoparietal subcortical area (*n*=2), right anterior medulla (*n*=1), body of fornix (*n*=1), and optic nerve (*n*=1).

Table 3

Descriptive Statistics for demographic and clinical variables

	Mean; Standard Deviation			Sample Size and Percentage of Sample		
Descriptive	RRMS (*n*=26)	Ctl (*n*=29)	Significance testing		RRMS *n* (%)	Ctl *n* (%)
Age (mean ± SD)	48.96 ±11.23	35.9 ±11.79	t (53) = 4.19, p=.000*	18-29 years 30-39 40-49 50-59 60-65	1 (3.9%) 5 (19.2%) 6 (23.1%) 8 (30.1%) 6 (23.1%)	12 (41.4%) 7 (24.1%) 5 (17.2%) 3 (10.3%) 2 (6.9%)
Sex (Female) N, %	23.1, 76.9	27.6, 72.4	$\chi^2(1) = 0.16$, p=0.69			
Education (mean ± SD)	14.65 ± 2.76	16.07 ± 2.2	t(53) = -2.11, p=.04	<12 years 12 12-15 16 17+	1 (3.8%) 7 (26.9%) 6 (23.1%) 5 (19.2%) 7 (26.9%)	0% 3 (10.3%) 4 (13.8%) 11 (37.9%) 11 (37.9%)
Disease Duration (mean ± SD)	16.42 ± 9.86	NA	NA	0-5 years 6-10 11-15 16 -20 21+	3 (11.5%) 4 (15.4%) 7 (26.9%) 6 (23.1%) 6 (23.1%)	NA

Note. Ctl=control group; RRMS=relapsing remitting multiple sclerosis group; MSFC = Multiple Sclerosis Functional Composite, NA = not applicable, Percentage=percentage within each subgroup, SD=standard deviation, *significance≥0.001.

Table 4

Radiology reports – most recent for each RRMS participant (one participant per cell).

				Specific brain structures with WM lesions								
MS Participant	WM disease present	Generalized Atrophy	Widespread WM disease	Periventricular WM *	Corpus callosum or pericallosal areas**	Bilateral basal ganglia	Brainstem and cerebellum	Left subcortical frontal lobe	Left temporo- or temporo-parietal subcortical area	Right anterior medulla	Body of fornix	Optic nerve
1	x		x									
2	x											
3	x			x								
4	x					x						
5	x	x	x				x					
6	x		x									
7	x		x									
8	x		x					x				
9	x	x		x								
10	x								x			
11	x			x								
12	x									x		
13	x		x									
14	x	x										
15	x				x							
16	x											
17	x			x	x							
18	x			x	x						x	
19	x								x			x
20	x											
21	x				x							
22	x											
23	x			x								
24	x			x								
25	x			x								
26	x											

Note. x=feature was described on most recent MRI scan or within summary statement of white matter lesion distribution that was provided by research coordinator of Rocky Mountain Neurological MS Clinic; *Specific periventricular areas included infratentorial and supratentorial regions, left hemisphere, frontal horn of the right and left lateral ventricle; ** Specific areas included left brachium pontes, and frontal, parietal, posterior temporal and occipital lobes; WM=White matter.

Effort

No control participants exhibited poor effort. Two RRMS participants exhibited questionable effort. One of these participants did not respond accurately to any Numbers Backward trials but was correct to five digits for Numbers Forward. This participant's MicroCog indices (Level 1, 2, and 3) ranged from 64 to 96, suggesting good effort on testing generally, and therefore their data was included in the final analysis. The second participant performed poorly on most indices (Level 1, 2, and 3 scores ranged from 61 to 75). In order to learn how removing this participant might influence results, the analysis for the first hypothesis (ANCOVA for Level 2 and 3 indices) was repeated with the participant's scores removed. Removal of the participant did not change the results. Therefore, the participant's data was included in the final analysis. Disease duration for this individual was 30 years which may explain the lower test scores.

Depression

Table 5 includes information for scores on the BDI-II, MSFC, and SDMT. The average BDI-II score for the RRMS group was 17.71 (SD=10.40). This score falls within the "mild" range of depression (Beck, Steer, & Brown, 1996). The average BDI-II score for the control group was 5.72 (SD=5.12). This average score falls below the cutoff for depression. The RRMS group had a higher average BDI-II score than the control group ($t(53)=-5.47$, $p=.000$).

Fifteen (57.7%) of the RRMS participants were on anti-depressants, including fluoxetine, buproprion, duloxetine, citalopram, and sertraline. Of those on antidepressants, utilizing BDI-II cutoff scores, five patients scores were below the cutoff for depression symptoms (e.g. no symptoms of depression) , three had mild symptoms, five had moderate symptoms, and two had severe symptoms. Of those not on antidepressants, three participants' scores were below the

cutoff for depression symptoms (e.g. no symptoms of depression), four had mild symptoms, three had moderate symptoms, and one had severe symptoms. Overall, there was no obvious differences between depression symptoms levels based on whether participants were on antidepressants.

Clinical Status Measure – Multiple Sclerosis Functional Composite

There was one RRMS participant who did not want to complete the PASAT because they found the test too anxiety provoking. The test was discontinued and this participant's MSFC total score and PASAT were excluded from analyses (9-HPT and TFFW were retained). The average MSFC z-score for the RRMS group was -1.97 (SD=1.22). The average 9-HPT z-score was -1.70 (SD=1.20), the average TFFW was 0.00 (SD=1.00), and the average PASAT was -1.86 (SD=1.35). The average MSFC z-score for the control group was 0.00 (SD=0.70). The average 9-HPT z-score was -1.70 (SD=1.20), the average TFFW was -2.28 (SD=2.95) the average PASAT was -1.70 (SD=1.20). The RRMS group had a lower average MSFC score than the control group ($t(53)=-7.42$, $p=.000$).

Processing Speed

The mean SDMT score for both groups was in the Average range. The average SDMT z-score for the RRMS group was -0.65 (SD=0.88). The average SDMT z-score for the control group was 1.05 (SD=0.87). The mean for the RRMS group was significantly lower than the control group mean ($t(53)=-7.19$, $p=.000$).

Table 5

Descriptive Statistics for BDI-II, MSFC, and SDMT

	Mean; Standard Deviation			Sample Size and Percentage		
Test	RRMS (n=26)	Ctl (n=29)	Significance testing	Scores[a] range	RRMS n (%)	Control n (%)
BDI-II (mean ± SD)	17.71 ± 10.40	5.72 ± 5.12	t(53) = -5.47, p=.000*	0 to 5 6 to 10 11 to 20 21 to 30 31 to 40 41+	5 (19.2%) 1 (3.8%) 11 (42.3%) 6 (23.1%) 2 (7.7%) 1 (3.8%)	18 (62.1%) 8 (27.6%) 2 (6.9%) 1 (3.4%) 0% 0%
MSFC (mean ± SD)	-1.90 ± 1.12	0.00 ± 0.70	t(53) = -7.63; p=0.00*	-5.0 to -2.5 -2.4 to -1.5 -1.4 to -0.5 -0.4 to 0.5 0.6 to 1.5	8 (30.8%) 7 (26.9%) 9 (34.6%) 2 (7.7(%) 0	0% 1 (3.4%) 6 (20.7%) 14 (48.3%) 8 (27.6%)
SDMT (mean ± SD)	-0.65 ± 0.88	1.05 ± 0.87	t(53) = -7.19; p=0.00*	-2.4 to -1.5 -1.49 to -0.5 -0.49 to 0.5 0.51 to 1.50 1.51 to 2.6	3 (11.5%) 12 (46.1%) 8 (30.8%) 3 (11.5%) 0%	0% 1 (3.4%) 7 (24.1%) 13 (44.8%) 8 (27.6%)

Note. BDI-II = Beck Depression Inventory-II, Ctl=control group, RRMS=relapsing-remitting multiple sclerosis group; MSFC = Multiple Sclerosis Functional Composite, Percentage = percentage within each subgroup, SD=standard deviation, SDMT =Symbol Digit Modalities Test, *significance ≥ 0.001, a=BDI-II scores are raw scores, MSFC and SDMT scores are z-scores.

