PSYCHOLOGICAL AND PSYCHOSOCIAL CORRELATES OF EXECUTIVE FUNCTIONING IN PEDIATRIC MULTIPLE SCLEROSIS

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Julia Nunan-Saah

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Julia Nunan-Saah
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The vast majority of multiple sclerosis (MS) cases are acquired in adulthood, but approximately 3−5% of MS cases occur in children and adolescents (i.e., about 8000 to 10,000 in the United States). This past decade has witnessed a growing literature on pediatric MS, which has revealed both similarities and fundamental differences between the pediatric and adult manifestations of the disease. In adults, MS is associated with executive dysfunction, anxiety, depression, fatigue, and lowered quality of life. Existing research suggests that similar problems may occur in pediatric MS, but the relationships between these variables have not yet been investigated. This study aimed to investigate the associations among some of the most salient cognitive (executive functioning, working memory), psychological (anxiety, depression), and psychosocial (fatigue, quality of life, externalizing symptoms) factors affecting children with MS.

This archival dataset, drawn from the largest sample studied to date, consisted of 79 patients with pediatric-onset MS (14.54 ± 2.92 years) who were evaluated through the UCSF Regional Pediatric Multiple Sclerosis Center. Participants completed a neuropsychological assessment battery including the Verbal Fluency Test, Trail Making Test, and Digit Span. Parents and children also completed rating forms assessing emotional functioning, fatigue, quality of life, and executive functioning. Correlation and regression analyses were conducted to assess the relationships between executive functioning and measures of psychological and psychosocial functioning.

Preliminary analyses demonstrated that age of onset, disease duration, and IQ significantly correlated with certain performance-based measures of executive functioning, while disease severity significantly correlated with fatigue. Main analyses revealed that higher levels of anxiety and depressive symptoms were associated with performance-based and self-reported executive dysfunction. Depression, anxiety, and self-reported executive dysfunction were predictive of psychosocial difficulties, including higher levels of fatigue, worse quality of life, and more severe externalizing symptoms. By contrast, working memory was not correlated with any measures of psychosocial functioning.

The present study furthers our knowledge of the psychological and psychosocial factors associated with neurocognitive outcomes in pediatric MS. Recognition of these variables can help guide medical and psychological treatment, as well as interventions in the home and community, to maximize a positive developmental trajectory.

Psychological and Psychosocial Correlates of Executive Functioning in Pediatric Multiple Sclerosis

This dissertation by Julia Nunan-Saah, directed and approved by the candidate's committee, has been accepted and approved by the Faculty of Pacific Graduate School of Psychology, Palo Alto University in partial fulfillment of the requirements for the degree of

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William Froming, Ph.D.
Provost

Dissertation Committee:

Rowena G. Gomez, Ph.D.
Chair

James A. Moses, Ph.D., ABPP
Committee Member

Wendy Packman, J.D., Ph.D.
Committee Member

Emmanuelle Waubant, M.D., Ph.D.
Committee Member

This dissertation was approved with the signatures of those indicated on this page. The original signatures are on file with the dissertation copy in the PAU Library.

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CHAPTER I

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) typically affecting young adults aged 20 to 40. An estimated 400,000 individuals in the United States have a diagnosis of MS, with a worldwide prevalence of roughly 2.1 million individuals (National Multiple Sclerosis Society, 2009). MS is a chronic condition that can cause both physical and cognitive disability, and its etiology is likely related to a combination of genetic and environmental factors. Approximately 3% to 5% of MS cases occur in children and adolescents[1] (Boiko et al., 2002; Cole & Stuart, 1995; Duquette et al., 1987; Ghezzi et al., 1997; Ruggieri, Polizzi, Pavone, & Grimaldi, 1999). Although there is a relative shortage of literature on pediatric MS, the research thus far suggests that the disease in these patients is unique in several respects.

It is estimated that approximately one third of children with MS experience cognitive impairment (Amato et al., 2008; Ghezzi, Goretti et al., 2010; Goretti et al., 2012; Julian et al., 2012; MacAllister et al., 2005). Similar to findings in the adult MS population, children with MS tend to show deficits in complex attention, visual-motor integration, verbal fluency, aspects of memory, and executive functioning (Banwell, Ghezzi, Bar-Or, Mikaeloff, & Tardieu, 2007). Children with MS may show additional

[1] For the purposes of this study, pediatric MS will be defined to include children and adolescents under the age of 18, consistent with the definitions proposed by the International Pediatric MS Study Group (Krupp, Banwell, & Tenembaum, 2007).

deficits in linguistic abilities that are more apparent than in adults, including problems with confrontation naming and receptive language (Amato et al., 2008).

Psychological functioning in pediatric MS has been relatively less studied than cognitive impairments, but the existing research points to many similarities with adult MS. Depression, anxiety, adjustment disorders, and attention deficit hyperactivity disorder (ADHD) are thought to be the most prevalent psychiatric disorders, with 30% to 60% of children with MS meeting criteria for one or more of these disorders (Amato et al., 2008; Boyd & MacMillan, 2005; MacAllister et al., 2005; Goretti et al., 2010; Thannhauser, 2009; Weisbrot et al., 2010). Concordant with adult MS research, depression is thought to be the most common disorder affecting children (Amato et al., 2008; Goretti et al., 2012; MacAllister et al., 2005).

Research on the psychosocial functioning of patients with pediatric MS has primarily considered factors such as fatigue, quality of life, and behavior problems. Fatigue is perhaps the most widely studied psychosocial variable, reported in 20% to 75% of children with MS (Amato et al., 2008; Goretti et al., 2012; Grover, Banwell, Kahn, & Yeh, 2013; Holland, Graves, Greenberg, & Harder, 2012; MacAllister et al., 2005, 2009). Other psychosocial variables are relatively less studied (e.g., quality of life, externalizing symptoms), but are also thought to be impacted by the disease (MacAllister et al., 2009; Mowry et al., 2010; Till, Udler, et al., 2012).

The relationship between neuropsychological functioning, psychological functioning, and psychosocial functioning in MS is an area of interest that has been studied in the adult population for a number of years. Studies of adult MS have investigated the relationship between neuropsychological deficits and depression,

anxiety, fatigue, quality of life, occupational functioning, and social support as well as the specific correlations between executive functioning, working memory, psychological, and psychosocial functioning (Arnett et al., 1999a, 1999b; Goretti et al., 2013; Prakash, Snook, Lewis, Motl, & Kramer, 2008; Rao, Leo, Ellington et al., 1991).

By contrast, only a handful of studies have examined the relationship between cognitive functioning, psychological, and psychosocial variables in pediatric MS. Additionally, no studies to date have investigated the relationship between executive functioning, working memory, and various aspects of psychological and psychosocial functioning in this population. Therefore, the purpose of the current study is to investigate these relationships. Examining these relationships could provide insight into clinical interventions targeting psychological and psychosocial functioning, which could in turn positively affect the cognitive deficits related to pediatric MS.

CHAPTER II

LITERATURE REVIEW

Overview

The following chapter discusses the diagnostic guidelines, disease characteristics and course, etiological theories, and treatment approaches for adult-onset multiple sclerosis (MS) and pediatric-onset MS. Additionally, it presents a review of the current literature regarding the cognitive, psychological, and psychosocial deficits that characterize pediatric and adult MS. It also discusses the research examining correlations between cognitive, psychological, and psychosocial variables most prevalent in this disorder. Lastly, this chapter discusses the goals and rationale for the current study.

Adult-Onset Multiple Sclerosis

MS is a chronic inflammatory demyelinating disease of the central nervous system (CNS) that is most often diagnosed between the ages of 20 and 40 years. The disease is characterized by episodes of neurological disturbance that are inflammatory and demyelinating in nature, involving destruction of the myelin sheath that surrounds the axons of neurons. These episodes result in lesions, which commonly affect white matter in the optic nerve, brain stem, basal ganglia, spinal cord, and white matter tracts near the lateral ventricles (Compston & Coles, 2008). It is believed that MS develops in genetically predisposed individuals who are exposed to specific triggers during a period of vulnerability (Banwell, Krupp, et al., 2007). MS is the most common of several demyelinating disorders, which also include clinically isolated syndrome (CIS), acute disseminated encephalomyelitis (ADEM), and neuromyelitis optica (NMO), among others. Roughly 50% of CIS cases, which involve a single demyelinating episode lasting

at least 24 hours, go on to be later diagnosed with MS (Dobson, Ramagopalan, & Giovanni, 2012).

MS commonly follows one of two primary disease courses: *relapsing* or *progressive*. Relapsing forms of MS are diagnosed when an individual has at least two distinctive attacks located at two separate sites in the CNS, in other words, "dissemination in time and space" (McDonald et al., 2001, p. 122). The term *relapsing-remitting* MS is used to describe clinical attacks followed by either partial or full recovery and clinical stability between attacks. Progressive forms of MS are diagnosed in individuals with MRI or clinical evidence of disease progression for at least one year, supported by laboratory findings with no other plausible cause (Thompson et al., 2000). These patients have no relapses or remissions from the time of onset, and may be termed *primary progressive* MS. When occasional relapses occur during a primary progressive course, this is called *progressive relapsing* MS. Over time, relapsing MS may also proceed to progressive MS, which is then termed *secondary progressive* MS.

As of 2009 in the United States, an estimated 400,000 individuals have a diagnosis of MS, and the worldwide prevalence is roughly 2.1 million individuals (National Multiple Sclerosis Society, 2009). There is enormous variability in the cognitive and physical manifestations of MS, which is partially attributable to the variety of areas in the CNS that can be affected. However, life expectancy in MS is only slightly lower than for the general population (median survival of 35 to 42 years after initial diagnosis; Ragonese, Aridon, Salemi, D'Amelio, & Savettieri, 2008).

Pediatric-Onset Multiple Sclerosis

Definition and Diagnostic Criteria

In 2007, the National Multiple Sclerosis Society organized an International Pediatric MS Study Group composed of adult and pediatric neurologists, as well as experts in genetics, immunology, epidemiology, neuropsychology, and nursing (Krupp, Banwell, & Tenembaum 2007). The purpose of the group was, for the first time, to develop consensus definitions for CNS demyelinating disorders in children and adolescents. The group proposed criteria for pediatric MS, ADEM, NMO, and CIS. In September 2013, the group met to revise the 2007 definitions to incorporate advances in understanding the clinical and neuroradiologic features of these disorders (Krupp et al., 2013).

A diagnosis of pediatric MS can be made if one of the four following criteria are met (McDonald et al., 2001; Polman et al., 2011): 1) Two or more nonencephalopathic (e.g., distinct from ADEM), clinical CNS events where the cause is presumed to be inflammatory; these events must be separated by more than 30 days and involve at least two areas of the CNS, 2) One nonencephalopathic episode typical of MS which is associated with MRI findings consistent with the 2010 Revised McDonald criteria for dissemination in space, and involves a follow-up MRI demonstrating at least one new lesion consistent with dissemination in time, 3) One ADEM attack followed by a nonencephalopathic clinical event at least three months after symptom onset, which must also be associated with new MRI lesions that fulfill the 2010 Revised McDonald criteria for dissemination in space, or 4) An initial, single, acute event not meeting ADEM

criteria, with MRI findings consistent with the 2010 Revised McDonald criteria for dissemination in time and space (applies only to children 12 years and older).

Prevalence Rate

The National Multiple Sclerosis Society (2013) reports that 8,000 to 10,000 children (age 18 or younger) in the United States have MS. Studies suggest that early onset of MS (onset before age 18) occurs in 3% to 5% of all cases of MS (Boiko et al., 2002; Cole & Stuart, 1995; Duquette et al., 1987; Ghezzi et al., 1997; Ruggieri et al., 1999), and that less than 1% of all MS cases have an onset before the age of 10 (Cole, Auchterlonie, & Best, 1995; Shaw & Alvord, 1987). However, up to 10% of all MS patients experience their first attack during their childhood years (Venkateswaran & Banwell, 2010). The overall incidence of pediatric MS has been reported to be between 0.18-0.9 per 100,000 children (Banwell et al., 2009; Langer-Gould et al., 2011; Vargas-Lowy & Chitnis, 2012). However, more research is needed in this area. What can be drawn from the research thus far is that pediatric MS is rare, and the vast majority of MS cases begin in adulthood.

Rates of pediatric MS have also been found to vary between ethnic groups. Incidence is reported to be highest in African American (4.4 per 100,000 person-years) and Asian/Pacific Islander (2.8 per 100,000 person-years) ethnic groups (Absoud et al., 2013; Langer-Gould et al., 2011). Caucasian (1.03 per 100,000 person-years) and Hispanic (1.5 per 100,000 person-years) children have slightly lower incidence rates. African American children are also significantly more likely to have MS than Caucasian children (Langer-Gould et al., 2011). While there is a significant female preponderance in adult-onset MS, with a ratio of 2.54:1 (Canadian Collaborative Project on Genetic

Susceptibility to MS), the female to male ratio in children has been reported as 1.45:1, and drops to 1.17:1 in children under 10 years (Ruggieri et al., 1999). This implicates hormonal factors in MS pathology (Banwell, 2004).

Age of Onset

MS can be diagnosed at any age, but most children with MS experience their first attack between the ages of 9 to 13 years (Banwell, 2004; Banwell, Ghezzi, et al., 2007). Children with an initial episode of ADEM who go on to develop MS appear to have a younger age of onset (Banwell, Krupp, et al., 2007; Mikaeloff, Adamsbaum, et al., 2004). In the largest pediatric prospective study to date conducted in France, 296 children were followed for a period of 2.9 ± 3 years (Mikaeloff, Suissa, et al., 2004). The study reported that 56.7% of children with their first episode of central demyelination developed a second episode and qualified for a diagnosis of MS. Age of onset may also vary by ethnicity. Unpublished data from a UCSF pediatric MS cohort demonstrated that age of onset was significantly younger in non-white children and Hispanic children compared to Caucasian children (as cited in Chabas, Strober, & Waubant, 2008).

Clinical Course

Unlike adult MS, over 95% of pediatric MS patients initially have a relapsing-remitting course (Banwell, Krupp, et al., 2007; Hahn, Shroff, Blaser, & Banwell, 2004; Venkateswaran & Banwell, 2010; Yeh, Chitnis, et al., 2009). Remission of neurological symptoms is followed by relapse rather than progressive neurological disability in 85.7% to 100% of cases (Boiko et al., 2002; Duquette et al., 1987; Renoux et al., 2007; Yeh, Chitnis, et al., 2009). Thus, primary progressive MS is rare in children. Studies that have examined patients with a mean disease duration of at least 10 years have estimated the

annual relapse rate to be higher than in the adult MS population, ranging from 0.38 to 0.87 (Boiko et al., 2002; Cole & Stuart, 1995; Ghezzi et al., 2002). Two prospective studies found that patients with disease onset before 18 years had an increased rate of relapse compared to adults during the first several years of their disease (Gorman, Healy, Polgar-Turcsanyi, & Chitnis, 2009; Simone et al., 2002).

There is significant variability in the proportion of individuals who convert to secondary progressive phase MS, as well as the overall rate of disability progression (Yeh, Chitnis, et al., 2009). On average, children with MS appear to convert to secondary progressive phase MS ten years later than the adult disease, as measured from time of onset (Yeh, Chitnis, et al., 2009). The estimated median time from onset of symptoms to reach a point where ambulation is limited is 28 to 29 years in pediatric MS, compared with 18 years in adult-onset patients (Boiko et al., 2002; Renoux et al., 2007). Thus, despite the fact that it takes pediatric MS patients longer to reach this disability status, on average they reach it at a younger age (Simone et al., 2002; Yeh, Chitnis, et al., 2009).

Etiology of Pediatric Multiple Sclerosis

There are many theories regarding the etiology of pediatric MS, but the most widely researched and validated include genetic and physiological predispositions, geographic latitude, infections, immunology, and hormonal factors. It is generally understood that pediatric MS is the product of multiple factors, both genetic and environmental, none of which is thought to be sufficient on its own to cause the development of MS (Kakalacheva, Munz, & Lunemann, 2011).

Genetic predispositions. Genetic influences are thought to contribute to the development of MS, in both adults and children. The lifetime risk of developing MS in the first-degree relatives of affected individuals is close to 5%, and individual risk increases with the number of affected relatives (Sadovnick, Dircks, & Ebers, 1999). In addition, twin studies have revealed a concordance of 30% in identical twins, which is six times higher than that of dizygotic twins and other siblings (Sadovnick et al., 1993). Familial risk is further increased if the affected relative has a younger age of onset (Sadovnick, Yee, & Ebers, 2000). However, the familial risk for first-degree relatives of pediatric MS patients remains unknown (Banwell, 2004). Family history data suggests that 6% to 23% of children with MS have a positive family history of MS in either a first or second degree relative, or in their extended family (Banwell, 2004; Venkateswaran & Banwell, 2010). This is similar to the 15% to 20% rate reported for adults with MS (Milo & Kahana, 2010; Sadovnick, Baird, & Ward, 1988).

Specific genetic haplotypes of immunologic genes are thought to be crucial in determining disease susceptibility. In particular, the human leukocyte antigen (HLA) gene complex has been associated with increased MS risk in both adults and children (Banwell et al., 2011; Barcellos et al., 2003; Dyment, Ebers, & Sadovnick, 2004; Ligers et al., 2001). MS patients are significantly more likely than the general population to carry the HLA DRB1*1501, DQA1*0102, and DQB1*0602 loci (Allen et al., 1994; Banwell et al., 2011; Hauser et al., 1989). HLA-encoded molecules are cell-surface glycoproteins that play an important role in the immune system's ability to recognize self- from non-self (Oksenberg, Baranzini, Sawcer, & Hauser, 2008). Interestingly, the HLA gene complex is also implicated in other neurodegenerative disorders such as

Parkinson's disease (Ahmed et al., 2012) and frontotemporal dementia (Girard & Rouleau, 2014).

New MS susceptibility loci outside the HLA region have been discovered more recently, including interleukin-2 receptor α, interleukin-7 receptor α, CD6, CD58, CLEC16A, IRF8, IL12A, Olig3-TNFAIP3, TNFRSF1A, PTGER4, and RGS1 genes (Hohlfeld, 2009). Some genes (e.g., HLA-DR15 and APOE4 alleles) may also affect rate of disease progression and age of onset (Chapman et al., 2001; Masterman et al., 2000).

Immunology. Immunological factors undoubtedly play a role in the pathogenesis of MS in both adults and children, but more research is still needed to understand these factors more thoroughly. MS is thought to be due to a loss of the normal regulation of the immune response (Oksenberg & Hauser, 1999). In MS specific immune cells (e.g., T cells), which normally reside outside the CNS, become activated and cross the blood-brain barrier to enter the CNS. They then go on to stimulate other types of immune cells (e.g., macrophages, cytokines, B cells). In addition, antibodies to the myelin sheath form, cross the blood-brain barrier, and attack the myelin.

Research continues to investigate whether this immune response is primary or secondary to another degenerative process in the brain (Banwell et al., 2008; Trapp & Nave, 2008). For example, a study in children with inflammatory demyelination found heightened T-cell reactivity to self and environmental antigens, but also found similar responses in children with other CNS injuries and Type I diabetes (Banwell et al., 2008). This challenges the prevailing view that MS is caused by a primary autoimmune process targeting the myelin sheath.