MicroCog

Table 6 includes descriptive statistics for MicroCog scores. Table 7 includes descriptive information for qualitative descriptors of MicroCog performance. For all index scores neither

the RRMS or control group mean score fell below the Average range. The RRMS group typically performed in the Average to Low Average range and the control group typically performed in the Average to Above Average range. Sixteen RRMS participants (61.5%) had one or more index scores in the Below to Low Average range (i.e., scaled score of 84 or less), and seven of these participants (27%) had five or more scores in this range. Eleven control participants (38%) had one or more index scores in this range, and only one (3%) had over three scores in this range. Mean differences in RRMS and control performance for each index score ranged from 4 to 17 points. Cognitive impairment was defined as two or more index scores being 1.5 standard deviations below the mean or lower, or at least one index score two standard deviations below the mean. Using this criteria, eight (30.7%) of the RRMS participants were impaired and two control participants (6.8%) were impaired on the MicroCog battery.

Table 6

Descriptive Statistics for Level 1, 2, and 3 index scores for RRMS and control groups

	RRMS			Ctl		
Index	Median	Mean	SD	Median	Mean	SD
GCF	94.5	90.04	14.35	106	104.86	9.39
GCP	88.5	88.46	14.03	108	106.03	10.42
IPS	95.5	95.85	13.46	112	110.65	8.68
IPA	90.5	88.19	12.95	100	97.55	12
Attention	96.5	95.85	13.17	104	103.79	11.54
Memory	101	96.38	16.02	113	111.17	13.46
Spatial	99	96.85	13.62	109	106.48	10.71
Reasoning	90.5	87.12	17.36	102	101.83	13.47
Reaction Time	96	93.69	14.15	99	98.52	10.09

Note. Ctl=control group; Level 1 Index includes Attention/Mental Control, Memory, Spatial Processing, Reasoning/Calculation, Reaction Time; Level 2 Index includes Information Processing Speed (IPS) & Information Processing Accuracy (IPA); Level 3 Index includes General Cognitive Proficiency (GCP) & General Cognitive Functioning (GCF); RRMS= relapsing-remitting multiple sclerosis group; SD=standard deviation; significance*=$p \leq .001$.

Table 7

Percentage of samples by qualitative descriptor for Level 1, 2, and 3 MicroCog scores

Scaled Score	Above Average		Average		Low Average		Below Average	
	RRMS n (%)	Ctl n (%)	RRMS n (%)	Ctl n (%)	RRMS n (%)	Ctl n (%)	RRMS n (%)	Ctl n (%)
GCF	0	3 (10%)	18 (69%)	25 (86%)	4 (15%)	1 (3%)	4 (15%)	0
GCP	0	5 (17%)	18 (69%)	22 (76%)	5 (19%)	2 (7%)	3 (11%)	0
IPS	1 (4%)	8 (28%)	18 (69%)	20 (69%)	7 (27%)	1 (3%)	0	0
IPA	0	0	15 (58%)	25 (86%)	8 (31%)	3 (10%)	3 (11%)	1 (3%)
Attention	1 (4%)	5 (17%)	21 (81%)	23 (79%)	2 (8%)	1 (3%)	2 (8%)	0
Memory	2 (8%)	14 (48%)	17 (65%)	15 (52%)	6 (23%)	0	1 (4%)	0
Reasoning	0	7 (24%)	16 (61%)	17 (59%)	5 (19%)	5 (17%)	5 (19%)	0
Spatial	2 (8%)	8 (28%)	20 (77%)	20 (69%)	3 (11%)	1 (3%)	1 (4%)	0
Reaction Time	0	0	21(81%)	26 (90%)	3(11%)	3 (10%)	2(8%)	0

Note. n=number of participants; %=percentage of sample within qualitative descriptor category rounded to nearest ones unit; Ctl=Control group; Level 1 Index includes Attention/Mental Control, Memory, Spatial Processing, Reasoning/Calculation, Reaction Time; Level 2 Index includes Information Processing Speed (IPS) & Information Processing Accuracy (IPA); Level 3 Index includes General Cognitive Proficiency (GCP) & General Cognitive Functioning (GCF); RRMS=relapsing-remitting multiple sclerosis group.

Hypothesis 1: Group differences in Level 1, 2, and 3 MicroCog performance

Level 2 and 3 outcomes. Visual inspection of histograms for Level 2 and 3 outcome scores suggested normality assumptions were sufficiently met so that analyses could proceed. Outliers were fenced to the median ± two interquartile range for the following variables: GCP, IPS, and IPA (which improved kurtosis and skewness in these cases). Z-scores for skewness and kurtosis were calculated for distributions of the RRMS and control group separately and then the

groups together. There were no significant z-scores for kurtosis. Two variables had significant z-scores (p=.05) at 1.96 for skewness. These included GCF (groups combined only, negative skew, z=2.94) and IPA (control only, negative skew, z=2.35). These violations were considered minor enough that analysis could proceed.

Preliminary data screening indicated there was one outlier for depression that was fenced (a score of 45 was outside two interquartile ranges of the median and was fenced to 41). The histogram for depression (i.e., BDI-II scores) had a positive skew. Removing the outlier improved normality of the histogram.

To assess for violations of the homogeneity of regression (whether there was an interaction between the RRMS and control group and the covariates), a preliminary ANCOVA was calculated with a custom model that included a covariate by group interaction term. There were no statistically significant interactions for any of the Level 2 or 3 outcome variables for depression (p-values were 0.06 (GCF), 0.08 (GCP), 0.26 (IPS), and 0.07 (IPA)), and therefore the final ANCOVA reported does not include an interaction term.

The Levene test was performed to assess violations of homogeneity of variance. The results of GCF and IPS variables were significant. In these cases, an independent samples t-test with equal variance not assumed was calculated in help ensure the violation did not impact results (GCF: t(42.3)=-4.48, p=0.00, two-tailed; IPS: t(41.91)=-4.90, p=0.00). The results aligned well enough with the ANOVA results (discussed below) that we proceeded with the ANCOVA analysis for these variables.

An ANOVA was calculated for all Level 2 and 3 outcome variables to learn about group differences without controlling for depression. There was a statistically significant difference for RRMS and control groups for three out of four outcome variables: GCF (F (1, 53) = 20.96,

p=0.000), GCP (F (1, 53) = 26.18, p=0.000), IPS (F (1, 53) = 24.00, p=0.000). There was not a statistically significant difference for IPA (F (1, 53) = 7.74, p=0.007).