Hormonal factors. Given the gender ratio in MS (2.54:1 females to males), hormonal factors are thought to play an important role in both the immune response as well as the clinical features of the disease (Chitnis, 2013). Relapse rates and lesion activity have been found to decline during pregnancy, particularly during the third trimester, and increase in the first three months postpartum (Confavreux et al., 1998; van Walderveen et al., 1994). MS symptoms may also be exacerbated during the premenstrual phase of the menstrual cycle (Zorgdrager & De Keyser, 2002). Zorgdrager and De Keyser (2002) suggest that this may be in part due to the role of estrogens, which may shift the immune response from pro-inflammatory (Th1) to anti-inflammatory (Th2).

Infection. Several lines of evidence have proposed that infections may cause and maintain the pathophysiological response in MS. Patients with MS have been found to contract common childhood illnesses at a later age than the general population (Granieri & Casetta, 1997). In addition, they have elevated levels of serum or antibodies to several viruses, in particular Epstein-Barr virus (Ascherio & Munger, 2010; Cook, 2011). Viral and bacterial infections are thought to also play a role in triggering relapses in MS. Several theories related to infections as a cause of MS have been proposed. One of the most well-known is the poliomyelitis-hygiene hypothesis, first proposed over 50 years ago, which posits that contact with an infectious agent during childhood protects against MS while later contact with this agent may trigger MS (Poskanzer, Schapira, & Miller, 1963). Another theory is the prevalence hypothesis, which postulates that MS can be triggered by viruses that are common in geographic regions of high MS frequency (Kesselring & Lassman, 1997; Kurtzke, 2005).

Similar patterns have started to emerge in the pediatric MS population. A multinational study of children with pediatric-onset MS found that Epstein-Barr seropositivity was associated with nearly a three times increased likelihood of MS (Banwell, Krupp, et al., 2007). However, a more recent study found that after adjusting for age of onset, the presence of remote Epstein-Barr infection did not significantly increase the likelihood of developing MS (Banwell et al., 2011). Although concerns about vaccines have also been raised, several studies have suggested no increased risk in developing MS or relapse rate following hepatitis B and tetanus vaccines (Mikaeloff, Caridade, Assi, Tardieu, & Suissa, 2007; Mikaeloff, Caridade, Rossier, Suissa, & Tardieu, 2007). Pediatric-onset MS does not appear to be associated with other childhood infections such as measles, mumps, rubella, varicella, pertussis, or scarlet fever (Bager et al., 2004).

Geographic latitude. The prevalence of MS is unevenly distributed throughout the world, implicating environmental factors in its pathology. Generally, MS frequency increases progressively with geographic latitude, such that it is less common in regions closer to the equator (Kurtzke, 2005). Regions of high prevalence include the northern United States, Canada, northern Europe, Israel, eastern Russia, New Zealand, and southeastern Australia (Rosati, 2001). MS is relatively rare in other parts of Asia, Africa, northern South America, and Japan. Immigration studies have suggested that risk for MS is associated with where an individual lives prior to the first two decades of life. For example, Europeans migrating to areas of low incidence before age 15 adopt the lower risk associated with their new country, while those migrating after age 15 inherit the risk of their country of origin (Kurtzke, 2000).

Sunlight and Vitamin D are thought to play a critical role in this geographic distribution. The skin produces Vitamin D when exposed to sunlight. Higher exposure to sunlight has been associated with decreased risk of developing MS, perhaps due to increased levels of Vitamin D (Milo & Kahana, 2010). Studies have proposed that Vitamin D deficiency is a mediator of the latitude gradient in MS (Kampman & Brustad, 2008). A review of these studies suggests that Vitamin D mediates a shift to an anti-inflammatory immune response, including increased T cell regulatory functioning (Smolders, Damoiseaux, Menheere, & Hupperts, 2008). While there is limited literature specifically on sun exposure and MS in the pediatric population, a recent prospective national cohort study found that low levels of Vitamin D are associated with increased risk of developing MS in children (Banwell et al., 2011).

Other factors. Several other factors have been proposed to play a role in risk for MS, but have not been studied in as much depth. These include psychological stress, heat, physical trauma, dietary fat and antioxidants, higher education, and cigarette smoking (Milo & Kahana, 2010). For example, in one population-based case-controlled study in France, children with MS onset prior to 16 years were examined as compared to the general population (Mikaeloff, Caridade, Tardieu, & Suissa, 2007). This study found that exposure to parental smoking was associated with an increased risk of developing pediatric MS, and that the duration of exposure also affected the level of risk.

Conclusion. The probability that an individual develops MS may be dependent on all or a combination of these factors, and research has yet to examine the extent to which these factors specifically contribute to pediatric MS. Genetics, geographic location, exposure to infections, immune activity, and hormonal factors all appear to

contribute to MS pathogenesis. Disease severity and likelihood of relapse may also be dependent upon these factors.

Neuroanatomy and Pathophysiology

Pathophysiology. The few pathological studies of pediatric MS suggest that it shares many features with the adult disease. The hallmark of adult MS is commonly understood to be the white matter plaque, characterized by loss of the myelin sheath around axons and proliferation of astrocytes, forming scar tissue termed gliosis (Compston & Coles, 2002; Noseworthy, Lucchinetti, Rodriguez, & Weinshenker, 2000). Active lesions generally consist of inflammatory cells (macrophages, T cells, and reactive astrocytes) as well as areas of remyelination, also known as shadow plaques. A large autopsy study has described four distinct subtypes of demyelinating lesions, suggesting heterogeneity across the adult MS population as well as distinct pathophysiological mechanisms that underlie MS (Lucchinetti et al., 2000; Lucchinetti, Brück, Rodriguez, & Lassmann, 1996). It is currently unknown whether the pathology of pediatric MS can be classified into these subtypes.

Axonal demyelination causes slowing or halting of nerve conduction, producing some of the earliest clinical symptoms in MS (Noseworthy et al., 2000). Active plaques may demonstrate signs of damage such as axonal transection and swelling (Trapp & Nave, 2008). After an attack, sodium channels become redistributed along the axons and remyelination begins to take place. However, over time neurological functioning is permanently decreased due to irreversible axonal injury, depletion of oligodendrocytes, and gliosis (Wingerchuk, Lucchinetti, & Noseworthy, 2001). In addition to white matter

lesions, accumulating evidence demonstrates that axonal damage also occurs in normal-appearing white matter (De Stefano et al., 2002; Waxman, 2000).

In children with MS this is also the case, with damage in normal-appearing intrahemispheric, interhemispheric, and projection white matter tracts (Vishwas, Chitnis, Pienaar, Healy, & Grant, 2010). Notably, a recent study has suggested that the extent of acute axonal damage in early active demyelinating lesions is increased by 50% in pediatric patients as compared to adults (Pfeifenbring et al., 2015). This finding may provide some explanation for the often observed severe onset in pediatric MS.

Neuroanatomy. While MS is primarily a disease affecting white matter, lesions can occur in any part of the CNS. In adult MS, lesions are most commonly found in the optic nerves, the corpus callosum, the periventricular region, and white matter of the cerebellum, brain stem, spinal cord (Noseworthy et al., 2000). In pediatric MS, infratentorial lesions (e.g., brainstem, pons, cerebellum), particularly in the pons, are more frequent and less well-defined as compared to adults (Bigi & Banwell, 2012).

Neuroimaging. Structural MRI plays an important role in the diagnosis of both pediatric and adult MS. On a conventional T2-weighted structural MRI, MS lesions can be identified as hyperintense bright spots (Fazekas et al., 1999). However, cortical gray matter lesions are not typically detectible as T2 hyperintense foci on MRI. Although MRI plays an important role in diagnosis, differential diagnosis remains an area of active research due to the overlap of pediatric MS with other demyelinating disorders (Banwell, Shroff, et al., 2007).

MRI features of pediatric MS are generally consistent with those seen in adult MS, with a few key exceptions. Pediatric MS tends to display increased T2 lesion

volume and lesion number on MRIs at the time of the first demyelinating event as compared to adults (Waubant et al., 2009; Yeh, Weinstock-Guttman, et al., 2009). These findings are suggestive of increased inflammation and a more active disease in children with MS as compared with adults. Despite the more aggressive nature of pediatric MS earlier on, disability is slower to accrue and the time to irreversible disability is longer in this age group (Renoux et al., 2007; Simone et al., 2002). Several reasons may exist for this paradox including shorter disease duration, the presence of greater tissue reserves, and greater reparative abilities (Yeh, Weinstock-Guttman, et al., 2009).

Children with MS generally display less dissemination in space than adults (Hahn et al., 2004). Very young children often have diffuse bilateral white matter lesions at the time of their first attack and poorly defined lesions involving deep gray matter structures. Relative to healthy controls, pediatric patients have lower total brain volume, thalamic volume, and gray matter volume (Mesaros et al., 2008; Till, Ghassemi, et al., 2011).

Poorly defined lesions involving deep gray matter structures are often seen in younger children with MS, which is commonly seen in ADEM cases as well (Absoud et al., 2013; Simone et al., 2002). Pediatric MS has been associated with early gray matter atrophy in the thalamus early in the disease course, with sparing of the cortex, suggestive of Wallerian degeneration (i.e., loss of axons due to being disconnected from their original cell bodies; Mesaros et al., 2008). While in adult MS gray matter atrophy correlates with degree of disability (Fisher, Lee, Nakamura, & Rudick, 2008; Geurts & Barkhof, 2008; Siffrin, Vogt, Radbruch, Nitsch, & Zipp, 2010), this association has not been found in pediatric MS.

Neuroimaging correlates of neuropsychological functioning. In adults, neuropsychological test performance relates fairly strongly to overall MS lesion volume on MRI (Rao, Leo, Haughton, St. Aubin-Faubert, & Bernardin, 1989; Rovaris & Filippi, 2000). However, fewer studies have correlated MRI with cognitive functioning in pediatric MS. One of the few studies to date correlated brain MRI measures with neuropsychological functioning in 35 pediatric-onset MS patients and 33 healthy controls (Till, Ghassemi, et al., 2011). The researchers found that thalamic volume accounted for significant variance in predicting global IQ, expressive vocabulary, and processing speed. In addition, thalamic volume differentiated patients with cognitive impairment from those who were not cognitively impaired.

Another study from the same group correlated MRI features with executive functioning measures (Till, Ho, et al., 2012). They found that whole brain and regional brain volumes were strongly correlated with task performance and parent ratings of executive functioning skills. Lesion volume was also correlated with these measures, but to a lesser extent. Interestingly, fractional anisotropy values in the corpus callosum, right frontal lobe, and parietal regions have also been found to correlate with arithmetic abilities in pediatric MS patients (Till, Deotto, et al., 2011). Thus far, brain lesion volume appears to be unrelated to psychosocial outcomes in children with pediatric MS (Till, Udler, et al., 2012).

Researchers have also begun to use functional MRI to examine functional connectivity networks in pediatric MS. A recent study combined structural and functional MRI to further characterize cognitive impairment in pediatric MS (Rocca, Absinta et al., 2014). They found that cognitively impaired patients had more T2 lesions,

more severe damage to the white and gray matter in the posterior parietal lobes (i.e., precuneus, posterior cingulum, and corpus callosum), and reduced functional connectivity of the precuneus than patients who were not cognitively impaired. Pediatric MS patients also demonstrate additional large-scale neuronal network abnormalities including decreased functional connectivity of the default-mode, sensorimotor, secondary visual, bilateral working memory, and executive control networks, and increased functional connectivity of right medial frontal gyrus of the attention network (Rocca, Valsasina et al., 2014). Table 1 compares the pathophysiology, neuroanatomy, and neuroimaging of pediatric and adult MS.

Table 1

Neurobiological Correlates of Pediatric and Adult MS

	Pediatric-Onset MS	Adult-Onset MS
Neuropathology	White matter plaque, axonal demyelination in lesions and normal-appearing white matter, gliosis More pronounced acute axonal damage in early active demyelinating lesions Lower axonal density in lesions	White matter plaque, axonal demyelination in lesions and normal-appearing white matter, gliosis

Table 1 (continued)

Neurobiological Correlates of Pediatric and Adult MS

	Pediatric-Onset MS	Adult-Onset MS
Anatomical Location	More infratentorial lesions, especially pons, also in brainstem and cerebellum	Lesions in spinal cord, optic nerves, corpus callosum, periventricular region, white matter of cerebellum, brain stem
Neuroimaging	Greater T2 lesion volume and increased number of lesions at time of first demyelinating event Decreased total brain, thalamic, and gray matter volume relative to controls Thalamic gray matter atrophy in early stages	Lower T2 lesion volume and fewer lesions at time of first demyelinating event Decreased thalamic and gray matter volume relative to controls Thalamic gray matter atrophy in early stages

Note. MS – multiple sclerosis.

Treatment of Pediatric Multiple Sclerosis

In 2012, the International Pediatric MS Study Group elected a steering committee to conduct a structured review of the existing disease modifying therapies for pediatric MS (Chitnis et al., 2012). Their consensus statement noted specific considerations for

pediatric MS, including the small numbers of patients available for inclusion in clinical trials. They also made recommendations regarding the use of existing first-line and second-line therapies, as well as recommendations for the use of emerging therapies (either in phase III clinical trials or recently approved for adult MS).

First-line therapies. Beta-interferons and glatiramer acetate are the primary first-line disease-modifying therapies recommended for pediatric MS, and they have been used in the adult MS population for over 15 years (Chitnis et al., 2012). These treatments work by suppressing the immune system, and they have an immediate impact on disease activity by reducing relapse rates and lesion formation. The short-term safety profile for these treatments appears similar in children to that of adults, but long-term safety data are lacking (Chitnis et al., 2012). High dose corticosteroids are considered standard treatment in adult MS to accelerate recovery after an attack, and they are recommended as an add-on to baseline therapy for pediatric MS for 6-12 months during phases of acute demyelination (Banwell, Ghezzi, et al., 2007; Chitnis et al., 2012). However, the side effects for steroid therapies increase with prolonged dosages and can include facial flushing, irritability, hyperactivity, poor sleep, and increased appetite in children (Banwell, 2005).

Second-line and emerging therapies. Several treatments are in phase III clinical trials or in the early approval process for the adult MS population, and have been considered for use in children. Small cohort studies have been conducted on both natalizumab (Tysabri; Borriello, Prosperini, Luchetti, & Pozzilli, 2009; Ghezzi, Pozzilli, et al., 2010; Huppke et al., 2008) and cyclophosphamide (Makhani et al., 2009) in children with MS, but larger studies are needed to identify dosing and long-term safety.

Initial studies with natalizumab in children suggest that it reduces clinical and MRI relapses (Ghezzi, Pozzilli, et al., 2010; Huppke et al., 2008). Other therapies under study include Mitoxantrone, Fingolimod, Rituximab, and Cladribine (Banwell, 2005).

Conclusion

Overall, the existing literature on pediatric MS suggests that while it is similar to adult MS on a variety of levels, it is also distinct in a number of ways. Pediatric-onset MS is much less common than adult MS, and most patients experience a relapsing-remitting course. While disability progression is slower in pediatric patients, significant disability may occur at a younger age and may be worse in certain ethnic groups. Like adults, the etiology of pediatric MS is thought to be related to a number of environmental and biological factors. Treatments for pediatric MS have preceded the completion of clinical trials, so many children are receiving the same treatments as adults without knowledge of their effects in children.

Cognitive Functioning in Multiple Sclerosis

Cognitive Functioning in Adult MS

Given the neurobiological characteristics of MS, it is not surprising that there are significant effects of MS on cognition. Studies have found that these cognitive deficits are often present in the domains of attention, processing speed, learning and memory, and executive functioning. However, because lesions can affect any part of the CNS, any aspect of neuropsychological functioning can be affected.

General intellectual functioning. In the MS literature, cognitive impairment is most often defined as performing 1.5 to 2 standard deviations below the normative mean on 18% to 30% of the neuropsychological tests (Fischer et al., 2014). Cognitive

impairment occurs in approximately 40% to 60% of adults with MS (Rao, Leo, Bernardin, et al., 1991). Factors mediating cognitive impairment include age and gender (Prakash et al., 2008). A significant difference has been found between verbal and nonverbal intellectual ability in MS, with patients showing greater impairment on tests of nonverbal intellectual ability (Prakash et al., 2008).

Attention and processing speed. Attention skills are a necessary precondition for most mental activities, and as such attention is virtually impossible to measure separately from other mental constructs (Kramer & Delis, 1998). Attention can be thought of as an individual's awareness of the environment and selective responsiveness to specific stimuli (Kolb & Winshaw, 2003). An individual's processing speed is the time it takes him or her to process information, which can be measured through tasks of reaction time, response latency, psychomotor speed, decision speed, and perceptual speed (Salthouse, 2000). Deficits in processing speed can create a higher burden on attention; thus these two capacities go hand in hand.

Impaired processing speed is a common finding in patients with MS, and it appears to partially account for other deficits such as in attention and working memory (Archibald & Fisk, 2000; Kail, 1998; Prakash et al., 2008). In Prakash and colleagues' (2008) meta-analysis of 57 studies of adult MS, patients showed their greatest cognitive deficits on measures of processing speed and selective/focused attention. The domain of selective/focused attention was comprised of measures including the Symbol Digit Modalities Test, Trail Making Test, and Stroop word and color readings (Prakash et al., 2008).

Working memory. Working memory is an individual's ability to store, encode, and recall a limited amount of information in memory for brief periods of time (Broadbent, 1958). Deficits in processing speed and working memory play an important role in contributing to deficits in verbal and nonverbal learning (Lezak, Howieson, Bigler, & Tranel, 2012). In a study examining a variety of executive functions, Foong and colleagues (1997) correlated neuropsychological performance to frontal lesion load in patients with MS (N = 42) and healthy controls (N = 40) between the ages of 24 and 50. They administered two tests of spatial working memory (the Spatial Span Test and the Spatial Working Memory Test). The study found that MS patients performed worse than controls on a spatial working memory task, and that this performance could not be explained by poor immediate recall or less efficient use of strategy. Thus, this finding indicated a specific impairment in spatial working memory. Other studies have also documented deficits in verbal working memory in patients with MS (Grafman, Rao, & Litvan, 1990; Litvan et al., 1988).

Language. Language skills encompass an individual's ability to communicate through reading, writing, and speaking, as well as comprehend language input. These abilities are thought to remain relatively intact in MS apart from those emphasizing rapid retrieval, which is highly dependent on processing speed. For example, performance on measures assessing verbal academic skills is similar to that of healthy controls (Prakash et al., 2008). Aphasia and alexia are rare, but can sometimes occur in the setting of an acute attack and quickly resolve at least to some degree (Day, Fisher, & Mastaglia, 1987; Devere, Trotter, & Cross, 2000; Dogulu, Kansu, & Karabudak, 1996; Mao-Draayer & Panitch, 2004). Of the deficits that do occur in this domain, verbal fluency has been

noted to be the most detrimentally affected (Friend et al., 1999; Rao et al., 1989; Tuncer, Mıdı, & Feyzioğlu, 2012), with one meta-analysis reporting an effect size of -0.689 (Prakash et al., 2008). Confrontation naming was also impaired in several studies, but it appears to be better preserved than verbal fluency (Henry & Beatty, 2006; Prakash et al., 2008).

Visual-spatial and visual-motor functions. Visual-spatial skills are an individual's ability to perceive objects in relation to other visual information. These skills encompass right hemisphere functions such as spatial orientation, construction, and visual orientation of figures (Lezak et al., 2012). Although vision impairments are frequently found in MS, these patients also often evidence difficulties with visual-perception (Rao, Leo, Ellington et al., 1991; Vleugels et al., 2000). Many aspects of visual-perception have been shown to be impaired in MS, including visual form perception (van den Burg, Van Zomeren, Minderhoud, Prange, & Meijer, 1987; Vleugels et al., 2000), facial perception (Beatty, Goodkin, Monson, & Beatty, 1989; Ward et al., 1999), and visual-spatial perception (Rao, Leo, Ellington et al., 1991). As noted above, many other functions can also affect visual-spatial abilities, including motor and executive abilities, which are also commonly impaired in MS (Lau, Chan, & Keung, 1998). Thus, effects of MS on visual-spatial abilities are difficult to isolate from other areas of functioning and must be interpreted cautiously.

Motor and psychomotor functioning. Motor symptoms are extremely common in patients with MS, with 80% to 90% of patients reporting limb weakness, spasticity, or coordination problems (Beard, Hunn, & White, 2003). Consequently, patients generally perform poorly on tasks requiring rapid coordination of motor responses and fine motor

skills, including on the Grooved Pegboard Test and Finger Tapping Test (Heaton, Nelson, & Thompson, Burks, & Franklin, 1985; Prakash et al., 2008; van den Burg et al., 1987). The measurement of other domains (e.g., processing speed using a written coding task) is often confounded by these motor deficits.

Learning and memory. Although global memory deficits are reported in MS, there is much inconsistency across studies, perhaps related to the heterogeneity of MS and disease duration. Verbal memory is an individual's ability to encode, store, and recall verbal or auditory information into episodic memory (Kramer & Delis, 1998). Patients with MS are specifically impaired in their use of learning strategies for verbal memory. For example, they are less likely to use visual imagery (Canellopoulou & Richardson, 1998) and semantic clustering (Arnett et al., 1997). Consequently, their performance on multi-trial word list or paired associate verbal learning tasks is often weak (Faglioni, Bertolani, Botti, & Merelli, 2000; Thornton, Raz, & Tucker, 2002). By contrast, they tend to perform better on story memory tasks, which give context to the verbal information (Beatty, 2004). A meta-analysis of cognitive impairments in relapsing-remitting MS found this population's greatest memory deficits to be in verbal delayed recall (Prakash et al., 2008).

Non-verbal or visual memory involves the ability to encode, store, and recall non-verbal information (Kramer & Delis, 1998). In a review of studies assessing memory functioning in MS by Thornton and Raz (1997), large effect sizes were found for nonverbal memory deficits, including free recall (.546), cued recall (.753), and recognition (.636).

Executive functioning. Executive function abilities include attentional control, mental flexibility, planning, and goal-directed behavior (Delis, Kaplan, & Kramer, 2001). These abilities are necessary for higher order functioning including activities of daily living (ADLs) and instrumental activities of daily living (IADLs), and they are mediated by the frontal lobes (Luria, 1966). Impairments in executive functioning are global, affecting multiple aspects of behavior and cognitive functioning, and they can limit an individual's capacity for independence and social relationships (Jurado & Rosselli, 2007).

Patients with MS have been noted to have difficulty with tasks requiring planning and sequencing, although differences between the patient and control group sometimes only emerge with the most difficult levels of tasks (Arnett et al., 1997; Foong et al., 1997). In addition, cognitive estimation (Foong et al., 1997), temporal ordering (Beatty & Monson, 1991), monitoring of internal and external stimuli (Landrø, Sletvold, & Celius, 2000), and self-regulation (Benedict, Priore, Miller, Munschauer, & Jacobs, 2001) have also been shown to be disrupted.

Summary of cognitive impairments in adult MS. Research indicates that adults with MS commonly show impairments in attention, processing speed, motor functioning, memory and learning, and executive functioning. They may also evidence difficulties with verbal fluency and confrontation naming, while other language skills generally remain intact. Although these patients also show impairments in visual-perceptual tasks, these findings are often inseparable from primary visual impairment and deficits in fine motor functioning. Longitudinally, studies in adults have found that cognitive impairment remains relatively stable over a one- to two-year period (Fischer et al., 2000; Kappos et al., 2009; Weinstein et al., 1999).

Cognitive Functioning in Pediatric MS

Although cognitive functioning in pediatric MS has received increased attention in the last decade, the findings are limited due to small sample sizes, heterogeneous populations, differing assessment batteries, and differences in study design. Nevertheless, the existing research suggests that the neuropsychological profile of pediatric MS resembles that of adult MS in a number of ways, but also shows some significant differences. Similar to adults, studies have found that a significant proportion of children with MS have deficits in general cognition, complex attention, visual-motor integration, aspects of memory, executive functioning, and verbal fluency (Banwell, Ghezzi, et al., 2007). In addition, children with MS may show additional deficits in linguistic abilities that are more apparent than in adults, including problems with receptive language (Amato et al., 2008).

General intellectual functioning. Estimates suggest that approximately one-third of pediatric MS patients experience cognitive impairment (Amato et al., 2008; Ghezzi, Goretti, et al., 2010; Goretti et al., 2012; Julian et al., 2012; MacAllister et al., 2005). While demographic and disease-related predictors of cognitive impairment remain unclear, some studies have found associations with age of onset (Amato et al., 2008; Banwell & Anderson, 2005), disease duration (Banwell & Anderson, 2005), disease severity (Julian et al., 2012; MacAllister et al., 2005), thalamic volume (Till, Ghassemi, et al., 2011), and IQ (Amato et al., 2008).

Attention and processing speed. Slowed information processing is one of the most commonly observed deficits in both adult and pediatric MS (Banwell & Anderson, 2005; Julian et al., 2012). Julian et al. (2012) measured processing speed using the

Coding/Digit Symbol subtest of the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV; for ages 16 and above) or the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; for ages 15 and below), as well as the Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test. Children with MS (mean age = 14.8 years) were significantly impaired in these tasks, confirming that this cognitive domain is susceptible to cognitive impairment across the lifespan in patients with MS. Several other studies have found similar impairment when measuring processing speed through the WISC-IV Processing Speed Index and the Symbol Digit Modalities Test (Banwell & Anderson, 2005; Smerbeck et al., 2011). Longitudinally, processing speed (specifically visual-motor speed) demonstrated the most pronounced decline in performance over time among children (Marin, Banwell, & Till, 2012).

Working memory. While short-term memory capacities appear to be relatively undisturbed, several studies suggest that working memory functions are deficient in children with MS (Amato et al., 2008; Banwell & Anderson, 2005; Blaschek et al., 2012; Charvet, O'Donnell et al., 2014; MacAllister et al., 2005). In a longitudinal evaluation of cognitive functioning, Charvet, O'Donnell et al. (2014) used Digit Span to measure attention and working memory in a sample of 67 children with MS or CIS aged 8 to 17 years. At both baseline and follow-up, they found that Digit Span (both Forward and Backward) was among the three most impaired measures in the sample.

A smaller pilot study of 10 pediatric MS patients aged 6 to 16 years aimed to measure a variety of neuropsychological functions including working memory (Banwell & Anderson, 2005). This domain was measured using the Concepts and Directions and Listening to Paragraphs subtests of the Clinical Evaluation of Language Fundamentals, as

well as the Freedom from Distractibility Index. The children in their cohort demonstrated deficits on all of these tasks. However, limitations of this study include its small sample size and the choice of tests used to measure working memory, as these subtests overlap with several other neuropsychological functions. Deficits in working memory found in this population are likely in part related to slow processing speed, although more research is needed to clarify this relationship.

Language. In contrast to adult MS where language abilities remain largely intact, pediatric MS frequently affects aspects of language functioning. Given that children are still developing language skills, these functions appear to be particularly vulnerable in this age group. Children with MS may show deficits in verbal fluency (Amato et al., 2010; MacAllister et al., 2005), receptive language (MacAllister et al., 2005), sentence comprehension (Amato et al., 2010), and crystallized knowledge (Ross, Schwebel, Rinker, Ness, & Ackerson, 2010), while other language abilities remain intact (Blaschek et al., 2012).

Julian et al. (2012) measured language functioning using the Wechsler Abbreviated Scale of Intelligence (WASI) Vocabulary subtest, the Wechsler Individual Achievement Test II Pseudoword Decoding, and the Expressive One-Word Picture Vocabulary Test (N = 187). Overall, the group did not show impairment on these language tasks, evidencing intact expressive language abilities and general knowledge. However, several smaller studies have revealed impaired confrontation naming as measured by the Boston Naming Test (MacAllister et al., 2005; MacAllister, Christodoulou, Milazzo, & Krupp, 2007), while one study found no difference between groups (Smerbeck et al., 2011). The larger of these two studies also showed impairment

in receptive language (MacAllister et al., 2005). Several studies have also shown poor performance on speed-dependent language functions such as verbal fluency (Amato et al., 2010; MacAllister et al., 2005).

Longitudinal research suggests that as compared with other cognitive functions, receptive language and verbal fluency show some of the most significant decline over a five-year period in patients aged 10 to 14 (Amato et al., 2010). Language functioning in MS also varies based on ethnicity, with African American children performing worse on both crystallized knowledge (WASI Verbal IQ) and expressive language abilities (Expressive One-Word Picture Vocabulary Test), but not on verbal fluency (mean age = 15.8 years; Ross et al., 2010). The fact that deficits in language occur with greater frequency in pediatric than adult MS suggests that demyelination in children may hinder the typical acquisition of language, which can significantly affect functioning in adulthood (Ross et al., 2010).

Visual-spatial and visual-motor functions. The initial symptoms of pediatric MS present as problems with vision in about 20% of patients (Banwell, Krupp, et al., 2007). However, it remains unclear whether visual-spatial functions are affected in this population independent of primary visual impairment and fine motor deficits. Julian and colleagues' (2012) study found a large degree of impairment on a measure of visual-motor integration and planning, the Beery-Buktenica Developmental Test of Visual-Motor Integration. On this task, moderate to severe impairment was reported for 16% of the sample, and mild impairment was found in 34% of the sample. However, on a visual-spatial measure that is independent of fine motor functioning (WASI Matrix Reasoning subtest), performances were relatively unimpaired (Julian et al., 2012). This suggests that

the deficits on tasks of visual-spatial functioning may be in part due to fine motor impairment.

Motor and psychomotor functioning. In the largest study of cognitive functioning in pediatric MS to date (N = 187), the most common impairment was on the Grooved Pegboard Test, a measure of fine motor speed and coordination (Julian et al., 2012). The authors attributed this finding to the effect of MS on both motor and cognitive functioning. A longitudinal study suggested that children with MS evidence a lack of developmentally appropriate gain in fine motor coordination over time, rather than a loss of function (mean age of onset = 7.4 years; Marin et al., 2012).

Learning and memory. Memory impairment is commonly reported in pediatric MS (Amato et al., 2008; MacAllister et al., 2005). A recent study examined verbal and nonverbal memory using the Test of Memory and Learning, Second Edition in children with MS (N = 32) aged 11 to 19 years and age- and sex-matched healthy controls (N = 26; Fuentes et al., 2012). In terms of verbal memory, pediatric MS patients performed worse than the control group on both the immediate and delayed conditions of the Memory for Stories subtest, but not on any other subtests. This indicated difficulty with both learning and memory, specifically in the context of stories. In another study (N = 37), verbal memory was measured among other neuropsychological functions using the Wide Range Assessment of Memory and Learning, Verbal Learning and Visual Learning subtests (MacAllister et al., 2005). Immediate verbal memory remained intact but delayed recall was impaired in 18.9% of patients. This finding was corroborated by a smaller study of 12 patients (mean age = 14 years) using the same measures (MacAllister, Christodoulou, Milazzo, & Krupp, 2007).

The role of nonverbal learning and memory in pediatric MS is unclear due to a limited number of studies. A study conducted by Smerbeck et al. (2011) assessed differences in visual-cognitive processing deficits between a pediatric MS group (N = 43) aged 9 to 18 years and an age-matched control group (N = 45). The Brief Visuospatial Memory Test-Revised was used to measure nonverbal learning and memory. The study found statistically significant differences between groups on Brief Visuospatial Memory Test-Revised Total Learning and Delayed Recall. Post-hoc analyses indicated that the impairments in visual learning and memory were partially due to deficits in encoding and consolidation of the information rather than retrieval. Another study demonstrated similar findings using the WRAML, with impairment in immediate recall of visual information for 8.1% of patients, and impairment of delayed recall in 11% of patients (mean age = 14.86 years; MacAllister et al., 2005).

Executive functioning. Children with MS have demonstrated impairment on a number of aspects of executive functioning. This is likely due to executive functions being mediated by the frontal systems, which are among the last to myelinate (MacAllister et al., 2013). MacAllister et al. (2005) used the Trail Making Test Parts A and B to assess visual scanning, motor speed, and complex attention in a pediatric MS group (N = 37) compared with normative data. They found the most common impairment among their cohort was in complex attention, or rapidly shifting attention between competing stimuli, with 29.7% of patients affected. This finding was corroborated in a later study done by the same group, which found the Trail Making Test Part B to be the most frequently impaired task in their sample (MacAllister, Boyd, Hollans, Milazzo, & Krupp, 2007).

Impairment in complex attention as measured by the D-KEFS Letter-Number Trail Making Task has been shown to vary by ethnicity in pediatric MS, with African American patients performing more poorly than their Caucasian peers (Ross et al., 2010). In a study that examined the cognitive trajectories of four pediatric patients with MS over ten years, the authors found one of the most pronounced neuropsychological declines to be on the Trail Making Test (Marin et al., 2012).

Regarding other executive function capacities, in Banwell and Anderson's (2005) pilot study discussed above, executive functioning was measured using the Wisconsin Card Sorting Test and the Rey-Osterreith Complex Figure Copy. Half of the children in this study achieved Copy scores in the poor (2^{nd} to 5^{th} percentile) or very poor ($<1^{st}$ percentile) range, suggesting impairment in self-generated organizational strategies. While these authors reported that their patients performed in the normal range on the Wisconsin Card Sorting Test, a recent larger study (N = 63) conducted by Amato and colleagues (2008) reported 12% to 40% of their sample to be impaired in the Modified Card Sorting Test. This discrepancy in findings may be attributable to a smaller sample size in Banwell and Anderson's study, as well as differences in disease duration between the two studies.

Summary of cognitive impairments in pediatric MS. While research is still relatively scarce, the findings thus far suggest that pediatric MS is characterized by deficits in general cognition, attention, information processing speed, memory, executive functions, and some aspects of language and visual-motor skills.

Although a thorough discussion of longitudinal data is not within the scope of this project, it is important to note that some earlier longitudinal studies of pediatric MS

demonstrated decline in certain cognitive functions over time (Amato et al., 2010; MacAllister, Christodoulou et al., 2007), while others have shown a lack of age-related gains relative to healthy controls (Charvet, O'Donnell et al., 2014; Till et al., 2013). A five-year follow-up study in pediatric MS found declines in roughly half of the participants, improvements in a quarter, and stability in a quarter (Amato et al., 2014). Declines in cognitive functioning have been linked to younger age at testing and age of MS onset (Amato et al., 2014; Hosseini, Flora, Banwell, & Till, 2014).

In terms of specific cognitive functions, longitudinal studies suggest that performance on measures of attention, processing speed, verbal fluency, visual-motor integration, visual memory, executive functions, calculation, and spelling are most likely to decline over time (Marin et al., 2012; Till et al., 2013). Further longitudinal studies are needed to clarify the frequency and severity of cognitive decline in this population.

Conclusion

In conclusion, the literature indicates that the cognitive deficits seen in pediatric and adult MS display significant overlap, with some notable differences. Both children and adults with MS display impairments in attention, processing speed, executive functioning, motor functioning, aspects of memory, and possibly visual-perceptual skills. Perhaps the most noteworthy difference between pediatric and adult MS is the greater involvement of linguistic functions in pediatric MS. While most language functions remain intact in adult MS (aside from verbal fluency and confrontation naming), childhood MS is more likely to involve deficits in receptive language, confrontation naming, and speed-dependent language tasks. With regard to working memory and executive functioning, it appears that both working memory and many aspects of

executive functioning such as complex attention, sequencing, and planning are impaired in both pediatric and adult MS. The impact of these cognitive deficits is potentially greater in children given that they are in a developmental period during which they are actively acquiring these cognitive capacities.

Psychological Functioning in Multiple Sclerosis

Psychological Functioning in Adult MS

Psychological disturbances are frequently seen in adult MS, with the most common disorders being depression, anxiety, bipolar disorder, and pathological laughing and crying (Cummings & Mega, 2003; Feinstein, Feinstein, Gray, & O'Connor, 1997; Schiffer & Babigan, 1984). Many patients also experience more psychological distress during relapses or increases in CNS inflammation (Feinstein, Ron, & Thompson, 1993; Kroencke, Denney, & Lynch, 2001).

Depression. Depression is characterized by the presence of a sad, empty, or irritable mood, accompanied by cognitive and somatic changes that significantly impact an individual's functioning (American Psychiatric Association, 2013). According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), depressive disorders include major depressive disorder, persistent depressive disorder (dysthymia), disruptive mood dysregulation disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specific depressive disorder, and unspecified depressive disorder (American Psychiatric Association, 2013).

Major depressive disorder is common in the MS population, with a prevalence rate between 27% and 54% (Minden & Schiffer, 1990; Sadovnick et al., 1996; Sullivan,

Weinshenker, Mikail, & Edgley 1995). In psychiatric interviews, 34% to 54% of MS patients reported a clinical history consistent with the symptoms of major depression (Joffe, Lippert, Gray, Sawa, & Horvath, 1987; Sadovnick et al., 1996). However, prevalence rates are lower for studies that are not clinic-based. A population-based study reported a 12-month prevalence rate of 25.7% for major depressive disorder in subjects aged 18 to 45, as compared with 8% of the general population (Patten, Beck, Williams, Barbui, & Metz, 2003). Suicide rates are also higher in this population (Stenager et al., 1992), and depressive symptoms tend to increase as MS progresses (Heesen et al., 2010).

Patients with MS exhibit less apathy and social withdrawal than other patients with depression, and instead show increased irritability, worry, and discouragement (Minden, Orav, & Reich, 1987; Ron & Logsdail, 1989). In addition, other features of MS such as fatigue and concentration difficulties may resemble depressive symptoms, making differential diagnosis more challenging. Interestingly, depression has been shown to have only a weak relationship with disease severity as measured by the Expanded Disability Status Scale (EDSS; Huber, Rammohan, Bornstein, & Christy, 1993; Patten & Metz, 1997).