An ANCOVA with depression as a covariate was calculated for each outcome variable. A Type III computational method was used because the primary focus was between group differences in MicroCog scores (therefore order of entry for the covariate was less important). The main effects for RRMS were not significant for GCF and IPA scores (Table 8). The main effects were significant for GCP and IPS. The strength of the association between group membership (i.e., RRMS) and outcome variables (e.g., GCF) as measured by partial eta squared (the amount of variance in outcome scores predictable by group membership after controlling for covariates) ranged from 0.05 to 0.22.

Table 8

ANCOVA for Level 1, 2, and 3 MicroCog Index Scores (RRMS as fixed factor, age and depression as covariates)

MicroCog Index Score	F (df=1, 55)	Significance (p-value)	Partial Eta Squared
GCF	10.18	0.002	0.16
GCP	14.12	0.00*	0.21
IPS	14.45	0.00*	0.22
IPA	2.77	0.10	0.05
Attention	1.67	0.20	0.03
Reasoning	6.96	0.01	0.12
Memory	9.55	0.003	0.15
Spatial	2.83	0.10	0.05
Reaction Time	0.28	0.60	0.00

Note. Level 1 Index includes Attention/Mental Control, Memory, Spatial Processing, Reasoning/Calculation, Reaction Time; Level 2 Index includes Information Processing Speed (IPS) & Information Processing Accuracy (IPA); Level 3 Index includes General Cognitive Proficiency (GCP) & General Cognitive Functioning (GCF); significance*=p≤.001..

Adjusted and unadjusted group means for the outcome variables are provided in Table 9. The adjusted means are estimates of what the outcome variable might have been if the treatment groups had been exactly equal on the covariates. For all outcome variables, the adjusted means were closer together for the groups than for the unadjusted means. That is, the means were more similar for the two groups when controlling for depression.

Table 9

Unadjusted and Adjusted Mean Scores

Outcome Variable	Unadjusted Mean		Adjusted Mean	
	RRMS	Ctl	RRMS	Ctl
GCF	90.04	104.86	90.97	104.03
GCP	88.46	106.03	89.43	105.16
IPS	95.85	110.65	95.96	110.55
IPA	88.19	97.55	89.40	96.46
Attention	95.85	103.79	97.17	102.60
Reasoning	87.12	101.83	87.51	101.47
Memory	96.38	111.17	95.95	111.56
Spatial	96.85	106.48	98.27	105.21
Reaction Time	93.69	98.52	95.09	97.26

Note. Ctl=control group; Level 1 Index includes Attention/Mental Control, Memory, Spatial Processing, Reasoning/Calculation, Reaction Time; Level 2 Index includes Information Processing Speed (IPS) & Information Processing Accuracy (IPA); Level 3 Index includes General Cognitive Proficiency (GCP) & General Cognitive Functioning (GCF); RRMS=relapsing-remitting multiple sclerosis group.

Level 1 outcomes. Visual inspection of histograms for Level 1 Index scores (Attention/Mental Control (Attention), Memory, Reasoning/Calculation (Reasoning), Spatial Processing (Spatial), and Reaction Time (RT)) suggested normality assumptions were sufficiently enough met so that analyses could proceed. There were some variables with a slight non-normal distribution, typically with a random or negative skew. Outliers were fenced to the median +/- two interquartile ranges for the Spatial variable (which improved kurtosis and skewness). Z-scores for skewness and kurtosis were calculated to better understand any violations or normality. These were calculated for distributions of the RRMS and control group separately and then the entire sample together. There were no significant z-scores for kurtosis.

Three variables had significant z-scores (p=.05) at 1.96 for skewness. These included Attention (groups combined, negative skew, z=2.69; RRMS only, negative skew, z=2.08), Spatial (groups combined, negative skew, z=2.85; control only, negative skew, z=2.06), Reaction Time (groups combined, negative skew, z=3.56; control only, negative skew, z=-2.43; RRMS only, negative skew, z=-2.15). These violations were considered minor enough that analysis could proceed.

The Levene test assessed homogeneity of variance. There were two variables for which the assumption was violated, Reasoning and RT. In these cases, a t-test where equal variance was not assumed was performed. For Reasoning, the mean scaled scores differed significantly, t(47.05)=-3.48, p=0.001, two-tailed. For RT, the mean scaled scores did not differ significantly, t(44.68)=-1.44, p=0.16, two-tailed. This was consistent with the ANOVA results for these variables and therefore we proceeded with ANCOVA analyses for these scores.

To assess for violations of the homogeneity of regression a preliminary ANCOVA was calculated with a custom model that included a covariate by group interaction term. There were no statistically significant interactions for any of the Level 1 outcome variables (p-values were 0.29 (Attention), 0.25 (Reasoning), 0.18 (Memory), 0.08 (Spatial), and 0.72 (RT)), and therefore the final ANCOVA reported does not include an interaction term.

An ANOVA was calculated for all Level 1 outcome variables without controlling for depression. There were significant differences found between the RRMS and control group for two Level 1 scores: Memory (F (1, 53) = 13.83, p=0.000) and Reasoning (F (1, 53) = 12.47, p=0.001). The RRMS and control groups did have not statistically significant differences for the other three Level 1 scores: Attention (F (1, 53) = 5.69, p=0.021), Spatial (F (1, 53) = 8.60, p=0.005), and Reaction Time (F (1, 53) = 2.15, p=0.148).

An ANCOVA was calculated for each Level 1 outcome variable with depression as a covariate. A Type III computational method was used. The main effects for the RRMS and control groups were not significant for any Level 1 score (Table 8, see above). The strength of the association between group membership and outcome variables (e.g., Memory) as measured by partial eta squared ranged from 0.00 to 0.15.

Adjusted and unadjusted group means for the outcome variables are listed in Table 9. For all outcome variables, the adjusted means were closer together for the groups than for the unadjusted means.

Hypothesis 2: Covariates of MicroCog Performance

Variables in this portion of the analysis (MSFC score, BDI-II, and disease duration) were screened for violations of normality assumptions. MSFC had a slight negative skew to its distribution but it was considered normal enough that analysis could proceed. There was one outlier for MSFC and this was fenced because this participant's score was low due to his being in a wheelchair. This improved normality for the distribution. As noted above, the histogram for BDI-II scores had a positive skew. One outlier was fenced which improved normality. The histogram for disease duration was approximately normal. There was one outlier that was fenced to two interquartile ranges from the median (a duration of 44 years was fenced to 40.5 years). Review of the scatterplots suggested all distributions were approximately linear.

The global score of cognitive and physical disability (MSFC) was significantly correlated for all Level 2 and 3 index scores with groups combined at p=0.00. The correlation coefficients (r) for these variables were as follows: GCF=0.61, GCP=0.61, IPS=0.51, IPA=0.49. See Figure 2 for scatter plots of these variables. Correlation coefficients were analyzed separately for each group to see how relationships between disability and MicroCog performance may differ for the

RRMS and control groups. For the control group the correlation between MicroCog and disability decreased (GCF: r=0.18, p=0.36, GCP: r=0.25, p=0.20, IPS: r=-0.07, p=0.73, IPA: r=0.26, p=0.18). The correlation also decreased for the RRMS group but less so and the significance level was significant at p≤0.05 for GCF, GCP, and IPA (GCF: r=0.47, p=0.02, GCP: r=0.40, p=0.05, IPS: r=0.31, p=0.13, IPA: r=0.42, p=0.03).