Anxiety. A diagnosis of an anxiety disorder involves excessive fear (emotional response to a real or perceived imminent threat) and anxiety (anticipation of a future threat), as well as related behavioral disturbances (American Psychiatric Association, 2013). Associated symptoms of anxiety can include physical symptoms of being "keyed up or on edge," difficulty concentrating, fatigue, irritability, muscle tension, and sleep disturbance (American Psychiatric Association, 2013). According to the DSM-5, anxiety disorders can include separation anxiety disorder, selective mutism, specific phobia,

social anxiety disorder, panic disorder, agoraphobia, generalized anxiety disorder, substance-medication-induced anxiety disorder, anxiety disorder due to another medical condition, other specified anxiety disorder, and unspecified anxiety disorder (American Psychiatric Association, 2013).

Anxiety is also common and often comorbid with depression in adult MS, with prevalence estimates ranging from 25% to 41% on self-report measures (Zorzon et al., 2001; Janssens et al., 2003; Feinstein, O'Connor, Gray, & Feinstein, 1999). Generalized anxiety disorder is reported to be the most common anxiety diagnosis in this population, with 18.6% of patients meeting criteria (Korostil & Feinstein, 2007). This is followed by 10% of patients meeting criteria for panic disorder and 8.6% meeting criteria for obsessive-compulsive disorder (Korostil & Feinstein, 2007). The majority of subjects in this particular study had not been diagnosed or treated for these disorders.

Other psychological disturbances. Other psychological disturbances are also common in MS, and they often take the form of affective instability. Diaz-Olavarrieta and colleagues (1999) reported that family members of patients with MS described these patients as having "sudden mood changes," as well as being "agitated" and "irritable." They also found that patients were frequently disinhibited and impulsive. In addition, nearly 10% of MS patients exhibit a phenomenon called "pathological laughing and crying," which resembles pseudobulbar affect (Chwastiak & Ehde, 2007). Patients who suffer from this disabling condition may suddenly lose emotional control in the form of laughing or crying disproportionately to the situation. They may also be more likely to be in the progressive stage of the disease and demonstrate more cognitive deficits (Feinstein et al., 1999).

Psychological Functioning in Pediatric MS

Chronic illnesses such as cystic fibrosis, diabetes, and sickle cell disease have been shown to significantly increase the risk of psychiatric disorders in childhood (Pinckney & Stuart, 2004; Schatz et al., 2001). For disorders that involve the CNS, the risk is even greater (King et al., 2007; Schatz et al., 2001). For children with MS, both the chronic nature of the illness as well as its CNS involvement renders this population highly vulnerable to psychological disturbance.

The prevalence of psychiatric disorders in childhood MS varies widely, with 30% to 60% of patients meeting criteria for mood disorder, anxiety disorder, attention deficit hyperactivity disorder (ADHD), or adjustment disorder (Amato et al., 2008; Boyd & MacMillan, 2005; Goretti et al., 2010; MacAllister et al., 2005; Suppiej & Cainelli, 2014; Thannhauser, 2009; Weisbrot et al., 2014). These disorders can have a devastating affect on all aspects of the child's life, including academic and school functioning as well as life at home. Psychological functioning is poorly understood in children with MS, and more research is needed in this area.

Depression. In the few studies that have examined depression, the prevalence in children with MS varies greatly, with estimates ranging from 6% to 50% (Amato et al., 2008; Goretti et al., 2010, 2012; Ketelslegers et al., 2010; MacAllister et al., 2005, 2009; Weisbrot et al., 2014). This large range is likely due to different assessment strategies, disease duration, and disease severity at the time of evaluation.

Till, Udler, et al. (2012) investigated the emotional and behavioral outcomes of adolescents with MS. The patient group had a mean age of 16.1 years (N = 31) and age-matched controls had a mean age of 15.5 years (N = 31). The Behavior Assessment

System for Children, Second Edition (BASC-2) was completed by all participants as well as their parents. Parents of youth with MS reported that their children exhibited more symptoms of depression and somatization than parents of controls. Almost 30% of patients with MS were rated by their parents as experiencing moderate to severe symptoms of depression. In concordance with their parents, adolescents with MS also endorsed symptoms of depression more often than controls.

Two larger studies (N = 57; N = 56) conducted by Goretti and colleagues (2010, 2012) investigated depression in children and adolescents with MS using the Children's Depression Inventory, finding that 17% to 21% of patients endorsed depressive symptoms. No study to the author's knowledge has yet examined depressive symptoms in pediatric MS as compared to other children with depression.

Anxiety. Anxiety in pediatric MS has only been examined in a few studies, generally as part of a larger neuropsychological examination. Among 45 pediatric MS individuals aged 8 to 17 years referred for psychiatric assessment, anxiety disorders were common (present in almost half) and included post-traumatic stress disorder, social anxiety disorder, and anxiety disorder NOS.

Another study evaluated cognitive functioning in 37 children with MS (aged 8 to 17 years) and also noted psychiatric diagnosis (MacAllister et al., 2005). Of the 13 patients in the study who underwent a psychiatric evaluation, 30% had a diagnosis of an anxiety disorder, which included generalized anxiety disorder, panic disorder, and anxiety disorder-not otherwise specified. In the larger study by Till, Udler, et al. (2012) previously discussed, clinically elevated symptoms of anxiety were self-endorsed by 31% of their sample, but these symptoms were not significantly different from controls. The

authors noted that youth with MS may underreport feelings of anxiety and depressed mood, which indicates the need for cross-informant reports.

Conclusion

The literature suggests that depression and anxiety play an important role in both adult and pediatric MS. In addition, other psychological disturbances such as pseudobulbar affect may affect adults with MS but have not been reported in children. Given that MS can cause physical and cognitive symptoms that are often associated with psychiatric disorders, clinicians are cautioned to take more care in diagnosing psychological disorders in this population.

Psychosocial Functioning in Multiple Sclerosis

MS can have far-reaching consequences for patients' functioning in their daily lives, whether in work, school, at home, or in the community. There are wide-ranging definitions for psychosocial functioning in the literature, but for the purposes of this study psychosocial functioning was defined as being comprised of variables that relate to an individual's psychological development in interaction with the social environment (Erikson, 1956).

Psychosocial Functioning in Adult MS

Psychosocial variables that have been most commonly examined in the adult MS population are fatigue, quality of life, occupational functioning, and social support. Other variables that have been less frequently examined include mobility, coping, hopelessness/helplessness, and relationships with significant others.

Fatigue. Fatigue in the context of MS has been defined as an overwhelming sense of tiredness, lack of energy, and exhaustion to the degree that it disrupts the

individual's ability to function (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998). One of the most common symptoms in MS, fatigue is reported in 65% to 95% of the adult MS population (Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994; Kos et al., 2008; Krupp, 1997; Lobentanz et al., 2004). Fatigue can be extremely disabling for many patients, restricting their efficiency and ability to engage in activities for extended periods of time. Physiologically, fatigue in MS is thought to arise from multiple factors including possible immune and neuroendocrine effects, impaired nerve conduction, physical deconditioning, cognitive impairment, depression, and anxiety (Krupp, 1997).

In adults with MS fatigue is fairly independent of physical disability, disease duration, and disease course (Fisk, Ritvo, Ross, Haase, Marrie, & Schlech, 1994; Ford et al., 1998). MS-associated fatigue has been linked to unemployment (Hadjimichael, Vollmer, & Oleen-Burkey, 2008; Julian, Vella, Vollmer, Hadjimichael, & Mohr, 2008; Smith & Arnett, 2005) as well as reduced quality of life (Amato, Ponziani, Rossi, Liedl, Stefanile, & Rossi, 2001; Schwartz, Coulthard-Morris, Zeng, 1996).

Commonly used measures of fatigue in adult MS include the MS-Specific Fatigue Severity Scale, the Fatigue Scale of Motor and Cognitive Functions (Penner, Raselli, Stocklin, Opwis, Kappos, & Calabrese, 2009), the Würzburg Fatigue Inventory for MS (Flacheneker, Muller, Konig, Meissner, Toyka, & Riekmann, 2006), and the Fatigue Descriptive Scale (Iriarte, Katsmakis, & de Castro, 1999). Some of the most commonly used self-report inventories for fatigue are the Fatigue Severity Scale (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) and the Modified Fatigue Impact Scale (Fisk et al., 1994).

Employment and occupational functioning. Occupational functioning can be defined as an individual's effectiveness at navigating his/her work environment, involving factors such as emotional attitude towards work, work-related symptoms, efficiency at work, and recovery after work (Hannula, Lahtela, Jarvikoski, Salminen, & Makela, 2006). The cognitive impairments associated with MS affect the occupational functioning of many patients with the disease (Amato, Ponziani, Siracusa, & Sorbi, 2001; Rao, Leo, Ellington et al., 1991). Reasons most often cited for lack of employment in this population include fatigue, cognitive dysfunction, and impaired mobility and dexterity (Simmons et al., 2010). Similarly, significant predictors of employment status include fatigue, neurological disability, and age (Krause et al., 2013). Interestingly, a recent study found that patients who disclosed their MS diagnosis were more likely to remain employed over the long-term and were more likely to receive tenure, supporting the role of disclosure in employment status (Kirk-Brown, Van Dijk, Simmons, Bourne, & Cooper, 2013).

Social support and social functioning. Robert Weiss's (1974) theory of relational provisions defines six primary components of social support, which reflect the major elements of most current conceptualizations of social support: attachment, social integration, reassurance of worth, reliable alliance, guidance, and opportunity for nurturance. Social support and positive interpersonal relationships have been shown to reduce the risk for depression and increase quality of life in patients with MS (Schwartz & Frohner, 2005). One study examined perceived social support and its relationship to patient gender, disease duration, and the presence or absence of spouses in 200 patients with MS with an average age of 47.4 years (Gulick, 1994). Significant gender

differences were found for perceived availability of affect, affirmation, and the provision of aid. They also found a relationship between the number of ADLs and perceived social support as well as number of friends, which was especially true for women.

In addition, social support is dependent on social cognition, an area that has just recently started receiving attention (Banati et al., 2010; Henry et al., 2009, 2011; Jehna et al., 2010; Krause et al., 2009; Ouellet et al., 2010; Schwartz & Frohner, 2005). Although there has been some variability in the findings, several studies now support that MS patients evidence theory of mind impairments independent of neuropsychological functioning (Banati et al., 2010; Ouellet et al., 2010). This suggests that impairments in social cognition may contribute to difficulties in interpersonal relationships and decreased social support for MS patients.

Quality of life. MS researchers have noted the need to capture the multidimensional impact of MS on physical functioning, social functioning, and emotional well-being (Cella et al., 1996). The terms "quality of life" and "health-related quality of life" have been used to encompass this concept. Quality of life is often used in psychology to refer to a person's subjective sense of well-being or satisfaction with important aspects of his/her life (Cella at al., 1996), which is the definition that will be used in this study.

MS frequently limits patients' independence within the community and at home (Amato, Ponziani, Rossi, et al., 2001). In a recent large prospective study, 201 outpatients with MS (mean age = 39.0 years) were assessed using the Multiple Sclerosis Quality of Life-54 (Vickrey et al., 1995), a multidimensional health-related quality of life measure combining both MS-specific and generic items. Factors found to predict overall

quality of life included social support, depression, religiosity, living area, and years of education (Yamout et al., 2013). Unemployment correlated with poor quality of life, while absence of fatigue correlated with good quality of life. The authors concluded that these factors should be evaluated for all MS patients, as they can contribute to treatment planning.

Summary of psychosocial functioning in adult MS. MS commonly impacts a number of psychosocial factors in adults, including fatigue, occupational functioning, social support, and quality of life. In addition, these factors appear to mutually influence each other. In particular, fatigue has been found to be an important factor that negatively affects occupational functioning, social support, and quality of life in adults with MS.

Psychosocial Functioning in Pediatric MS

Children with MS are at greater risk of experiencing psychosocial difficulties both due to the nature of chronic illness and due to MS-specific factors. Factors that can lead to psychosocial disturbances include challenges associated with neurological impairments such as physical disability, the unpredictable nature of the disease course, and the isolation of being affected with a rare condition. In the pediatric MS population, the psychosocial variables that have been most frequently examined include fatigue, quality of life, and externalizing symptoms. Other variables that have been less frequently examined but may still play an important role include relationships with parents, coping and adaptability, and self-esteem/self-efficacy.

Fatigue. Fatigue is reported in 20% to 75% of children with MS, suggesting that it may be as common in children as in adults with MS (Amato et al., 2008; Goretti et al., 2010, 2012; Grover et al., 2013; Holland et al., 2012; MacAllister et al., 2005, 2009;

Parrish, Weinstock-Guttman, Smerbeck, Benedict, & Yeh, 2013). Still, there are only a handful of studies examining fatigue in pediatric MS. Fatigue in pediatric MS is often measured using the Pediatric Quality of Life Inventory (PedsQL) Multidimensional Fatigue Scale (MFS) or the Krupp Fatigue Severity Scale. Parents tend to report more significant concerns regarding fatigue than their children report, suggesting that perception of fatigue differs among children with MS and their caregivers (Holland et al., 2012). A recent prospective study examined the relationship between depression, exercise, and fatigue in 75 patients with pediatric MS aged 5 to 18 years (Grover et al., 2013). They found that greater participation in aerobic activities correlated with less fatigue and shorter disease duration.

Quality of life. There have been very few formal studies of quality of life in pediatric MS. In the studies that have been done, quality of life is typically measured using the PedsQL (Varni, Seid, & Rode, 1999). This scale was developed by the World Health Organization, and quantifies quality of life according to physical functioning, emotional functioning, school functioning, and social functioning. Thus, academic functioning in pediatric MS has been generally examined as part of the broader construct of quality of life. This contrasts with adult MS studies, which have generally defined occupational functioning as being separate from other quality of life variables.

As compared with controls, children with MS (mean age = 14 years) report worse overall health-related quality of life (Mowry et al., 2010). One of the first studies to examine quality of life in pediatric MS patients (mean age = 14.8 years) found that patients reported greater physical and academic problems compared to published healthy control normative data, but no significant difference in social and emotional functioning

(MacAllister et al., 2009). By contrast, parent-reported quality of life suggested elevated problems with physical, emotional, and academic problems, while parents did not report significant social difficulties in their children. In another study of 26 pediatric MS patients aged 7 to 18 using this same measure, severe problems in emotional functioning were reported in 26.9% of patients by self-report and 30.8% based on parent-report (Holland et al., 2012).

The findings of academic difficulties are consistent with recent work suggesting that children with MS show a downward educational trajectory (e.g., school discontinuation, lower grades, and increased special education services) over a 14-year period, possibly linked to greater T2 lesion volume (Grover et al., 2014). The authors suggested that this educational trajectory may negatively influence subsequent employment in adulthood, which would have a significant impact on quality of life.

Although studies have reported intact social functioning in children with MS (based on self- and parent-report), recent evidence suggests some deficits in social cognition. One study recently replicated the findings in adult MS, demonstrating that pediatric MS patients (N = 28) performed worse than healthy controls (N = 32) on three theory of mind tasks measuring facial affect recognition, detection of social faux pas, and perspective taking (Charvet, Cleary, Vazquez, Belman, & Krupp, 2014). This difference remained significant even after accounting for deficits in processing speed. While in adult MS deficits in social cognition have been linked to difficulties in interpersonal relationships, this does not appear to be the case in the pediatric population.

In summary, there is evidence to suggest that physical, emotional, academic, and social problems are significant factors affecting quality of life in patients with pediatric

MS, but more research is needed to understand these problems more fully and in larger samples.

Externalizing symptoms. The construct of externalizing behavior problems refers to negative behaviors that are manifested outwardly and directed towards the external environment (Campbell, Shaw, & Gilliom, 2000; Eisenberg et al., 2001; Liu, 2004). These can include disruptive, hyperactive, and aggressive behavior (Hinshaw, 1987). Externalizing symptoms and behavior problems have been measured in pediatric MS patients using the BASC-2. On the BASC-2 Parent-Report, externalizing problems include hyperactivity, aggression, and conduct problems, while there is also a separate scale for attention problems. The BASC-2 Self-Report includes a measure of inattention/hyperactivity, as well as an Emotional Symptoms Index that includes attention problems and hyperactivity.

Till, Udler, et al. (2012) gave the BASC-2 to 31 adolescents with pediatric MS (aged 12 to 19 years), 31 age-matched controls, and their parents. Parents rated 22.6% of youth with MS as having problems with aggressiveness. They were also rated as having more problems with attention than controls. On the self-report measure, youth with MS differed from the control group with respect to the inattention/hyperactivity scale. Concordance between parent and patient reports on the hyperactivity scale was low. Interestingly, youth who had poorer parent relations were more likely to be rated by their parents as having behavior problems, as reflected by a higher Externalizing Problems Composite and Behavioral Symptoms Index.

Summary of psychosocial functioning in pediatric MS. Because onset of pediatric MS occurs during the key formative years of development in adolescence, it has

the potential to cause unique and possibly more severe psychosocial deficits than those seen in adults. MS in children has been shown to affect level of fatigue, quality of life, and behavior. In adults, the psychosocial effects of the disease are thought to be related to the psychological factors associated with having a chronic illness, as well as the direct impact of the disease on brain networks responsible for emotional and behavioral regulation (Till, Udler, et al., 2012). Whether these mechanisms play a role in psychosocial functioning in pediatric MS remains to be determined.

Psychosocial Functioning in Children with Neurological Conditions

Given the scarcity of research on the psychosocial aspects of pediatric MS, it is helpful to consider psychosocial functioning in children with similar medical conditions. This section will discuss research focusing on children with neurological conditions, which include brain injuries as well as chronic conditions such as epilepsy, hydrocephalus, and cerebral palsy. Physical disorders are also briefly considered given the common sensory and motor symptoms often seen in MS. The most frequent psychosocial variables that have been examined in these populations include quality of life, externalizing symptoms, self-concept, and self-esteem.

Quality of life. A recent study had 187 family caregivers of children with neurological illnesses complete questionnaires regarding the severity of the disorder and perceptions of their child's health-related quality of life (Moore, Mah, & Trute, 2009). The neurological disorders included epilepsy, neuromuscular disorders, hydrocephalus, brain tumors, myelomeningocele, and acquired brain injuries. Using the PedsQL to measure quality of life, the authors found that all mean subscale scores (Physical, Emotional, School, Social) were lower than the norms, and the majority of children

exhibited some level of dependence (i.e., need for supervision or assistance) to complete daily activities.

Externalizing symptoms. The few studies that have examined psychosocial outcomes in children with neurological conditions have reported significant findings with regard to maladaptive behavior. In a large study on adolescents with chronic conditions with and without neurological involvement (N = 165) and healthy controls (N = 49), adolescents with neurological conditions were more likely to have behavior problems including aggression, hyperactivity, and immaturity (Howe, Feinstein, Reiss, Molock, & Berger, 1993). In another study using the Vineland Adaptive Behavior Scales as the primary outcome measure, children with traumatic brain injury and frontal lesions displayed deficits in socialization and maladaptive behavior, while children with non-frontal lesions did not display poorer psychosocial outcomes (Levin et al., 2004). A second study of children with traumatic brain injury found the most common changes in personality to be increased aggressive behavior and poor social judgment (Max et al., 2005, 2006). In a large meta-analysis of children with physical disorders, those with traumatic brain injury were also found to be at greatest risk of externalizing problems such as hyperactivity and aggression (Lavigne & Faier-Routman, 1992).

Self-concept and self-esteem. Examining self-concept in children with neurological and other medical conditions has generated inconsistent results. One meta-analysis conducted in the 1990s reported that children with physical disorders had a significantly lower self-concept than that of healthy children, but only when comparisons were made with norms or carefully matched controls (Lavigne & Faier-Routman, 1992). Among children with physical disorders, children with sensory and neurological

disorders were at greatest risk of low self-concept. By contrast, Le Bovidge et al. (2003) found no effect on self-concept for children with chronic arthritis. This variability may be due to differences between specific physical conditions.

Conclusion

Overall, much research is still needed on the psychosocial aspects of pediatric MS. Still, some important similarities and differences can be noted between pediatric and adult MS when comparing the two bodies of literature. Fatigue is a significant feature of both pediatric and adult MS, as well as lowered quality of life. Social support and social difficulties are also a problem for adult MS patients, but appear to be less of a factor for pediatric patients. In fact, one of the only studies to examine social support in pediatric MS patients found that this population had higher than normal perceived peer support and friendship (Kalb et al., 1999). In addition, research has just started to examine several other psychosocial factors in pediatric patients, including externalizing/behavior problems, adaptability and coping, and self-reliance/self-esteem. However, conclusions about how these areas are impacted by MS remain unclear.

Table 2 compares the cognitive, psychological, and psychosocial aspects of adult and pediatric MS. However, it should be noted that the often shorter disease duration for pediatric MS at the time of evaluation, as compared with adults studies, makes direct comparison difficult.

Table 2

Neuropsychological Correlates of Pediatric and Adult MS

	Pediatric-Onset MS	Adult-Onset MS
	Cognitive	
Attention & Processing Speed	Relatively intact simple attention Slowed information processing	Impaired attention Slowed information processing
Working Memory	Impaired working memory	Impaired working memory
Language	Deficits in verbal fluency, receptive language, sentence comprehension, and crystallized knowledge Relatively intact expressive language abilities; mixed evidence for confrontation naming	Relatively intact, with exception of confrontation naming and timed language tasks
Visual Spatial	Impaired visual perceptual skills, especially involving fine motor tasks	Impaired visual perceptual skills, including visual form, facial, and spatial perception
Motor & Psychomotor	Impaired fine motor speed and	Impaired fine motor speed and

Table 2 (continued)

Neuropsychological Correlates of Pediatric and Adult MS

	Pediatric-Onset MS	Adult-Onset MS
	coordination	coordination
Learning & Memory	Impaired verbal learning and memory Limited evidence of nonverbal deficits	Impaired verbal learning and memory, especially for delayed recall Impaired nonverbal memory
Executive Functions	Impaired in rapid set-shifting and organizational ability Mixed findings on card sorting	Impaired problem-solving, strategy, planning, sequencing, inhibition, and cognitive estimation
	Psychological	
Depression	6-50% prevalence rates, may be lower than adult MS Higher rates reported by parents than their children	27-54% prevalence rates, may be higher than pediatric MS
Anxiety	Limited studies on anxiety	25-41% prevalence rates Often comorbid with

Table 2 (continued)

Neuropsychological Correlates of Pediatric and Adult MS

	Pediatric-Onset MS	Adult-Onset MS
		depression
		Psychosocial
Fatigue	20-75% prevalence rates	65-95% prevalence rates
	Children report less fatigue compared to their caregivers	Comorbid with physical symptoms of MS and mood disturbances
Quality of Life	Impaired mental, physical, emotional, and school/academic functioning	Impaired work/occupational functioning and social functioning
	Similar social functioning compared to controls	

Note. MS – multiple sclerosis.

Relationships Among Cognitive, Psychological, and Psychosocial Variables in Multiple Sclerosis

Relationship Between Cognitive and Psychological Functioning in MS

Research indicates that there is a relationship between cognitive and psychological functioning in both adult and pediatric MS. The psychological variables

that have been most frequently examined with respect to cognitive functioning are depression and anxiety, and therefore these correlations will be reviewed here.

Cognitive and psychological functioning in adult MS. In adults with MS, depressive symptoms are associated with increased cognitive complaints (Deloire et al., 2006) and poorer performance on tasks of processing speed, working memory (Arnett et al., 1999a, 1999b), and planning efficiency (Arnett, Higginson, & Randolph, 2001; Randolph, Arnett, and Feske, 2004). Depression and anxiety have also been shown to negatively affect executive functioning, particularly working memory (Arnett et al., 1999a, 1999b; Gilchrist & Creed, 1994; Julian & Arnett, 2009; Stenager, Knudsen, & Jensen, 1994). A recent study also found that, in 140 female patients with MS, state anxiety affected information processing speed on the Symbol Digit Modalities Test, and to a lesser degree it correlated with working memory and the presence of cognitive impairment (Goretti et al., 2013).

Julian and Arnett (2009) specifically examined the relationships among anxiety, depression, and executive functioning in 77 adults with MS. The Chicago Multiscale Depression Inventory was used as a measure of depression and the State-Trait Anxiety Inventory was used as a measure of anxiety. Neuropsychological measures used to assess executive functioning included the Test of Everyday Attention Visual Elevator Subtest, Paced Auditory Serial Attention Test, Symbol Digit Modalities Test, and the Reading Span Task. The study found that anxiety and depression both independently predicted performance on a composite index of executive functioning. In addition, after controlling for depression, anxiety was uniquely associated with cognitive functioning. This

suggests that although anxiety is relatively less studied than depression in MS, it is still predictive of specific cognitive functions such as executive functioning.

Cognitive and psychological functioning in pediatric MS. Literature on the relationships between psychological and cognitive variables in pediatric-onset MS has only begun to emerge in the last few years, with conflicting findings (Goretti et al., 2012; Holland et al., 2012; Weisbrot et al., 2014). In one study examining the relationship between fatigue, depression, and cognitive functioning in 57 patients with relapsing-remitting MS and 70 healthy controls, depression was not related to number of tests failed, overall cognitive impairment, or worsening cognitive performance at follow-up (Goretti et al., 2012).

However, in another study examining the relationship between fatigue, emotional functioning, and executive dysfunction in 26 patients aged 7 to 18 with either MS or CIS, significant results were reported (Holland et al., 2012). Higher anxiety and depression scores were correlated with poorer performance on all measures of executive functioning except Letter Fluency. Anxiety had a strong negative correlation with Trail Making Test Part B, and moderate negative correlations with Trail Making Test Part A and Digit Span. Depression demonstrated a strong negative correlation with Trail Making Test Part B and Digit Span, and a moderate negative correlation with Trail Making Test Part A. Another recent study examined psychiatric diagnoses and cognitive impairment in 45 pediatric MS patients aged 8 to 17 (Weisbrot et al., 2014). This study found that children diagnosed with an anxiety or mood disorder showed the highest frequency of cognitive impairment, as compared with other psychiatric diagnoses (e.g., ADHD, oppositional defiant disorder).

Limitations to the latter two studies include relatively small sample sizes and lack of control groups. Overall, results suggest that psychological variables may demonstrate some relationship to aspects of cognitive functioning in pediatric MS, but the exact relationships remain to be elucidated.

Conclusion. There is evidence to suggest relationships between cognitive deficits, anxiety, and depression in MS. Much of the research on adult MS supports the idea that depression and anxiety specifically affect processing speed, working memory, and executive functioning. However, the research on cognitive deficits and psychological factors in pediatric MS is more variable, and more research is needed.

Relationship Between Cognitive and Psychosocial Functioning in MS

Research has also examined the relationship between cognitive and psychosocial functioning in both adult and pediatric MS patients. Much of the research to date has focused cognition in relation to fatigue, occupational functioning, quality of life, and social stress in adult-onset MS. The few articles examining these correlations in pediatric MS have focused on cognition in relation to fatigue and quality of life.

Cognitive and psychosocial functioning in adult MS. Contrary to the intuitive link between fatigue and cognitive functioning, subjective fatigue and fatigue induced by neuropsychological testing does not appear to be strongly correlated with neuropsychological test performance in adults (Krupp & Elkins, 2000; Morrow et al., 2009; Paul, Beatty, Schneider, Blanco, & Hames, 1998; Schwartz, Coulthard-Morris, & Zeng, 1996). Most of these studies have used self-report measures of fatigue, and one hypothesis for the lack of correlation suggests that it reflects MS patients' greater effort to maintain their cognitive performance (Krupp et al., 2010). A number of studies have

found greater brain activation in MS patients during performance on neuropsychological tests, suggesting that they may require greater cognitive resources when performing these tasks (Krupp et al., 2010).

One study specifically examined the contribution of cognitive dysfunction to problems with daily living (Rao, Leo, Ellington et al., 1991). One hundred MS patients were classified as either cognitively intact (N = 52) or cognitively impaired (N = 48). Patients underwent a comprehensive neuropsychological examination and an in-home occupational therapy evaluation, completed questionnaires on social functioning and mood, and were rated by a close friend or relative on several personality traits. The researchers found that patients who were classified as cognitively impaired engaged in fewer social activities, reported greater sexual dysfunction, had more difficulty with basic household tasks, and demonstrated higher rates of psychopathology. This study suggests that cognitive dysfunction in MS has an important impact on quality of life for these patients.

Cognitive dysfunction has been inconsistently related to occupational functioning and employment status in MS (Beatty et al., 1995; Glanz et al., 2012; Rao, Leo, Ellington et al., 1991; Smith & Arnett, 2005). One large study by Rao, Leo, Bernardin et al. (1991) classified 100 MS patients as either cognitively intact (N = 52) or cognitively impaired (N = 48). The authors found that patients in the cognitively impaired group were less likely to be working. These findings were confirmed in a seven-year longitudinal study, which found that cognitive impairment increased the risk of changing vocational status over this time period (Ruet et al., 2013). In contrast, Glanz and colleagues (2012) specifically examined presenteeism (i.e., productivity while working), and they did not

find a significant association with cognitive functioning. It remains unclear how strongly overall cognitive dysfunction or certain cognitive domains are associated with unemployment or reduced work productivity.

Research has also demonstrated some association between cognitive functioning and social support in adults with MS. Cognitively impaired patients with MS engage in fewer social and vocational activities (Rao, Leo, Ellington et al., 1991). In line with this finding, one archival study found that higher levels of perceived social support correlated with improved neuropsychological functioning (Schultz & Ferraro, 2009). Other studies have specifically found an association between social stress and poor auditory verbal memory (Gilchrist & Creed, 1994) as well as overall memory performance (Feinstein, Kartsounis, Miller, Youl, & Ron, 1992). This suggests that cognitive impairment negatively affects social support in MS, and that social support may be linked to memory performance.

Cognitive and psychosocial functioning in pediatric MS. Research examining the effect of fatigue on cognitive functioning in pediatric MS has produced inconsistent results. Goretti and colleagues' (2012) study reported associations between fatigue and specific cognitive functions in pediatric MS. Specifically, higher levels of self-reported cognitive fatigue were associated with impaired performance on a problem-solving test (Tower of London Test), and higher levels of parent-reported cognitive fatigue were correlated with impaired performance on tests of verbal learning (Selective Reminding Test-Long Term Storage), verbal comprehension (Token Test), and processing speed and complex attention (Trail Making Test B). Fatigue was not related to number of tests failed, overall cognitive impairment, or worsening cognitive performance at follow-up.

This is somewhat consistent with adult findings, where subjectively assessed cognitive fatigue was not associated with cognitive impairment on neuropsychological tests. However, the results do suggest a relationship between cognitive fatigue and tasks requiring prolonged and effortful mental activity (Goretti et al., 2012).

Another study of 26 children with CIS or MS examined fatigue, emotional functioning, and executive dysfunction (Holland et al., 2012). Fatigue was measured using the MFS, while executive functioning was measured through a variety of neuropsychological tests including D-KEFS Letter Fluency, Digit Span, and Trail Making Test Parts A and B, as well as the Behavior Rating Inventory of Executive Functioning (BRIEF) Parent-Report. Parent-reported general fatigue was moderately correlated with performance on Trail Making Test Part B (greater fatigue associated with worse performance), while self-reported general fatigue was moderately associated with both Trail Making Test Parts A and B. The authors suggested that this association may be due in part to the motor component of the Trail Making Test, given that motor functioning is often affected by fatigue. Fatigue did not affect performance on Letter Fluency. These findings are consistent with those reported by Goretti et al. (2012) mentioned previously. By contrast, several other studies have failed to show an effect of fatigue on cognitive profile (Amato et al., 2008; MacAllister et al., 2005).

Fewer studies have examined quality of life in relationship to cognitive functioning. Amato and colleagues (Amato et al., 2008; Amato et al., 2010) conducted a two-year follow-up study assessing cognitive and psychosocial functioning in patients with pediatric MS (N = 63) and healthy controls (N = 57). They measured cognitive functioning through a typical battery of neuropsychological tests, and quality of life

through a structured interview gathering information about school and everyday activities. In terms of academic functioning, they found that 10% of their sample required teacher support due to cognitive difficulties, and 22% of patients who were cognitively impaired had to reduce or quit their hobbies and sports activities. The authors concluded that cognitive problems in pediatric MS play an important role in negatively affecting school, everyday, and social activities.

To the author's knowledge, only one study has examined the relationship between cognitive functioning and externalizing problems in pediatric MS (Till, Udler, et al., 2012). In this study, parents reported behavioral changes in 16 cases in their sample (39%), seven of whom were classified as cognitively impaired (Amato et al., 2008). Of these cases, three were reported to have increases in disruptive behavior, including aggressiveness towards family members and peers. More research is needed looking at specific neuropsychological functions (rather than general cognitive impairment) and their relationships to externalizing behavior.

Conclusion. The research on cognitive and psychosocial functioning reveals important differences between adult and pediatric MS. In adults with MS, cognitive dysfunction is not associated with fatigue, but it does appear to be related to other psychosocial variables such as quality of life, occupational functioning, and social support. By contrast, fatigue in children has been shown to predict aspects of cognitive functioning, notably executive functioning, verbal learning, and verbal comprehension. Cognitive impairment in pediatric MS also appears to be associated with worse quality of life and increased externalizing behavior, but the relationships between these psychosocial factors and specific neuropsychological functions remains unclear.

Relationship Between Psychological and Psychosocial Functioning in MS

There is also evidence to suggest that a relationship exists between psychological functioning and aspects of psychosocial functioning in both adult and pediatric MS patients. Most of the research to date has focused on these relationships in the adult MS population, and more research is needed to examine the interaction between psychological variables (e.g., anxiety and depression) and psychosocial variables in pediatric-onset MS.

Psychological and psychosocial functioning in adult MS. Consistent with expectations, depression and fatigue are highly correlated in MS, and depression is a significant predictor of fatigue (Induruwa, Constantinescu, & Gran, 2012; Kroencke et al., 2000; Mills & Young, 2011). There is significant symptom overlap between depression and fatigue, including lack of motivation, sleep disturbance, and inability to complete tasks (Krupp, Serafin, & Christodoulou, 2010). In addition, if depression is present, fatigue is unlikely to remit (Krupp et al., 2010). Although the relationship between fatigue and anxiety has not been given as much attention in the literature, the available research also suggests a consistent relationship between fatigue and anxiety (Chwastiak et al., 2005; Ford, Trigwell, & Johnson, 1998; Iriarte, Subira, & Castro, 2000; Skerrett & Moss-Morris, 2006; Trojan et al., 2007). Specifically, anxiety appears more strongly associated with mental than physical fatigue (Iriarte et al., 2000; Trojan et al., 2007). Depression predicts later fatigue and anxiety in MS, while fatigue and anxiety predict later depression (Brown et al., 2009).

Depressed mood is also consistently associated with poorer quality of life in adults with MS, as well as perceived social support (McIvor, Riklan, & Reznikoff, 1984;

Wang, Reimer, Metz, & Patten, 2000). Dubayova and colleagues (2013) found that both anxiety and depression were significantly associated with lower scores on both the mental and physical subscales of a quality of life inventory. The relationship between depression and quality of life has also been confirmed in Chinese patients with MS (Chen, Fan, Hu, Yang, & Li, 2013). A 2-year prospective study assessed quality of life and depression in patients treated with interferon beta-1b, and found that positive coping strategies in addition to supportive elements (autoinjectors, nurses) had a significant impact on quality of life and depression (Pozzilli, Schweikert, Ecari, Oentrich, & Bugge, 2012).

Occupational functioning has also been examined in relation to psychological variables. Unemployment in MS has been shown to be associated with anxiety (Krocavcova et al., 2010) as well as depression, although the strength of the latter association varies between studies (Beatty, Hames, Wilbanks, Paul, & Hames, 1995; Glad, Nvland, Aarseth, Riise, & Myhr, 2011; Smith & Arnett, 2005). A recent study of 377 patients with relapsing-remitting MS or CIS examined work productivity in MS and its relationship to a variety of psychological and psychosocial factors including disability, depression, fatigue, anxiety, cognition, and health-related quality of life (Glanz et al., 2012). They found that higher levels of depression, fatigue, and anxiety were all associated with reduced productivity while working, with fatigue showing the strongest effect.

Social support as it relates to psychological factors is relatively less researched than other aspects of psychosocial functioning. Most research has focused on the association between depression and social support, finding that lower levels of social support are associated with increased depression (Gulick, 1997; McIvor et al., 1984;

O'Brien, 1993). Social stress is also associated with depressive symptoms (Gilchrist & Creed, 1994; Ron & Logsdail, 1989). One hypothesis for this association is that depression in MS may stem from cognitive impairments that cause difficulties in occupational functioning, which in turn negatively affects close interpersonal relationships. A recent comparative outcome trial assessed treatment for depression in MS and its relationship to social support (Mohr, Classen, & Barrera, 2004). The authors found that depression treatment was associated with significant increases in perceived social support, satisfaction with social support, and utilized social support, as well as a reduction in the need for emotional support. These findings support the notion that treating depression in these patients can improve social support. A more recent study has examined anxiety in MS and its relationship to social stress, finding that patients with anxiety disorders were more likely to report social stress and limited social support (Korostil & Feinstein, 2007).

Psychological and psychosocial functioning in pediatric MS. The association between depression and fatigue has generally been upheld in research on pediatric MS, but further research is needed before definitive conclusions can be made. In a relatively large case controlled study, Goretti and colleagues (2012) assessed depression using the Children's Depression Inventory and the Kiddie-SADS-Present and Lifetime Version diagnostic interview, while they assessed fatigue using the MFS. The researchers found that self- and parent-reported general and cognitive fatigue were associated with self-assessed depressive symptoms. However, when just considering the diagnosis obtained from the Kiddie-SADS psychiatric interview, only a relationship between sleep fatigue and presence of psychiatric disorders (mostly depression) was found.

Another study of 51 patients with pediatric MS corroborated this finding (MacAllister et al., 2009). Using the MFS to measure fatigue and the PedsQL to measure other variables including emotional functioning, they found that self-reported fatigue was strongly related to emotional difficulties ($r = 0.62$, $p < 0.01$). The same pattern was observed for parent-reported fatigue.