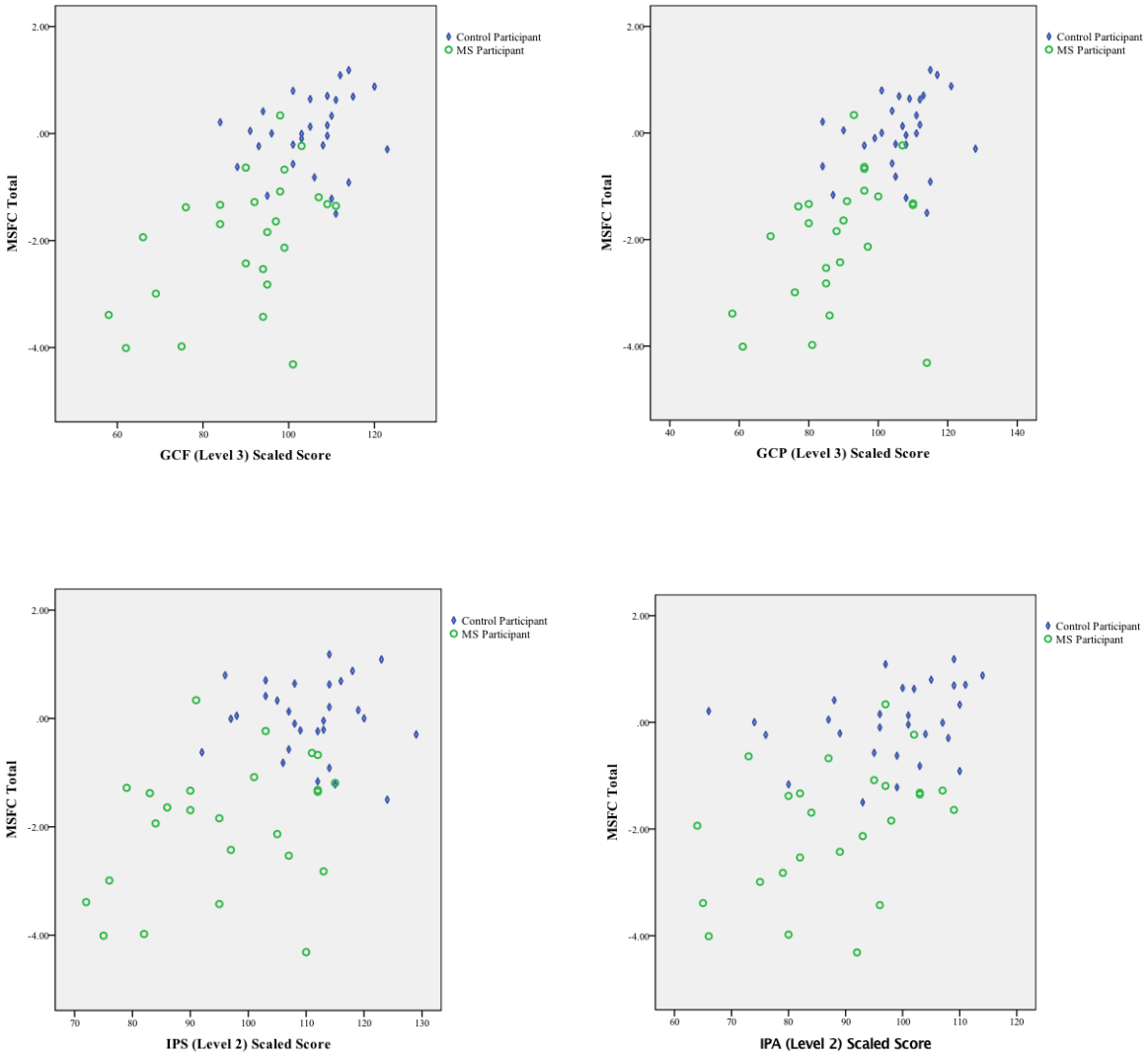

Figure 2. Scatter plots for MSFC and Level 2 and 3 MicroCog scores.

Depression (BDI-II) was originally not significantly related to any Level 2 and 3 index scores except for GCP (GCF: r=-0.39, p=0.003; GCP: r=-0.42, p=0.001; IPS: r=-0.35, p=0.009; IPA: r=-0.308, p=0.022). There was one bivariate outlier identified for each calculation (this participant's BDI-II score was zero and they scored Below Average on MicroCog indices). In order to learn its influence on these correlations, this participant was removed from this analysis and correlations were recalculated. With this participant removed, the correlations reached significance for all but one Level 2 and 3 Index score. (GCF: r=-0.50, p=0.00; GCP: r=-0.52, p=0.00; IPS: r=-0.43, p=0.001; IPA: r=-0.37, p=0.005). Review of the scatter plots suggested a negative relationship between depression and MicroCog performance (higher depression scores were associated with worse cognitive scores). Correlation coefficients were analyzed separately for the RRMS and control group. For the control group the correlations between Level 2 and 3 index scores and depression were not significant (significance ranged from 0.1 to 0.21 and r ranged from 0.23 to 0.31). No significant relationships were identified for the RRMS group, though GCF, GCP, and IPA were significant at p=0.01 (GCF: r=-0.495, p=0.01; GCP: r=-0.49, p=0.01; IPS: r=-0.27, p=0.20; IPA: r=-0.51, p=0.01).

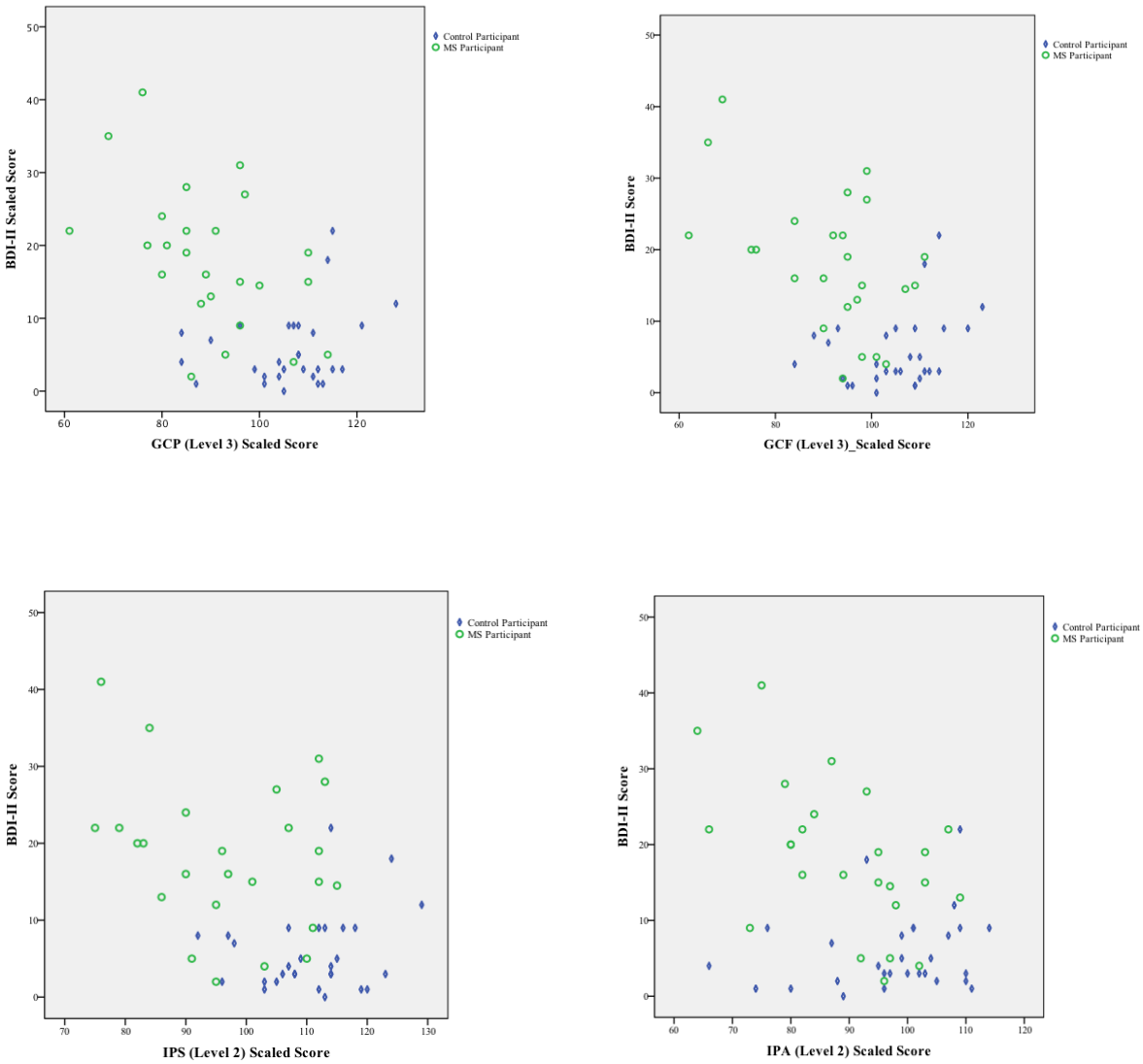

Figure 3. Scatter plots for BDI-II and Level 2 and 3 MicroCog scores.

RRMS disease duration did not reach statistical significance for any MicroCog index score (Figure 4) (GCF: r=-0.47, p=0.01, GCP: r=-0.58, p=0.002, IPS: r=-0.43, p=0.03, IPA: r=-0.34, p=0.09). Scatterplots suggested a negative, linear relationship between MicroCog scores (particularly GCF and GCP) and disease duration.

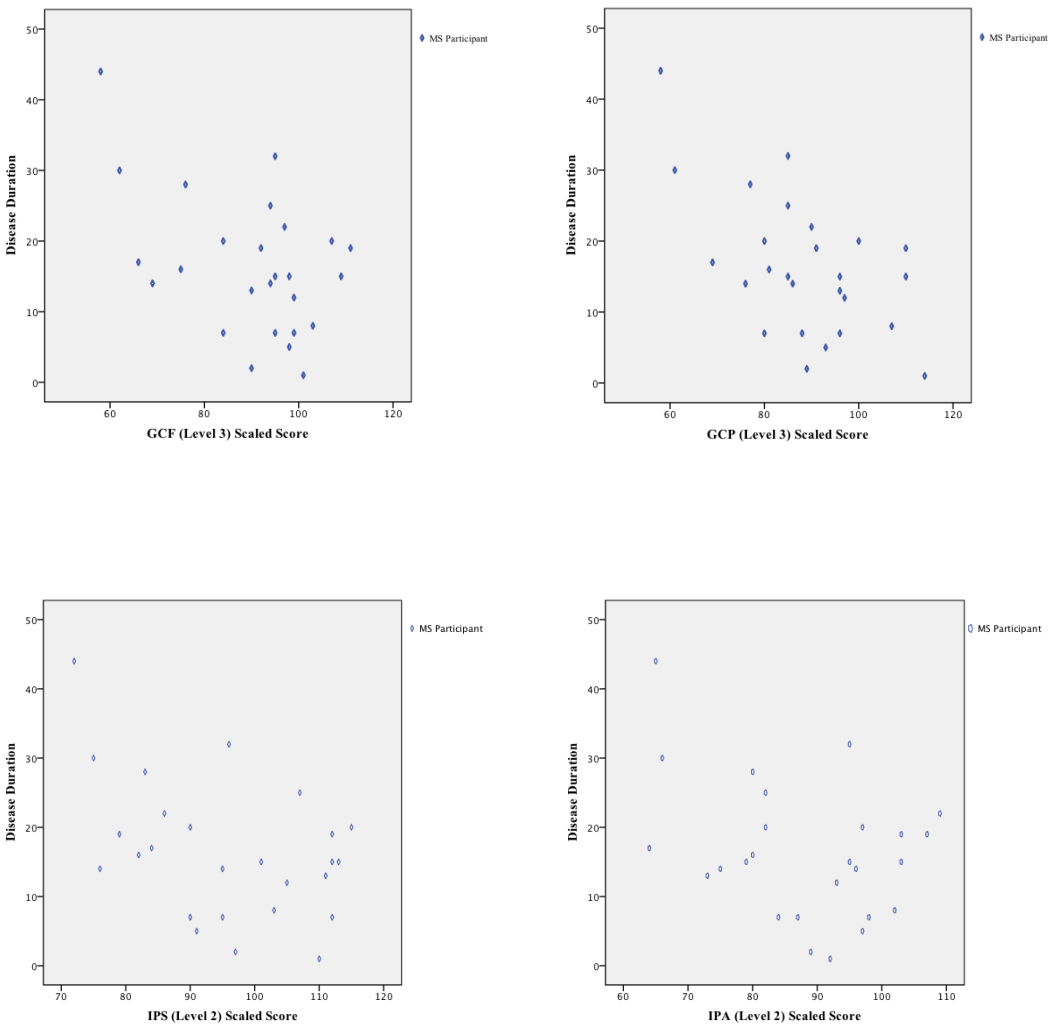

Figure 4. Scatter plots for disease duration and Level 2 and 3 MicroCog scores.

As predicted, sex did not account for a significant portion of the variance for Level 2 or 3 index scores. Point biserial r correlations were as follows: GCF: r_{pb}=-0.18, p=0.19; GCP: r_{pb}=-0.24, p=0.08; IPS: r_{pb}=-0.11, p=0.44; IPA: r_{pb}=-0.19, p=0.16.

In sum, both global score of cognitive and physical disability (MSFC) and depression (BDI-II) were significantly correlated with Level 2 and 3 MicroCog performance when RRMS and control groups were combined. When the analyses were repeated for the RRMS and control

groups separately, the correlations were not significant for either group. It is plausible significant relationships would exist with a larger sample size (more power for the analysis), particularly for the RRMS group given that for both disability and depression, correlations reached statistical significance at $p<0.05$ and there was a linear relationship on scatter plots. Disease duration was not significantly correlated with MicroCog performance though scatterplots suggested a negative, linear relationship for GCF and GCP. Sex was significantly correlated with MicroCog performance.