In another case controlled study of 31 adolescents with MS and 31 age-matched healthy controls, Till, Udler, et al. (2012) measured emotional symptoms using the BASC-2 and fatigue using a clinical interview that defined fatigue as "a sustained feeling of physical tiredness and lack of energy persisting for more than 2 months" (Till, Udler, et al., 2012, p. 1172). They found that the association between patient-reported fatigue and emotional symptoms (i.e., anxiety and depression) approached significance. Youth with poorer parent relations were more likely to be rated by their parents as having emotional difficulties, including anxiety and depression.

The variability between these studies may be due to the range of measures used, as well as the variation in sample sizes. Besides fatigue, which affects a large proportion of patients with pediatric MS, other psychosocial variables (e.g., quality of life, externalizing symptoms) have not been examined with respect to their relationship to psychological functioning (e.g., anxiety, depression).

Conclusion. The existing literature confirms a strong relationship between psychosocial variables and psychological functioning in adult MS, but most of these associations have not been examined in pediatric MS. For adults with MS, depressive symptoms are significantly related to fatigue, quality of life, occupational functioning, and social support. Anxiety has also shown some relationship to fatigue, unemployment

and work productivity, social stress, and limited social support. The few studies focusing on pediatric MS generally support the relationship found in adults between fatigue and depression, but other relationships have not yet been investigated.

Summary of Literature Review and Rationale

A review of the literature highlights the relative paucity of research on pediatric MS compared with adult MS, particularly in the areas of cognitive, psychological, and psychosocial functioning. In addition, much of the research on pediatric MS has utilized limited sample sizes and often lacks controls, simply as a consequence of the rarity of the condition. Given these limitations, many of the conclusions drawn from the pediatric MS literature are relatively less supported than conclusions for the adult MS population.

Based on the literature that does exist, the neuropsychological profile of pediatric MS appears similar to that of adult MS, with several key exceptions. The majority of cognitive deficits in adult MS have been noted in the following domains: attention, processing speed, learning and memory, and executive functioning. Similarly, children with MS are noted to have deficits in general cognition, complex attention, aspects of memory, and executive functioning. Children with MS show additional deficits in linguistic abilities that are more apparent than in adults, including problems with confrontation naming and receptive language. However, more research on cognitive functioning in pediatric MS is needed to determine conclusive relationships.

Few studies have investigated the relationships between cognitive, psychological, and psychosocial functioning in pediatric MS. Although limited, current research indicates that, similar to adult MS, psychological issues such as anxiety and depression may be related to worse cognitive functioning in pediatric MS, specifically on tasks of

executive functioning. Research examining the correlations between psychological and psychosocial variables has only considered depression as related to fatigue, and has generally supported the finding in adult MS that fatigue is strongly correlated with depressive symptoms. Lastly, psychosocial variables such as fatigue and quality of life have been shown to be related to specific aspects of cognitive functioning, particularly executive functioning; however, more research is needed to determine if these correlations are consistent across samples.

To the author's knowledge, no study to date has investigated the relationships between executive functioning, working memory, psychological functioning (e.g., depression, anxiety), and psychosocial functioning (e.g., fatigue, quality of life, externalizing behavior) within the same pediatric MS population. Thus, the current study aims to investigate these relationships.

Hypotheses

Hypothesis 1. Anxiety and depression will predict executive functioning.

Hypothesis 2. Anxiety and depression will predict psychosocial functioning.

Hypothesis 3. Executive functioning will predict psychosocial functioning.

Hypothesis 4. Working memory will predict psychosocial functioning.

Hypothesis 5. Working memory and executive functioning will have unique predictive value for psychosocial functioning.

CHAPTER III

METHOD

Archival Dataset

This cross-sectional study was conducted using an archival dataset that was collected as part of a multicenter study of patients with pediatric-onset multiple sclerosis (MS). The data were originally collected on participants who were evaluated between 2006 and 2011. Participants were seen at one of six Pediatric MS Centers of Excellence, which included University of California, San Francisco (San Francisco, California); Mayo Clinic (Rochester, Minnesota); University of Alabama at Birmingham (Birmingham, Alabama); State University of New York, Buffalo (Buffalo, New York); State University of New York, Stony Brook (Stony Brook, New York); and Harvard University, Massachusetts General Hospital, and Partners Health Care (Boston, Massachusetts).

This nationwide network of centers was established by the National MS Society and collects neuropsychological and other clinical data on children with MS and other demyelinating disorders. Each site received individual approval for human subject data collection and sharing by its respective institutional review board. For further information about the original study, the reader is referred to Julian and colleagues' (2012) study titled "Cognitive Impairment Occurs in Children and Adolescents with Multiple Sclerosis: Results From a United States Network."

For the current study, only the dataset from the UCSF Regional Pediatric Multiple Sclerosis Center was used. Emmanuelle Waubant, M.D., Ph.D., principal investigator of the original study, as well as representatives from the United States network, granted

permission for use of the database. Following the original study, the dataset was expanded to include all participants seen at the UCSF Regional Pediatric Multiple Sclerosis Center from 2011 to 2014.

Participants

As shown in Table 3, the study sample included 79 participants with pediatric-onset relapsing-remitting MS (33 male and 46 female). The participants had a mean age of 14.54 years (SD = 2.92, range 6.5-18.0). The subset of participants was obtained from the database detailed above through the UCSF Regional Pediatric Multiple Sclerosis Center.

Inclusion and Exclusion Criteria

Participants were included in the study if they met criteria for a diagnosis of pediatric MS (Krupp et al., 2007) and were younger than 18 years of age at time of disease onset. Participants were also required to be younger than 18 years of age at the time of neuropsychological assessment and have completed at least one measure of executive functioning. In addition, they were required to speak and read English and to have sufficient motor and visual capabilities to complete neuropsychological testing.

Table 3

Participant Characteristics

Variable	*n*	%	M	SD	Range
Age at Testing			14.54	2.92	6.5-18.00
Age at Symptom Onset			12.21	3.73	3.32-17.54
Disease Duration			2.33	2.39	.08-12.85
Disease Severity (EDSS Score)			1.68	1.33	0-8
WASI FSIQ-2			100.50	11.47	75-123
Sex					
Male	33	41.8			
Female	46	58.2			
Race					
Caucasian	25	31.6			
African-American	8	10.1			
Latino	24	30.4			
Asian	5	6.3			
Pacific Islander	2	2.5			
Other	15	19.0			
Ethnicity					
Hispanic	39	49.4			
Non-Hispanic	40	50.6			
Mother Education Level					
Elementary School (Grade 1-8)	6	7.6			

Table 3 (continued)

Participant Characteristics

Variable	*n*	%	M	SD	Range
Some High School (Grade 9-11)	6	7.6			
High School Graduate or GED	14	17.7			
Some College, No Degree/ Technical or Trade School	30	38.0			
Bachelor's Degree (4-Year College)	12	15.2			
Graduate Degree (MS, MD, PhD)	4	5.1			
Unknown	7	8.9			
Father Education Level					
Elementary School (Grade 1-8)	4	5.1			
Some High School (Grade 9-11)	9	11.4			
High School Graduate or GED	18	22.8			
Some College, No Degree/ Technical or Trade School	14	17.7			
Bachelor's Degree (4-Year College)	16	20.3			
Graduate Degree (MS, MD, PhD)	8	10.1			
Unknown	10	12.7			

Note. EDSS – Expanded Disability Status Scale; FSIQ-2 – Full Scale IQ, Two-Subtest Form; GED – General Educational Development; WASI – Wechsler Abbreviated Scale of Intelligence.

Measures

The Pediatric Multiple Sclerosis Centers of Excellence use a comprehensive network battery which consists of 11 tests addressing the following domains: 1) general cognitive ability—Wechsler Abbreviated Scale of Intelligence (WASI), 2 subtest battery including Vocabulary and Matrix Reasoning subtests; 2) attention, processing speed, and working memory—Digit Span and Coding subtests from the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV; for ages 16 and above) or Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; below age 16); 3) language—Wechsler Individual Achievement Test II Pseudoword Decoding, Expressive One-Word Picture Vocabulary Test, and the WASI Vocabulary subtest; 4) visual-spatial functioning—Beery-Buktenica Developmental Test of Visual-Motor Integration, Sixth Edition and WASI Matrix Reasoning subtest; 5) motor and psychomotor functioning—Grooved Pegboard Test and Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test: Motor Speed Condition; 6) verbal learning and memory—California Verbal Learning Test II or California Verbal Learning Test, Children's Version; 7) executive functioning—Contingency Naming Test, D-KEFS Trail Making Test.

As an adjunct to this comprehensive network battery, the UCSF Regional Pediatric Multiple Sclerosis Center battery includes the following additional tests: Brief Visuospatial Memory Test, Revised; D-KEFS Verbal Fluency Test; Behavior Rating Inventory of Executive Functioning (BRIEF), Parent Questionnaire and Self-Report Version; Behavioral Assessment System for Children, Second Edition (BASC-2), Parent Rating Scales and Self-Report of Personality; Pediatric Quality of Life Inventory, Version 4.0 (PedsQL), Parent-Proxy Report and Child Self Report; PedsQL

Multidimensional Fatigue Scale (MFS), Parent-Proxy Report and Child Self Report; PedsQL Family Impact Module. A subset of these tests will be used for the current study, each of which will be described below.

Wechsler Abbreviated Scale of Intelligence (WASI)

The WASI is a screening instrument designed to provide a brief estimate of general intelligence (Wechsler, 2011). It was developed for use as a brief screener when a more complete assessment of IQ is unnecessary, such as for research. The test measures both verbal and nonverbal abilities, and it consists of four subtests: Vocabulary, Block Design, Similarities, and Matrix Reasoning. Research has demonstrated that these four subtests have high loadings on a general intellectual ability factor (*g*) and represent both verbal/crystallized and nonverbal/fluid abilities.

There are two options for administration to yield a Full-Scale IQ (FSIQ). A four-subtest form can be given, which results in an IQ score (FSIQ-4) as well as a Verbal IQ made up of Vocabulary and Similarities subtests and Performance IQ consisting of Block Design and Matrix Reasoning. There is also a two-subtest form of the WASI consisting of Vocabulary and Matrix Reasoning subtests, which also provides an IQ (FSIQ-2). The two-subtest form was administered for the original study, and the resulting FSIQ-2 Standard Score was used as a measure of IQ for the current study.

WASI reliability and validity. Reliability coefficients for the subtests and IQ scales of the WASI range from .80 to .90 (Axelrod, 2002). In adults, the average coefficients range from .92 to .94 for subtests and .96 to .98 for Verbal IQ, Performance IQ, and FSIQ (The Psychological Corporation, 1999). In children, reliability is slightly lower, with reliability coefficients ranging from .97 to .92 for subtests and .86 to .94 for

the IQ scales. The average reliability coefficient for the FSIQ-2 is .96 (The Psychological Corporation, 1999). Test-retest reliability over a 2 to 12 week period for the FSIQ-2 was reported to be .85 for children and .88 for adults, while coefficients for the FSIQ-4 were .93 for children and .92 for adults (The Psychological Corporation, 1999).

The WASI measures similar constructs to its counterparts on the WISC-III and the WAIS-III. Correlations between the WISC-III and the WASI corresponding subtests have been reported to range from .69 (Similarities) to .74 (Block Design; The Psychological Corporation, 1999). The WISC-III FSIQ correlated .87 with the WASI FSIQ-4 and .81 with the WASI FSIQ-2 (The Psychological Corporation, 1999). Validity coefficients correlating the WASI and WAIS-III ranged from .66 (Matrix Reasoning) to .88 (Vocabulary; The Psychological Corporation, 1999). The WAIS-III FSIQ was highly correlated with the WASI FSIQ-4 (r = .92) and the WASI FSIQ-2 (r = .87; The Psychological Corporation, 1999).

WAIS-IV and WISC-IV Digit Span

Digit Span is one of the 10 core subtests of the WAIS-IV (Wechsler, 2008) and the WISC-IV (Wechsler, 2003). It is part of the Working Memory Index for both the WAIS-IV and WISC-IV, and it assesses sustained attention, working memory, and mental manipulation.

The subtest is divided into three parts for the WAIS-IV (Digit Span Forward, Digit Span Backward, and Digit Span Sequencing) and two parts for the WISC-IV (Digit Span Forward and Digit Span Backward). On Digit Span Forward, the examinee is read a sequence of numbers and is asked to recall the numbers in the same order, while on

Digit Span Backward the examinee is asked to recall the numbers in reverse order. On Digit Span Sequencing (WAIS-IV only), the examinee is read a sequence of numbers and is asked to recall the numbers in ascending order.

Digit Span Forward is said to assess rote learning and memory, attention, and initial registration of stimuli (Wechsler, 2008). Digit Span Backward assesses these capabilities as well as the individual's ability to hold and manipulate the information in mind (i.e., working memory), transformation of information, and visual-spatial imaging (Sattler, 2008). Digit Span Sequencing is similar to other tasks that are designed to measure working memory and mental manipulation (Werheid et al., 2002), and it was developed in order to increase the working memory demands of the Digit Span subtest relative to previous versions. Process scores include Longest Digit Span Forward, Longest Digit Span Backward, and Longest Digit Span Sequencing (WAIS-IV only). This study used the WAIS-IV and WISC-IV Digit Span Backward Raw Score as a measure of working memory.

Digit span reliability and validity. The average reliability coefficient for WAIS-IV Digit Span is excellent (r = .93), ranging from .89 to .94 depending on the age bracket (Wechsler, 2008). Average reliability coefficients for process scores in the normative sample were as follows: Digit Span Forward (r = .81), Digit Span Backward (r = .82), and Digit Span Sequencing (r = .83). Test-retest reliability was tested over an average interval of 22 days, resulting in a stability coefficient of .83. WISC-IV Digit Span also demonstrates internal consistency (α = .87) and test-retest reliability (r = .83 to .89; Wechsler, 2003).

Both the WAIS-IV and WISC-IV demonstrate construct validity (Wechsler, 2003, 2008). Within the WAIS-IV, Working Memory subtests (Digit Span, Arithmetic, Letter-Number Sequencing) show high correlations with other Working Memory subtests and moderate to high correlations with Verbal Comprehension subtests, likely due to the auditory comprehension and verbal expression demands of all of these subtests (Wechsler, 2008). Like the WAIS-IV, the Working Memory subtests that make up the WISC-IV also correlate most highly with other working memory subtests and with Verbal Comprehension subtests (Wechsler, 2008). The intercorrelations of the component tasks of Digit Span are also moderate to high (Wechsler, 2008).

Delis-Kaplan Executive Function System (D-KEFS)

The D-KEFS is a collection of nine tasks designed to assess key components of executive functions spanning verbal and spatial modalities (Delis et al., 2001). Its subtests include: Trail Making Test, Verbal Fluency Test, Design Fluency Test, Color-Word Interference Test, Sorting Test, Twenty Questions Test, Word Context Test, Tower Test, and the Proverb Test. The D-KEFS can be used with individuals aged 8 to 89 years, with the exception of the Proverb Test (ages 16 to 89 years). The D-KEFS was designed based on a cognitive-process approach, meaning that each task provides multiple conditions and scores in order to isolate the source of any impairment. In addition, the test is meant to be used flexibly, such that any test can be administered in isolation or in combination with the other tests.

For the current study, participants were administered the Verbal Fluency Test and the Trail Making Test as part of the standard battery. The Verbal Fluency Test measures fluent production in the verbal domain (Delis et al., 2001). The test requires examinees

to say words as quickly as possible that begin with a certain letter (Letter Fluency), say words that belong to a designated category (Category Fluency), and alternate between saying words from two different categories (Category Switching). The participant is given 60 seconds to complete each portion of this test. In this study, the Verbal Fluency Test, Condition 3: Category Switching, Total Correct Responses Raw Score was used as a measure of executive functioning.

The Trail Making Test measures visual scanning and attention, sequencing, and task switching, and it is believed to tap aspects of executive functioning including working memory, processing speed, and self-initiation (Strauss, Sherman, & Spreen, 2006). The test asks examinees to scan numbers and letters and mark all of the number 3's (Condition 1: Visual Search), connect the numbers in ascending order (Condition 2: Number Sequencing), connect the letters in alphabetical order (Condition 3: Letter Sequencing), switch between connecting numbers and letters in ascending order (Condition 4: Number-Letter Switching), and draw a line over the dotted line as quickly as possible (Condition 5: Motor Speed). All conditions are timed. While all conditions were given for the study, only the Trail Making Test, Condition 4: Number-Letter Switching Raw Score was used as a measure of executive functioning.

D-KEFS reliability and validity. The D-KEFS was standardized on a large normative sample (N = 1750) aged 8 to 89 years, chosen to be representative of the United States population in terms of age, sex, race/ethnicity, education, and geographic region (Delis, Kaplan, & Kramer, 2001). The internal consistency of the normative sample ranged greatly depending on the subtest and age group (α = < .59 to > .90). The internal consistency of the Verbal Fluency Test has been reported as .83 for Condition 1:

Letter Fluency (Tombaugh, Kozak, & Rees, 1999), .53 to .76 for Condition 2: Category Fluency (Delis et al., 2001), and .51 to .73 for Condition 3: Category Switching (Delis et al., 2001). For the Trail Making Test, the Combined Number & Letter Sequencing Composite demonstrated adequate reliability (.57 to .81). However, internal consistency was reported to be low for Conditions 1-4 of the Trail Making Test ($\alpha \leq .59$). Test-retest reliability for the D-KEFS also ranged depending on the subtest (r = < .59 to > .90), but has been reported to be high for Letter Fluency (r = .80), Category Fluency (r = .79), and the Trail Making Test Combined Number & Letter Sequencing Composite (r = .78 for ages 8-19; Delis et al., 2001). Test-retest reliability for all age groups was reported to be lower for Category Switching (r = .52; Delis et al., 2001).

The authors report numerous correlations within and between tasks on the D-KEFS, and these correlations vary greatly by task and age group (Delis et al., 2001). Correlations between tasks on average are low, suggesting that these tasks are not interchangeable. Correlations between the D-KEFS and the Wisconsin Card Sorting Test (another measure of executive functioning) were reported to be moderate to high (r = .31 to .59), depending on the subtest.

Behavior Rating Inventory of Executive Function (BRIEF)

The BRIEF is a rating scale designed to measure executive functioning in children and adolescents (Gioia, Isquith, Guy, & Kenworthy, 2000). The original test included Parent and Teacher Forms, but there is also a Self-Report Version for adolescents (Guy, Isquith, & Gioia, 2004), an Adult Version that includes self- and informant-reports (Roth, Isquith, & Gioia, 2005), and a Preschool Version (Gioia, Espy, & Isquith, 2003). For

ease of discussion, the BRIEF Self-Report and BRIEF Parent Form will be referred to as the BRIEF Self-Report and BRIEF Parent-Report, respectively.