Hypothesis 3: Correlation between MicroCog and Traditional Processing Speed Measure

Results indicated that the MicroCog IPS scores and SDMT scores were significantly, positively correlated ($r=0.57$, $p=0.00$). See Figure 5 for a scatterplot of this correlation. There was a wider range of variability in SDMT scores around the average range of IPS scores relative to Above or Below Average IPS scores. In order further explore the relationship of IPS and paper-pencil subtests of processing speed, a separate Pearson's r correlation was calculated for PASAT and IPS scores. Similar to the SDMT results, the relationship between IPS and the PASAT was significant ($r=0.58$, $p=0.00$). See Figure 6 for a scatterplot of this correlation.

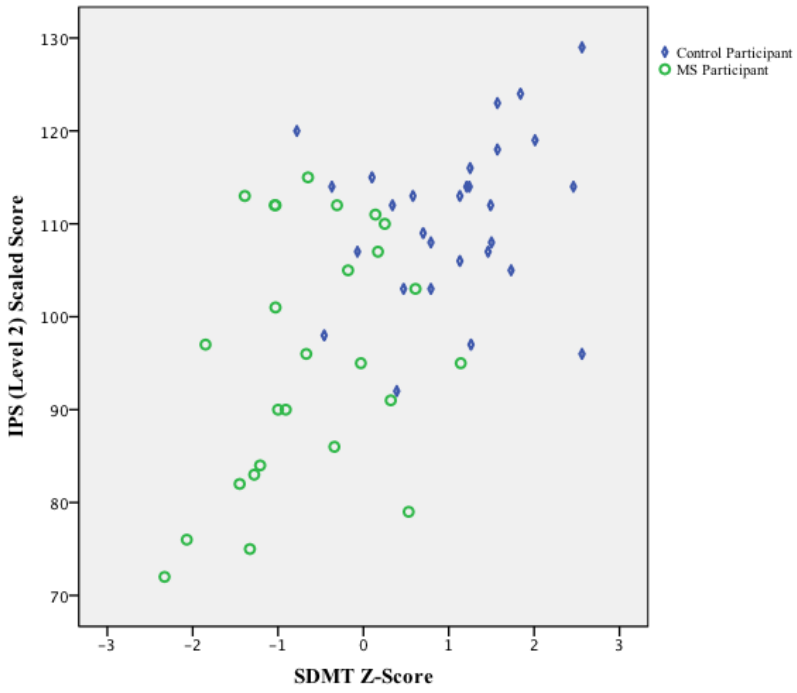

Figure 5. Correlation between SDMT (paper pencil) and MicroCog IPS (computer based).

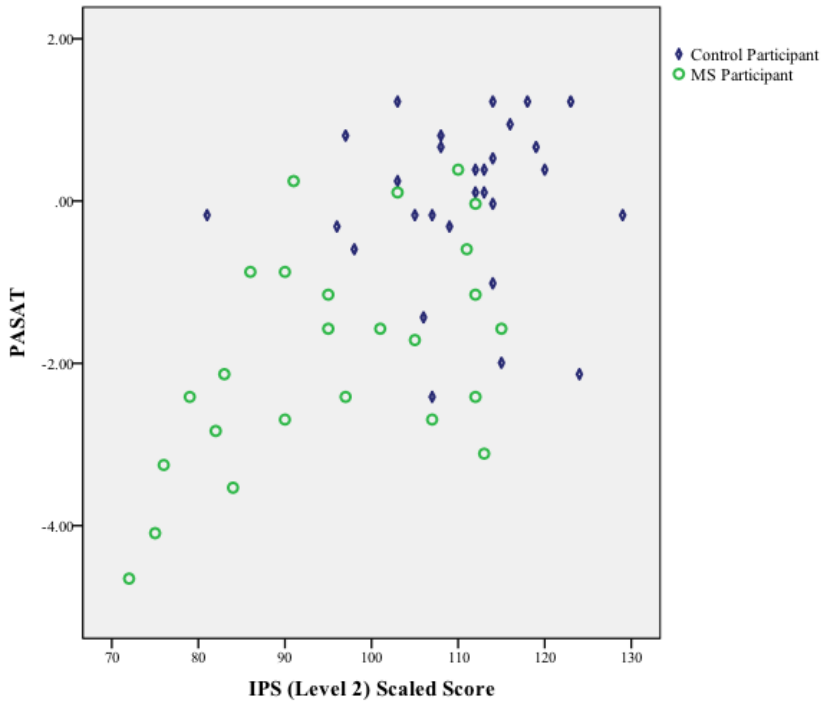

Figure 6. Correlation between PASAT (paper pencil) and MicroCog IPS (computer based).

Post-hoc Analysis

Criterion validity of the MicroCog. Analysis of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and receiving operating characteristic curve (ROC) were performed in order to learn about the criterion validity of the MicroCog in RRMS. We categorized cognitive impairment in our RRMS sample using performance on traditional measures of cognitive impairment in MS, the SDMT and the PASAT. A RRMS participant was considered to have cognitive impairment if they scored either two standard deviations below the mean on either the PASAT or SDMT, or if they scored 1.5 standard deviations below the mean or more on both the PASAT and the SDMT. Using this criteria, 12 RRMS participants met criteria for cognitive impairment. All performed two standard deviations or lower on the PASAT, two participants performed two standard deviations or lower on the SDMT, and two performed 1.5 standard deviations or lower on the SDMT. See Table 10 for the results of criterion validity analyses. The MicroCog had a sensitivity value of 58.33 and a specificity value of 92.96. Calculation of PPV and NPV was based on a prevalence rate of 40% for cognitive impairment in RRMS. The PPV was 84.49 and NPV was 76.97. The area under the curve (AUC) for the ROC was 0.76 (95% CI [0.56 to 0.95]). A different approach was taken where the MicroCog IPS index score was utilized as the predictor variable for cognitive impairment (as opposed to all MicroCog index scores). The results for the criterion validity of the IPS (including sensitivity, specificity, PPV, and NPV) were identical to those for overall MicroCog performance. Because IPS is a continuous variable, the ROC was examined to learn about cut-scores that would offer the best balance of sensitivity and specificity. A cut-score of 93 on the IPS produced a sensitivity of 66.7 and a specificity of 78.6.

Table 10

Criterion validity of the MicroCog in RRMS sample

Correctly Classified	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV
76.9	58.33 (27.67 to 84.83)	92.86 (66.13 to 99.82)	84.49	76.97
True Positives	False Negatives	True Negatives	False Positives	
7	5	13	1	

Note. * Cognitive impairment was defined as two or more MicroCog index scores being 1.5 standard deviations below the mean or lower, or at least one index score two standard deviations below the mean; CI=confidence interval; PPV=positive predictive value; NPV=negative predictive value.

Hypothesis 1 with age equivalent groups. To better understand the potential influence of RRMS, age, and depression on differences in MicroCog performance (examined in Hypothesis 1), post-hoc analyses were performed for Level 2 and 3 index scores with a sample of participants aged 30 to 53 years old. This range was chosen because it allowed for equivalent ages between groups with the largest sample size. The sample size for each group was 14 (total n=28). There was no mean differences in age between groups ($t(26)= 1.01$, $p=.32$). There were no outliers for Level 2 or 3 index scores. There was one outlier for BDI-II scores that was fenced which improved normality (a score of 45 was fenced to 40). Bonferroni correction was not applied for this portion of the analyses.