The Parent-Report and Teacher Form contain 86 items, and 18 of these items differ across the two forms. Respondents are asked to rate the individual's behavior on a three-point scale ("Never," "Sometimes," and "Often"). The BRIEF Parent-Report and Teacher Form yield eight empirically derived subscales that each reflect a specific aspect of executive functioning, including: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor. Subscales for the BRIEF Self-Report Form include the majority of scales from the Parent-Report and Teacher Form, with a few differences: Inhibit, Shift, Emotional Control, Monitor, Working Memory, Plan/Organize, Organization of Materials, and Task Completion. The subscales result in two broad composite scores, the Behavioral Regulation Index and the Metacognition Index, as well as an overall score, the Global Executive Composite. The Behavioral Regulation Index is made up of the Inhibit, Shift, and Emotional Control subscales, while the Metacognition Index is made up of the Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor subscales. The test also includes two scales that assess validity (Inconsistency and Negativity).

For the current study, parents and patients were asked to complete the BRIEF Parent-Report and BRIEF Self-Report. All subscales and composite t-scores were used as a complement to findings on performance-based measures of executive functioning. For the BRIEF, higher t-scores indicate more executive function difficulties.

BRIEF reliability and validity. In the standardization sample (N = 2139), Chronbach's alphas for the Global Executive Composite for both the Parent-Report and

Teacher Form ranged from .80 to .98 (Gioia et al., 2000). Internal consistency was moderate to high for the BRIEF Self-Report, with a Chronbach's alpha of .96 for the Global Executive Composite and .72 to .96 for the clinical scales (Guy et al., 2004). Interrater reliability between the Parent-Report and Teacher Form was moderate (r = .32), which is consistent with expectations for different environmental settings. When comparing the BRIEF Parent-Report and the BRIEF Self-Report, interrater reliability on the Global Executive Composite was strong (r = .56; Guy et al., 2004). The test-retest reliability correlation across clinical scales for the Parent-Report was .81 over an average interval of two weeks. For the Global Executive Composite, Behavioral Regulation Index, and the Metacognition Index, test-retest correlations were .86, .84, and .88, respectively (Gioia et al., 2000).

The BRIEF appears to have good content validity, with scale structure derived from literature review and an expert panel, and then verified through factor analysis (Gioia, Isquith, Retzlaff, & Espy, 2002). This analysis suggested that the BRIEF measures executive functions in terms of multiple dimensions, rather than a single unitary dimension. Generally, only modest correlations have been reported between the BRIEF and neuropsychological tests of executive functioning (Anderson, Anderson, Northam, Jacobs, & Mikiewicz, 2002; Mahone et al., 2002; Mangeot et al., 2002).

Behavior Assessment System for Children, Second Edition (BASC-2)

The BASC-2 is a rating scale designed to facilitate the classification of a variety of emotional and behavioral disorders in children ages 2 through 25 and to facilitate intervention planning (Reynolds & Kamphaus, 2004). The forms include Teacher Rating Scales, Parent Rating Scales, Self-Report of Personality, Student Observation System,

and Structured Developmental History. In the current study, each participant completed the Self-Report of Personality and his/her parents completed the Parent Rating Scales. Thus, only these measures will be reviewed here. For ease of discussion, the BASC-2 Self-Report of Personality and BASC-2 Parent Rating Scales will be referred to as the BASC-2 Self-Report and BASC-2 Parent-Report, respectively.

The BASC-2 Parent-Report contains 134-160 items and takes about 10-20 minutes to complete. Parents complete the Parent-Report at three age levels: preschool (ages 2 to 5), child (ages 6 to 11), and adolescent (ages 12 to 21). Parents are asked to rate their child's behavior on a four-point scale ("Never," "Sometimes," "Often," and "Almost Always"). The BASC-2 Parent-Report yields a subset of 16 adaptive and clinical scales that vary depending on the age level. The possible adaptive scales include: Activities of Daily Living, Adaptability, Functional Communication, Leadership, Social Skills, and Study Skills. The possible clinical scales include: Aggression, Anxiety, Attention Problems, Atypicality, Conduct Problems, Depression, Hyperactivity, Learning Problems, Somatization, and Withdrawal. The ratings result in four composite scores: Externalizing Problems (Hyperactivity, Aggression, Conduct Problems), Internalizing Problems (Anxiety, Depression, Somatization), Behavioral Symptoms Index (Hyperactivity, Aggression, Depression, Atypicality, Withdrawal, Attention Problems), and Adaptive Skills (Adaptability, Social Skills, Leadership, Activities of Daily Living, Functional Communication). Validity (F, L, and V) and response set indices are also provided.

The BASC-2 Self-Report takes about 30 minutes to complete and is divided into three age levels: child (ages 8 to 11), adolescent (ages 12 to 21), and college (ages 18 to

25). Respondents are asked to rate their own behavior on a two-point response format ("True" or "False") and a four-point response format ("Never," "Sometimes," "Often," and "Almost Always"). The Self-Report yields a subset of 16 adaptive and clinical scales that vary depending on the age level. The possible adaptive scales include: Relations with Parents, Interpersonal Relations, Self-Esteem, and Self-Reliance. The possible clinical scales include: Hyperactivity, Anxiety, Depression, Somatization, Attention Problems, Atypicality, Attitude to School, Attitude to Teachers, Sensation Seeking, Locus of Control, Social Stress, and Sense of Inadequacy. The ratings result in four composite scores: Internalizing Problems (Atypicality, Locus of Control, Social Stress, Anxiety, Depression, Sense of Inadequacy, Somatization), School Problems (Attitude to School, Attitude to Teachers, Sensation Seeking), Inattention/Hyperactivity (Attention Problems, Hyperactivity), Emotional Symptoms Index (Social Stress, Anxiety, Depression, Sense of Inadequacy, Self-Esteem, Self-Reliance), and Personal Adjustment (Relations with Parents, Interpersonal Relations, Self-Esteem, Self-Reliance).

For the current study, the BASC-2 was used as a measure of self- and parent-reported psychological and psychosocial functioning. Scores on the Validity Indices were examined to ensure that they do not exceed recommended cut-off values as reported in the manual. The Depression subscale t-score on both the Self- and Parent-Report was used as a measure of depression, while the Anxiety subscale t-score on the Self- and Parent-Report was used as a measure of anxiety. The Externalizing Problems Composite t-score on the Parent-Report was used as a measure of externalizing behavior. For these scales, a higher score implies more emotional and behavioral problems.

BASC-2 reliability and validity. The BASC-2 Self- and Parent-Report both have general and clinical norm samples, and samples were selected to be representative of the United States population (Reynolds & Kamphaus, 2004). The authors reported that the BASC-2 has moderate to good reliability. For the Parent-Report, composite score reliabilities ranged from .85 to .95, and individual subscale reliabilities ranged from .70 to .88. Similarly, composite score reliabilities for the Self-Report ranged from .83 to .96, and individual subscale reliabilities ranged from .61 to .89. More specifically, the Anxiety and Depression scales on the Parent-Report have demonstrated internal consistency and reliability for children and adolescents (α = .79 to .88 for Anxiety; α = .87 to .93 for Depression). These scales have also been shown to demonstrate strong internal consistency in the pediatric MS population (Till, Udler, et al., 2012).

The authors provided scale intercorrelations and factor analysis that supports the validity of grouping of scales into composites (Reynolds & Kamphaus, 2004). That is, correlations within the clinical scales and adaptive scales were positive, while correlations between clinical and adaptive scales were negative. The Parent-Report was also correlated with the Achenbach System of Empirically Based Assessment (ASEBA) Child Behavior Checklist. Similarly named composite scores and scales tended to show moderate to strong correlations, ranging from .65 to .84. The Parent-Report also showed moderate to high correlations with the BRIEF. The Global Executive Composite on the BRIEF correlated highly with the BASC-2 Parent-Report Externalizing Problems composite and the Behavioral Symptoms Index. Clinical scales on the BASC-2 Parent-Report correlating most highly with the BRIEF were Hyperactivity, Atypicality, Attention Problems, Adaptability, and Functional Communication.

Pediatric Quality of Life Inventory, Version 4.0 (PedsQL)

The PedsQL is a modular instrument for measuring health-related quality of life in healthy children and adolescents, as well as those who have health conditions (Varni, Burwinkle, Katz, Meeske, & Dickinson, 2002). The test was empirically derived from data collected from 291 pediatric cancer patients and their parents at several stages of treatment. The PedsQL 4.0 Generic Core Scales consist of 23 items and takes less than four minutes to complete. The test includes a Parent Proxy-Report for ages 2 to 18, and a Child Self-Report for ages 5 to 18. It has been designed for use in community, school, and clinical pediatric populations. For ease of discussion, the PedsQL Child Self-Report and PedsQL Parent Proxy-Report will be referred to as the PedsQL Self-Report and PedsQL Parent-Report, respectively.

Respondents are asked to rate items on a five-point response format ("Never," "Almost Never," "Sometimes," "Often," and "Almost Always"). The test results in four Generic Core Scales which were designed to measure the core dimensions of health outlined by the World Health Organization: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items). There are also three summary scores, the Total Scale Score (23 items), the Physical Health Summary Score (8 items), and the Psychosocial Health Summary Score (15 items).

In addition to the PedsQL 4.0 Generic Core Scales discussed above, many other modules have been developed to address more specific aspects of health-related quality of life. The PedsQL Disease-Specific Modules were developed as a complement to the PedsQL 4.0 Generic Core Scales for use in clinical populations. Thus far, modules have

been developed for asthma, arthritis, cancer, cardiac disease, diabetes, eosinophilic esophagitis, gastrointestinal symptoms, neuromuscular diseases, sickle cell disease, and transplant recipients.

In addition, a PedsQL Family Impact Module was developed to assess the impact of pediatric chronic health conditions on the family by measuring parent self-reported physical, emotional, social, and cognitive functioning, communication, and worry (Varni, Sherman, Burwinkle, Dickinson, & Dixon, 2004). The MFS was also developed to assess fatigue, and it will be discussed in detail below (Varni, Seid, & Rode, 1999).

For the purposes of this study, both patients and their parents completed the PedsQL 4.0 Generic Core Scales, the MFS, and the PedsQL Family Impact Module. The composite scores for Physical, Emotional, Social, and School Functioning, as well as the Total Scale Score on the PedsQL Parent- and Self-Reports, were used as measures of quality of life. Of note, the PedsQL is reverse scored and linearly transformed to a 0-100 scale (0 = 100; 1 = 75; 2 = 50; 3 = 25; 4 = 0), such that higher scores indicate better quality of life. To compute scale scores, then mean is computed as the sum of the items over the number of items answered (if more than 50% of items are missing, the scale score is not computed).

PedsQL reliability and validity. The PedsQL 4.0 Generic Core Scales demonstrate strong internal consistency ($\alpha = .83$ for Child Self Report and $\alpha = .86$ for Parent Proxy-Report; Varni et al., 1999). Internal consistency has been demonstrated for children as young as five years ($\alpha = .86$), and reliability generally increases slightly with age (Varni, Limbers, & Burwinkle, 2007).

Construct validity for the PedsQL was assessed using standardized measures of emotional distress, social support, and perceived competency such as the Children's Depression Inventory and the Child Behavior Checklist (Varni et al., 1999). Within the test, correlations between the 11 subscales were small to medium, providing support for the multidimensional measurement model. The authors demonstrated discriminant validity for patients on- versus off-treatments (Varni et al., 1999). In addition, Varni and colleagues (2007) have demonstrated a statistically significant difference in health-related quality of life between healthy children and children with chronic health conditions for all scales and summary scores (Varni et al., 2007). The PedsQL has been shown to be sensitive to quality of life issues in other conditions such as pediatric cancer, cerebral palsy, cardiac disease, and pediatric MS (Mowry et al., 2010; Varni, Limbers, & Burwinkle, 2007).

PedsQL Multidimensional Fatigue Scale (MFS)

The MFS is a specific module of the Pediatric Quality of Life Inventory, Version 4.0. It was designed as a generic symptom-specific instrument to measure fatigue in pediatric patients as well as healthy school and community populations (Varni, Seid, & Rode, 1999). There is an Acute and Standard version for the following age groups: Toddlers (2-4 years), Young Child (5-7 years), Child (8-12 years), Adolescent (13-18 years), Young Adult (18-25 years), and Adult (≥ 26 years). This scale can be either Interviewer Administered, Self-Administered, or Proxy-Rated. The format, instructions, and response-format are identical to that of the PedsQL 4.0 Generic Core Scales. For ease of discussion, the MFS Child Self-Report and MFS Parent Proxy-Report will be referred to as the MFS Self-Report and MFS Parent-Report, respectively.

The 18-item scale results in three subscales: 1) general fatigue (6 items), 2) sleep/rest fatigue (6 items), and 3) cognitive fatigue (6 items). In addition, it results in a total score that measures total fatigue. Sleep/rest fatigue asks patients to rate difficulties with aspects of sleep (e.g., problems sleeping through the night), and provides a measure of sleep disturbance. The cognitive fatigue scale includes a report of cognitive difficulties (e.g., difficulty paying attention, difficulty with memory, etc.). General fatigue includes items such as tiredness and physical weakness. For the purposes of this study, all three fatigue subscales and the total score were selected to represent various aspects of fatigue. Of note, the MFS is also reversed scored in the same manner as the PedsQL such that higher scores indicate fewer problems.

MFS reliability and validity. MFS was developed through reviews of the adult and pediatric cancer fatigue literature in order to derive the constructs. The scale has also been shown to be sensitive to problems associated with other diseases in children and adolescents including acute lymphoblastic leukemia (Meeske et al., 2004; Varni et al., 2002), rheumatic diseases (Varni, Burwinkle, & Szer, 2004), and pediatric brain tumor (Meeske, Katz, Palmer, Burwinkle, & Varni 2004). The MFS demonstrates acceptable internal consistency, with the Multidimensional Fatigue Total Scale Score demonstrating a Chronbach's alpha of .89 for Self-Report and .92 for Parent-Report (Varni et al., 2002). All subscale scores for Self- and Parent-Report approached or exceeded a minimum reliability standard of .70.

The validity of the scale was demonstrated through hypothesized intercorrelations with dimensions of generic and cancer specific health-related quality of life (Varni et al., 2002). In terms of construct validity, the MFS total score and subscale scores

demonstrated significant differences between the healthy population group and the children with cancer group. Correlations between the MFS total score and the PedsQL 4.0 Generic Core Scales total score were in the medium to large effect size range. The correlation between the Self- and Parent-Report total score was .56.

Sociodemographic and Clinical Variables

Sociodemographic variables in the original database include sex, race, ethnicity (Hispanic or not Hispanic), mother and father education level, and age at neuropsychological evaluation. Clinical variables in the database include diagnosis, age at symptom onset (years), disease duration (years), and disability as measured by the EDSS (Kurtzke, 1983).

Procedures

Procedure of the Original Study

Participants were patients with pediatric MS who were seen at one of the six Pediatric MS Centers of Excellence described above. In each center, the test battery was administered by a clinical neuropsychologist or trained and supervised psychometrician. Testing took approximately 2.5 hours to complete and participants were given breaks as needed. The purpose of the original study was to examine cognitive functioning in pediatric MS by comparing performance to published, age-stratified normative data (Julian et al., 2012).

Procedure of the Present Study

Archival data from the Pediatric MS Centers of Excellence multicenter study was used. Only patients seen through the UCSF Regional Pediatric Multiple Sclerosis Center were included in the study. Additional data was also entered from patients who were

seen at the UCSF Regional Pediatric Multiple Sclerosis Center from 2011 to 2014. This combined database was used to answer the research questions posed by the current study.

Data Analysis

The data were analyzed using the software program, the Statistical Package for Social Sciences (SPSS Inc.) Version 20 (SPSS Inc., 2011). Raw scores were used for analyses with the exception of the WASI, BRIEF, and BASC-2, which were analyzed using t-scores. In addition, the MFS and PedsQL were analyzed using composite scores.

Preliminary Analyses

Other possible covariates that were considered in the analyses included sex, race, mother and father education level, age at testing, age of onset, disease duration, disease severity, and IQ. If any of these variables correlated with any of the dependent variables, they were controlled for in the analyses. Correlations between continuous variables were assessed using the Pearson correlation coefficient and correlations involving ordinal variables (e.g., mother and father education level, disease severity) were assessed with the non-parametric Spearman rank correlation coefficient. Analysis of variance (ANOVA) was used to look at the effects of nominal variables (e.g., sex and race) on other covariates and outcome variables.

Main Analyses

Hypothesis 1: Anxiety and depression will predict executive functioning. Hierarchical regression analyses were conducted with each executive functioning variable as the dependent variable, sex, race, mother and father education level, age at testing, age of onset, disease duration, disease severity, and/or IQ as covariates entered at Step 1, and anxiety and depression entered at Step 2.

Hypothesis 2: Anxiety and depression will predict psychosocial functioning. Hierarchical regression analyses were conducted with each psychosocial variable as the dependent variable, sex, race, mother and father education level, age at testing, age of onset, disease duration, disease severity, and/or IQ as covariates entered at Step 1, and anxiety and depression entered at Step 2.

Hypothesis 3: Executive functioning will predict psychosocial functioning. Hierarchical regression analyses were conducted with each psychosocial variable as the dependent variable, sex, race, mother and father education level, age at testing, age of onset, disease duration, disease severity, and/or IQ as covariates entered at Step 1, and executive functioning variables entered at Step 2.

Hypothesis 4: Working memory will predict psychosocial functioning. Hierarchical regression analyses were conducted with each psychosocial variable as the dependent variable, sex, race, mother and father education level, age at testing, age of onset, disease duration, disease severity, and/or IQ as covariates entered at Step 1, and working memory entered at Step 2.

Hypothesis 5: Working memory and executive functioning will have unique predictive value for psychosocial functioning. Hierarchical regression analyses were conducted with each psychosocial variable as the dependent variable, sex, race, mother and father education level, age at testing, age of onset, disease duration, disease severity, and/or IQ as covariates entered at Step 1, working memory entered at Step 2, and executive functioning variables entered at Step 3.

CHAPTER IV

RESULTS

Overview

This chapter first presents the results of the preliminary analyses, which were conducted to determine which subscales and measures would be used in the main analyses. This includes descriptive analyses for all variables of interest in this study, descriptions for any multicollinearity, correlations between covariates and outcome variables, and zero-order correlations between all variables of interest in the study. Results for the main analyses are then presented, which test the study's hypotheses. For all analyses, the Type I error rate was set at .05.

Preliminary Analyses

Descriptives of Variables of Interest

Table 4 provides the descriptive statistics for the variables of interest in the study sample. The table is divided into variables measuring working memory, executive functioning, psychosocial functioning, and psychological functioning.