An alternate approach to forming age matched pairs was considered where RRMS and control group participants were included in the sample if they were the same age. The resulting

groups of participants were similar enough to the sample described above that the analysis was not repeated for this sample (ages of RRMS participants ranged from 23 to 61 and there were 14 participants in each group).

Tables 11 shows that a similar pattern emerged in MicroCog scores for this smaller sample as with the full participant sample. RRMS participants' mean scores were lower than controls for each Level 2 and 3 outcome variable. The GCF, GCP, and IPS variables all had mean differences of about 11 points (RRMS scores were lower). These were significant at $p<0.05$, including for GCF ($F(1, 27)=5.31$), GCP ($F(1, 27)=4.61$), and IPS ($F(1, 27)=5.09$). The IPA mean difference was about 7 points, a non-significant difference ($F(1, 27)=1.52$). These results were similar to those of the ANOVA calculations in Hypothesis 1 and because groups were similar for age in this case, we can be more certain that RRMS and/or depression accounted for a significant portion of variance in MicroCog performance differences for GCF, GCP, and IPS.

Table 11

Group differences in Level 1, 2, and 3 MicroCog score for participants 30 to 53 years in age

	RRMS (n=14)			Ctl (n=14)				One-way ANOVA	
Index	Median	Mean	SD	Median	Mean	SD	Mean Difference	F	p-value
GCF	96.00	91.57	15.13	105.50	102.64	9.68	-11.07	5.31	0.03
GCP	93.00	92.50	14.55	108.00	103.64	11.19	-11.14	4.61	0.04
IPS	99.00	97.43	13.70	108.50	108.78	9.09	-11.35	5.09	0.03
IPA	92.50	89.50	13.56	99.50	96.29	12.52	-6.79	1.52	0.23

Note. n=sample size, Level 2 Index include Information processing speed (IPS) & Information processing accuracy (IPA); Level 3 Index include General cognitive proficiency (GCP) & General cognitive functioning (GCF); RRMS=relapsing-remitting multiple sclerosis group; Ctl=control group.

In order to further explore the relationship between depression, RRMS, and MicroCog performance, an ANCOVA was calculated for each Level 2 and 3 index score, with depression as a covariate. The tests for homogeneity of regression assumption indicated there was a significant interaction for RRMS and depression for GCF (p=0.03) and GCP (p=0.02). The assumption was not violated for IPS (p=0.06) or IPA (p=0.16).

For GCF and GCP variables, a regression was calculated as opposed to an ANCOVA so that an interaction term for RRMS and depression could be included in the analysis. For GCF the proportion of variance explained by the entire set of predictor variables included in the analysis (R^2) with no interaction term included was 0.32. The overall regression was statistically significant (F(2,27)=5.85, p=0.008). The main effect for RRMS was not significant (b=-0.15, t-

score=-0.78, p=0.44). Depression was a significant predictor of GCF scores (b=-0.46, t-score=-2.34, p=0.03). The regression was calculated again, this time with an interaction term for depression and RRMS included in the model. A greater amount of variance was explained by this model (R^2=0.45) and the overall model was statistically significant (F(3,27)=6.51, p=0.002). The RRMS by depression interaction term was significant (b=-1.38, t-score=-2.38, p=0.026, confidence interval= -2.58 to -.183). The corresponding effect size from the portion of GCF uniquely predicted from this interaction was $sr^r_{interaction}$ = 0.19. Overall, the results of the regression suggested the impact of depression on GCF score differs for the RRMS and control groups, where a higher number of depression symptoms leads to a sharper decline in GCF score in the RRMS group. To even further explore this possibility, a one-way ANOVA was calculated, comparing RRMS participants with high levels of depression (as measured by the BDI-II; n=6) and RRMS participants with low levels of depression (n=8). "High" levels of depression were defined as participants with "Moderate" or "Severe" depression (scores of 20 or greater on the BDI-II). "Low levels" of depression was defined as scores of "Minimal" or "Mild" depression (scores of 19 or below). The difference between the two groups was significant (F(1,13)=20.80, p=0.001). Unfortunately, the same comparison could not be calculated for the control group because there were not enough control participants with "high" levels of depression symptoms for the analysis.

Similar results were identified for GCP. The proportion of variance explained by the entire set of predictor variables included in the regression analysis (R^2) for GCP with no interaction term included was 0.42. The overall model was statistically significant (F(3,27)=5.83, p=0.004). An interaction term was then added to the model. The RRMS by depression interaction term was significant (b=-1.48, t-score=-2.41, p=0.02, confidence interval=

-2.75 to -.21). The corresponding effect size from the portion of GCP uniquely predicted from this interaction was $sr^{r}_{interaction}$ = 0.19. The one-way ANOVA comparing RRMS participants with "high" versus RRMS participants with "low" levels of depression was significant (F(1,13)=17.69, p=0.001).

An ANOVA was calculated for IPS and IPA indices with depression as a covariate. A Type I computational method was used to learn more about variance predictable from depression (order of model entry was depression then RRMS). For IPS, depression was a significant predictor in the model (F (1, 27) = 7.86, p=0.01) and not RRMS (F (1, 27) = 0.91, p=0.35). A similar pattern occurred for IPA (depression: F (1, 27) = 2.64, p=0.05; RRMS: F (1, 27) = 0.02, p=0.88).

To summarize, the relationship between these age matched samples and MicroCog scores were similar to the results of our main analysis (above) in that there was a significant difference in performance between RRMS and control groups for three out of four Level 2 and 3 outcome variables (when not controlling for depression). There were not significant between group differences for IPA. For GCF and GCP, a regression analysis support the differences between groups were best accounted for by an interaction term between RRMS and depression. Further analysis showed RRMS participants with "high" levels of depression perform worse on GCF and GCP than RRMS participants with "low" depression levels. For IPS and IPA, RRMS did not predict performance after controlling for depression.

Discussion

The results of the present study confirmed many but not all of our original hypotheses and align well with findings from past studies of cognitive functioning in RRMS.

MicroCog as a Measure of Cognitive Function in RRMS

The MicroCog was considered a promising candidate for measuring cognition in RRMS based on its psychometric properties, normative data, evidence for its ability to detect cognitive impairment in other clinical groups, and ease of administration. Before this study, there was no evidence for how well the instrument detected cognitive impairment in RRMS.

In our sample of RRMS participants, 30.7% met criteria for cognitive impairment on the MicroCog. This number is comparable to previously reported prevalence rates of cognitive impairment in MS (Fischer et al., 2014). There were significant group differences between groups for two index scores (GCP and IPS). While differences were not significant for Level 1 scores, effect sizes for Memory and Reasoning, two cognitive domains commonly impaired in MS (Amato et al., 2011), were large. PASAT and SDMT were correlated with the MicroCog IPS supporting construct validity. Correlations with covariates were similar to those identified in past research in RRMS (discussed below).

The post-hoc analyses provided an estimate of the MicroCog's ability to accurately identify cognitive impairment in RRMS. Results indicated the MicroCog has high specificity but low sensitivity, with an AUC value of 75.6. A cut-score of 93 on the IPS resulted in an improved balance between sensitivity and specificity (66.7 and 78.6, respectively). These results suggest the MicroCog was a fair to good test in discriminating cognitive impairment in this sample and that its criterion validity is similar to other screening instruments for cognitive impairment in MS (Parmenter, Weinstock-Guttman, Garg, Munschauer, & Benedict, 2007).

In order to learn how our findings matched past studies of cognitive impairment in RRMS, effect sizes from our study were compared to those from the 2008 meta-analysis by Praskash et al. Effect sizes for our study were calculated (*SSbetween/SStotal*) and then converted

into Cohen's d utilizing supplementary materials provided by Lakens (2013). Our results were overall similar those in Praskash et al. (Table 12). The exception was Reasoning and Reaction Time Level 1 index scores where we found a larger effect for reasoning and a smaller effect for reaction time. This may have to do with differences in how the constructs were measured between the two studies, or a characteristic of our sample.

Table 12

Comparison between effect sizes of current study and past meta-analysis

	Cohen's *d* (current study)	Hedge's *g*; cognitive domain (Praskash et al., 2008)
IPS	0.97	0.65; information processing speed
Attention	0.34	0.54; attention*
Reasoning	0.70	0.31; concept formation and reasoning
Memory	0.82	0.61; memory
Spatial	0.44	0.53; construction
Reaction Time	0.14	0.56; vigilance/sustained attention

Note. *=Attention effect size from Prakash et al. 2008 was calculated by averaging effect sizes from the following domains: vigilance/sustained attention, short term storage capacity, working memory, selective/focused attention. GCP, GCF, and IPA were not compared because there were no comparable constructs measured in Prakash et al. 2008.

Overall, these results support the MicroCog as a promising measure for cognitive impairment in RRMS as they align well with past research. Further research into the psychometrics of the MicroCog in RRMS (e.g., reliability, validity) is needed.

Clinical Implications for Cognition in RRMS

Regarding those MicroCog index scores with significant group differences in control and MS performance for ANOVAs (GCF, GCP, IPS, Memory, and Reasoning), when the covariate depression was included in the analyses there were still significant group differences for GCP and IPS. There were no longer significant group differences for GCF, Memory, or Reasoning although effect sizes were large and low power and our conservative alpha likely contributed to non-significant findings. The results of post-hoc analyses (where age was equivalent between groups; age range was 30 to 53) indicated an interaction term between depression and group membership (i.e., control or RRMS) accounted for a significant proportion of variance for GCF and GCP. That is, higher depression scores were associated with worse cognitive scores for the RRMS group than the control group. This was likely due to the fact that few individuals in the control group reported symptoms of depression. Future studies would need to include a depressed group of participants without RRMS in order to further verify an interaction exists. The finding that RRMS participants with higher levels of depression performed worse than RRMS participants with lower levels of depression supports that these conditions combined may lead to worse performance on cognitive measures in RRMS. Of note, for IPS and IPA scores, RRMS did not predict performance after controlling for depression.

There is evidence to support the possibility that depression in combination with RRMS might put one at greater risk for performance difficulties on the MicroCog. First, the MicroCog manual includes results for 19 participants with major depression diagnoses with an average BDI-II score of 22.17 and no other mental health or medical conditions. The manual normative data indicated the group mean performance was within the Average range for all index scores, suggesting that depression alone does not typically influence MicroCog performance. Second,

past reviews of depression in MS (discussed in "Introduction" section above) described MS participants with severe depression had greater difficulties with working memory, executive functioning, and information processing speed than participants with fewer depression symptoms. Overlap between the physical symptoms of depression and MS have also been studied (see below).

Regarding clinical covariates, the correlation between MSFC and MicroCog scores were significant. Clinical status (MSFC score) should continue to be considered as a potential correlate for MicroCog performance. This is an encouraging finding for the utility of the MicroCog, given the MSFC is currently the gold standard for measuring clinical status in MS (Ontaneda, LaRocca, Coetzee, & Rudick, 2012). Consistent with the findings in the post-hoc analysis there was also a significant correlation identified between depression (BDI-II) and MicroCog performance. Disease duration was not significantly related with MicroCog performance but the scatterplots suggested a negative, linear relationship was present. This variable should continue to be assessed with MicroCog performance, with a larger sample size. There are inconsistent findings in the literature regarding correlation between disease duration and cognitive impairment (Prakash et al. 2008, Rao et al., 1991c, Amato et al., 2001) suggesting the influence of this variable is not fully understood. Prakash et al., 2008 identified in their meta-analysis that disease course may be domain specific and more likely impacting measures of learning and memory. We may have not detected a relationship because our analyses included global summary scores of cognitive functioning or due to our small sample size resulting in lower power. It may also be that disease duration correlates differently with cognitive impairment depending on the period of disease duration (e.g., first five years, first 10 years, 10 to 20 years). Data suggests that cognitive deterioration may be most prominent in the first five

years after disease onset (Reuter et al., 2010). In our sample, seven out of the 26 RRMS participants had disease durations of seven years or less, and 19 participants' disease duration was 12 years or longer. Sex was not significantly correlated with MicroCog performance.

Of note, this study did not differentiate between somatic and non-somatic symptoms of depression in RRMS and control subjects. This has become a more widely used strategy in MS research, given the high overlap of somatic symptoms between MS and depression (Feinstein et al., 2014). In fact, scores for the non-somatic symptoms of depression have been found to be a stronger predictor of cognitive impairment than the somatic symptoms or when these symptoms are combined (Sundgren, Maurex, Wahlin, Piehl, & Brisman, 2013). Future studies might help differentiate between these symptom types and their relationships with MicroCog performance.

The a MicroCog was straightforward test to administer and almost all participants reported no difficulties understanding the instructions provided. There were times that participants had questions or comments for the examiner. These issues were resolved after a short explanation was provided by the examiner. In a clinical setting it may be helpful for examiner to be in the room to take notes on any behavioral observations (e.g., if a participant says a certain cognitive task has been difficult for them their whole life, and not solely since their RRMS diagnosis).

Conclusion

In conclusion, this study served as an important step in learning how the MicroCog computerized battery of neuropsychological function might be utilized in clinical care with RRMS patients and how it compares to past research of cognition in RRMS. The study supports the MicroCog as a promising tool for use with RRMS patients.

Overall the results of the current study aligned well with prior studies of cognition in RRMS, including that RRMS participants performed worse than controls on cognitive tests and high levels of depression likely influenced performance. Future studies can help confirm and clarify these findings by including a larger sample size and comparison groups with a wider range of depression and disability symptoms. This would help confirm how factors (e.g., RRMS, depression) account for a significant portion of cognitive difficulties as our small sample may have influenced our ability to identify significant relationships and the analyses. Further studies can also continue to establish psychometric properties of the MicroCog in RRMS including reliability, validity, and sensitivity/specificity.

Strengths of the MicroCog are its straightforward administration, extensive normative data, and the wealth of information available to the clinician about a patient's performance. It also has a specific measure of how processing speed influences performance within each subtest. This is helpful in a patient population like RRMS, where performance deficits can vary so widely between patients and processing speed is a dominant deficit.

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