Table 4

Means, Standard Deviations, and Ranges for the Variables of Interest

Measures	*n*	M	SD	Range
Working Memory Variables				
Digit Span Backward	72	6.75	1.90	2-11
Executive Functioning Variables				
D-KEFS Trail Making Test[a]	65	93.25	49.24	24-300
D-KEFS Verbal Fluency Test[a]	46	12.46	3.45	6-18

Table 4 (continued)

Means, Standard Deviations, and Ranges for the Variables of Interest

Measures	*n*	M	SD	Range
BRIEF Self-Report				
Inhibit	48	49.08	11.40	34-79
Shift	48	52.27	12.42	32-88
Emotional Control	48	52.56	12.69	34-88
Working Memory	48	54.00	12.92	33-83
Plan/Organize	48	50.00	12.44	31-81
Organization of Materials	48	50.54	10.49	33-78
Task Completion	48	51.60	12.34	35-83
Monitor	48	52.67	11.40	36-80
Behavioral Regulation Index	48	51.71	12.94	31-90
Metacognition Index	48	51.85	13.01	31-85
Global Executive Composite[a]	48	52.04	13.54	30-90
BRIEF Parent-Report				
Inhibit	63	49.75	10.70	37-81
Shift	63	52.63	11.65	37-82
Emotional Control	63	53.16	11.30	36-78
Initiate	63	52.95	10.80	35-74
Working Memory	63	55.83	11.90	40-82
Plan/Organize	63	54.13	11.94	37-82
Organization of Materials	63	50.78	9.83	36-71

Table 4 (continued)

Means, Standard Deviations, and Ranges for the Variables of Interest

Measures	*n*	M	SD	Range
Monitor	63	50.48	11.04	336-81
Behavioral Regulation Index	63	52.10	11.61	36-85
Metacognition Index	63	53.68	11.64	35-79
Global Executive Composite[a]	63	53.19	11.25	35-79
Psychosocial Variables				
MFS Self-Report				
General Fatigue	49	66.16	21.05	8.33-100
Sleep/Rest Fatigue	49	61.56	21.45	12.5-100
Cognitive Fatigue	49	68.20	25.30	4.17-100
Total Fatigue[a]	49	65.31	18.71	20.83-100
MFS Parent-Report				
General Fatigue	55	59.85	24.30	12.5-100
Sleep/Rest Fatigue	55	62.73	24.06	4.17-100
Cognitive Fatigue	55	72.05	22.99	25-100
Total Fatigue[a]	55	64.87	19.46	29.17-100
PedsQL Self-Report				
Physical Functioning	55	69.41	22.01	.25-100
Emotional Functioning	55	62.78	27.35	.20-100
Social Functioning	55	84.17	17.18	20-100
School Functioning	54	60.56	24.47	5-100

Table 4 (continued)

Means, Standard Deviations, and Ranges for the Variables of Interest

Measures	*n*	M	SD	Range
Total Scale Score[a]	55	69.30	17.47	29.57-100
PedsQL Parent-Report				
Physical Functioning	57	61.01	24.69	0-96.88
Emotional Functioning	57	61.12	23.43	20-100
Social Functioning	56	75.98	19.40	40-100
School Functioning	57	59.12	23.28	0-100
Total Scale Score[a]	56	63.13	18.30	30-93.48
Psychological Variables				
BASC-2 Self-Report				
Anxiety[a]	59	52.31	12.19	32-80
Depression[a]	59	51.36	11.63	39-85
BASC-2 Parent-Report				
Anxiety[a]	67	53.67	12.45	32-96
Depression[a]	67	54.48	9.76	37-78
Externalizing Problems[a]	67	47.69	8.25	37-77

Note. BASC-2 – Behavioral Assessment System for Children, Second Edition; BRIEF – Behavior Rating Inventory of Executive Functioning; D-KEFS – Delis-Kaplan Executive Function System; PedsQL – Pediatric Quality of Life Inventory; MFS – PedsQL Multidimensional Fatigue Scale.

[a] Due to multicollinearity, only these subscales and tests were used in the main analyses.

Tests for Multicollinearity Correlations

Some of the dependent and independent variables in this study were measured using more than one measure, subtest, or subscale. Tests for multicollinearity were conducted accordingly to determine which subscale or measure would be used to represent the variables in the main analyses. If these subscales or measures were highly correlated, one of the measures was chosen to represent the variable. If not highly correlated, they were analyzed as separate indices of the same variable.

Covariate correlations. Correlations and relationships among the possible covariates (e.g., sex, race, mother and father education level, age at testing, age at symptom onset, disease duration, disease severity, and IQ) were examined for multicollinearity (see Tables 5-7). The following significant correlations were found: mother education level was correlated with father education level ($r = .60$, $p < .001$), age at testing was correlated with age of onset ($r = .77$, $p < .001$), age of onset was correlated with disease duration ($r = -.62$, $p < .001$), and IQ was correlated with mother education level ($r = .45$, $p < .001$), father education level ($r = .40$, $p = .001$), disease duration ($r = -.38$, $p = .001$) and disease severity ($r = -.24$, $p = .041$).

In addition, one-way ANOVAs revealed no significant effect of either sex or race on the other covariates (e.g., mother and father education level, age at testing, age at symptom onset, disease duration, disease severity, and IQ).

All covariates were retained for future analyses, as none of them met the .08 criteria set by Cohen (1988). Although age at testing and age of onset were highly correlated, both were retained based on prior research (Amato et al., 2008; Banwell & Anderson, 2005; Holland et al., 2012).

Table 5

Two-Tailed Pearson and Spearman Correlations Among Possible Covariates

Variable	2	3	4	5	6	7
1. Mother Education Level[a]	.60***	-.20	.05	-.16	.45***	.06
2. Father Education Level[a]		-.16	.04	.12	.40**	.02
3. Age at Testing			.77***	.03	-.22	.11
4. Age of Onset				-.62***	.08	.08
5. Disease Duration					-.38**	.04
6. IQ						-.24*
7. Disease Severity (EDSS Score)[a]						

Note. EDSS – Expanded Disability Status Scale.

[a] Correlations conducted using Spearman rank correlation coefficient.

* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 6

Analysis of Variance (ANOVA) Between Sex and Other Possible Covariates

Variable	*n*	*df*	*F*	*p*
Race	78	1,77	1.86	.177
Mother Education Level	78	1,77	0.00	.952
Father Education Level	78	1,77	0.02	.886
Age at Testing	78	1,77	2.22	.141
Age at Symptom Onset	78	1,77	2.89	.093
Disease Duration	78	1,77	0.66	.420
Disease Severity	78	1,77	1.78	.186
IQ	71	1,70	0.08	.783

Table 7

Analysis of Variance (ANOVA) Between Race and Other Possible Covariates

Variable	*n*	*df*	*F*	*p*
Sex	78	5,73	1.22	.308
Mother Education Level	78	5,73	0.57	.724
Father Education Level	78	5,73	1.00	.426
Age at Testing	78	5,73	1.04	.401
Age at Symptom Onset	78	5,73	0.76	.585
Disease Duration	78	5,73	1.42	.227
Disease Severity	78	5,73	0.11	.990
IQ	71	5,66	2.91	.020

Correlations within measures.

D-KEFS correlations. The D-KEFS Verbal Fluency Test and Trail Making Test were used as performance-based measures of executive functioning. As displayed in Table 8, the correlation between these two measures was moderate (r = -.51, p < .001). Thus, they were considered separate variables.

Table 8

Two-Tailed Pearson Correlations of the D-KEFS

Variable	2
1. D-KEFS Trail Making Test	-.51
2. D-KEFS Verbal Fluency Test	

Note. Zero-order correlation was significant at the .001 level.

BRIEF correlations. All subscales and composite scores from the BRIEF Parent-Report and Self-Report were considered as report-based measures of executive functioning. As displayed in Tables 9 and 10, correlation analyses indicated that the eight subscales were significantly correlated, ranging from .46 to .85 (ps < .001) for the BRIEF Self-Report, and .32 to .78 (ps < .05) for the BRIEF Parent-Report. The composite scores were highly correlated, ranging from .88 to .97 (ps < .001) for the BRIEF Self-Report and .88 to .97 (ps < .001) for the BRIEF Parent-Report. Due to its high correlations with all subscales and summary scores, the Global Executive Composite for the BRIEF Self- and Parent-Report was chosen as the best summary score to represent report-based executive functioning.

Table 9

Two-Tailed Pearson Correlations of the BRIEF Self-Report

Variable	2	3	4	5	6	7	8	9	10	11
1. Inhibit	.77	.70	.73	.82	.83	.64	.69	.93	.83	.90
2. Shift		.62	.58	.82	.81	.75	.82	.86	.88	.89
3. Emotional Control			.69	.61	.74	.56	.59	.88	.70	.80
4. Monitor				.60	.64	.46	.49	.82	.61	.72
5. Working Memory					.81	.63	.76	.82	.90	.90
6. Plan/Organize						.78	.85	.88	.96	.95
7. Organization of Materials							.72	.71	.82	.79
8. Task Completion								.76	.92	.87
9. Behavioral Regulation Index									.88	.96
10. Metacognition Index										.97
11. Global Executive Composite										

Note. All zero-order correlations were significant at the .01 level.

Table 10

Two-Tailed Pearson Correlations of the BRIEF Parent-Report

Variable	2	3	4	5	6	7	8	9	10	11
1. Inhibit	.64	.68	.53	.59	.48	.32	.69	.87	.58	.76
2. Shift		.76	.65	.52	.49	.28	.66	.89	.58	.76
3. Emotional Control			.53	.41	.37	.32	.62	.92	.49	.72
4. Initiate				.74	.76	.68	.78	.63	.89	.87
5. Working Memory					.82	.62	.76	.56	.90	.86
6. Plan/Organize						.70	.78	.49	.94	.86
7. Organization of Materials							.53	.34	.78	.69
8. Monitor								.73	.87	.90
9. Behavioral Regulation Index									.61	.83
10. Metacognition Index										.94
11. Global Executive Composite										

Note. All zero-order correlations were significant at the .05 level.

BASC-2 correlations. The Anxiety and Depression subscales from the BASC-2 Self-Report and Parent-Report were used as measures of anxiety and depression. In addition, the Externalizing Problems Composite from the BASC-2 Parent-Report was used as a measure of externalizing behavior. Correlations within the BASC-2 Self- and Parent-Report are displayed in Tables 11 and 12. For the BASC-2 Self-Report, anxiety and depression were only moderately correlated ($r = .58$, $p < .001$), and thus they were treated as separate variables. For the BASC-2 Parent-Report, anxiety was moderately

correlated with depression ($r = .62$, $p < .001$) and not significantly correlated with externalizing symptoms ($r = .20$, $p = .105$). Depression was moderately correlated with externalizing symptoms ($r = .53$, $p < .001$). Thus, anxiety, depression, and externalizing symptoms were all kept as separate variables.

Table 11

Two-Tailed Pearson Correlations of the BASC-2 Self-Report

Variable	2
1. Anxiety	.58
2. Depression	

Note. Zero-order correlation was significant at the .001 level.

Table 12

Two-Tailed Pearson Correlations of the BASC-2 Parent-Report

Variable	2	3
1. Anxiety	.62	.20
2. Depression		.53
3. Externalizing Problems		

Note. All zero-order correlations greater than .20 were significant at the .001 level.

MFS correlations. Fatigue was measured using the MFS Self- and Parent-Report. The scale results in three summary scores (general fatigue, sleep/rest fatigue, cognitive fatigue), and one total score (total fatigue). For the MFS Self-Report,

correlation analyses (Table 13) revealed significant correlations between general fatigue, sleep/rest fatigue, and cognitive fatigue, ranging from .36 to .89 (*p*s < .05). The total score was highly correlated with all three summary scores (*r* = .74 to .89, *p*s < .001) and was therefore selected to measure self-reported fatigue.

Table 13

Two-Tailed Pearson Correlations of the MFS Self-Report

Variable	2	3	4
1. General Fatigue	.52	.70	.89
2. Sleep/Rest Fatigue		.36	.74
3. Cognitive Fatigue			.85
4. Total Fatigue			

Note. All zero-order correlations were significant at the .05 level.

For the MFS Parent-Report, correlation analyses (Table 14) revealed moderate correlations of general fatigue with sleep/rest fatigue and cognitive fatigue (*r* = .61 to .64, *p*s < .001), while the correlation between cognitive fatigue and sleep/rest fatigue was insignificant (*r* = .25, *p* = .066). Similar to the MFS Self-Report, the total score was again highly correlated with all three summary scores (*r* = .75 to .92, *p*s < .001). Thus, the total score was selected as the best measure of parent-reported fatigue.

Table 14

Two-Tailed Pearson Correlations of the MFS Parent-Report

Variable	2	3	4
1. General Fatigue	.64	.61	.92
2. Sleep/Rest Fatigue		.25	.78
3. Cognitive Fatigue			.75
4. Total Fatigue			

Note. All zero-order correlations greater than .30 were significant at the .001 level.

PedsQL correlations. Quality of life was measured with the PedsQL, which contains four generic core scales and one total summary score. Correlations for the PedsQL Self-Report are displayed in Table 15. For the PedsQL Self-Report, the generic core scales showed only moderate correlations with one another, ranging from .29 to .54 ($ps < .05$). However, as expected, the total score was highly correlated with all of the other core scales ($r = .68$ to .83, $ps < .001$). Thus, the PedsQL Self-Report total score was selected to represent self-reported quality of life.

Table 15

Two-Tailed Pearson Correlations of the PedsQL Self-Report

Variable	2	3	4	5
1. Physical Functioning	.48	.46	.44	.83
2. Emotional Functioning		.29	.45	.76
3. Social Functioning			.54	.68
4. School Functioning				.76
5. Total Scale Score				

Note. All zero-order correlations were significant at the .05 level.

Similarly, for the PedsQL Parent-Report (Table 16), the generic core scales showed only moderate correlations with one another, ranging from .42 to .61 (*p*s < .01). The Total Scaled Score was highly correlated with the other core scales (*r* = .75 to .85, *p*s < .01). Therefore, the Total score for the PedsQL Parent-Report was selected to represent a summary score measuring parent-reported quality of life.

Table 16

Two-Tailed Pearson Correlations of the PedsQL Parent-Report

Variable	2	3	4	5
1. Physical Functioning	.42	.57	.49	.85
2. Emotional Functioning		.49	.61	.75
3. Social Functioning			.52	.77
4. School Functioning				.77
5. Total Scale Score				

Note. All zero-order correlations were significant at the .01 level.

Parent- and child-report correlations. Self- and parent-reports summary scores for the BRIEF, BASC-2, MFS, and PedsQL were examined for multicollinearity, the results of which are displayed in Table 17. Correlations between the parent- and self-report summary scores for these measures were as follows: BRIEF General Executive Composite (r = .40, p = .011), BASC-2 Anxiety (r = .30, p = .036) and Depression (r = .37, p = .009), MFS Total Score (r = .70, p < .001), and PedsQL Total Score (r = .44, p = .003). None of these parent- and self-reports was highly correlated, except for the MFS Total Score. Although parent and child ratings for the MFS Total Score were highly correlated, it still fell below the threshold of .80 set by Cohen (1988), and thus they were analyzed separately.

Table 17

Two-Tailed Pearson Correlations Between Self- and Parent-Reports

Variable	*r*	*p*
BRIEF	.40	.011
BASC-2		
Anxiety	.30	.036
Depression	.37	.009
MFS	.70	.000
PedsQL	.44	.003

Note. BASC-2 – Behavior Assessment System for Children, Second Edition; BRIEF – Behavior Rating Inventory of Executive Function; MFS – PedsQL Multidimensional Fatigue Scale; PedsQL – Pediatric Quality of Life Inventory.

Correlations between measures.

Executive functioning correlations. Correlations among measures of executive functioning are shown in Table 18. Correlations between the Trail Making Test and the BRIEF Self-Report Global Executive Composite ($r = .12$, $p = .463$) and BRIEF Parent-Report Global Executive Composite ($r = .00$, $p = .994$) were not significant. Similarly, correlations between the Verbal Fluency Test and the BRIEF Self-Report Global Executive Composite ($r = -.02$, $p = .929$) and BRIEF Parent-Report Global Executive Composite ($r = -.17$, $p = .346$) were not significant. Thus, the D-KEFS and the BRIEF were considered as separate measures of executive functioning.

Table 18

Two-Tailed Pearson Correlations Between Measures of Executive Functioning

Variable	2	3	4
1. D-KEFS Trail Making Test	-.51***	.12	.00
2. D-KEFS Verbal Fluency Test		-.02	-.17
3. BRIEF Self-Report			.40*
4. BRIEF Parent-Report			

Note. BRIEF – Behavior Rating Inventory of Executive Function; D-KEFS – Delis-Kaplan Executive Function System.

* $p < .05$. *** $p < .001$.

Psychosocial functioning correlations. Correlations among measures of psychosocial functioning are displayed in Table 19. The MFS Self-Report was moderately correlated with the PedsQL Self-Report ($r = .62$, $p < .001$) and Parent-Report ($r = .45$, $p = .004$). Similarly, the MFS Parent-Report was moderately correlated with the PedsQL Self-Report ($r = .51$, $p = .001$) and Parent-Report ($r = .75$, $p < .001$). The BASC-2 Externalizing Problems was significantly correlated with the MFS Parent-Report ($r = -.42$, $p = .001$) and PedsQL Parent-Report ($r = -.43$, $p = .001$). It was not correlated with the MFS Self-Report ($r = -.30$, $p = .056$) or the PedsQL Self-Report ($r = -.19$, $p = .204$). As none of these correlations reached .08, quality of life, fatigue, and externalizing symptoms were considered as separate measures of psychosocial functioning.

Table 19

Two-Tailed Pearson Correlations Between Measures of Psychosocial Functioning

Variable	2	3	4	5
1. MFS Self-Report	.70***	.62***	.45**	-.30
2. MFS Parent-Report		.51**	.75***	-.42**
3. PedsQL Self-Report			.44**	-.19
4. PedsQL Parent-Report				-.43**
5. BASC-2 Externalizing Problems				

Note. BASC-2 – Behavior Assessment System for Children, Second Edition; MFS – PedsQL Multidimensional Fatigue Scale; PedsQL – Pediatric Quality of Life Inventory. ** $p < .01$. *** $p < .001$.

Correlations Analyses for Variables of Interest

Correlations of covariates with outcome variables. Two-tailed Pearson correlations, two-tailed Spearman correlations, and one-way ANOVAs were conducted as preliminary analyses to investigate which outcome variables had significant relationships with possible covariates (e.g., sex, race, mother and father education level, age at testing, age of onset, disease duration, disease severity, and IQ). Results are displayed in Tables 20-22.

Sex. Sex had a significant effect on the MFS Self-Report [$F(1, 47) = 8.82$, $p = .005$], MFS Other-Report [$F(1, 53) = 4.91$, $p = .031$], and the PedsQL Self-Report [$F(1, 53) = 10.44$, $p = .002$]. There was not a significant effect of sex on the Trail Making Test [$F(1, 63) = 3.18$, $p = .080$], the Verbal Fluency Test [$F(1, 44) = 0.02$, $p = .893$], BRIEF

Self-Report [$F(1, 46) = 0.12$, $p = .728$], BRIEF Parent-Report [$F(1, 61) = 0.12$, $p = .727$], PedsQL Parent-Report [$F(1, 54) = 10.44$, $p = .002$], or BASC-2 Externalizing Problems [$F(1, 65) = 0.14$, $p = .709$]. Thus, for regressions that involve the PedsQL Self-Report, MFS Self-Report, and MFS Other-Report, sex was included as a covariate at Step 1 of the regression.

Table 20

Analysis of Variance (ANOVA) Between Sex and Outcome Variables

Variable	*n*	*df*	*F*	*p*
D-KEFS Trail Making Test	64	1,63	3.18	.080
D-KEFS Verbal Fluency	45	1,44	0.02	.893
BRIEF Self-Report	47	1,46	0.12	.728
BRIEF Parent-Report	62	1,61	0.12	.727
MFS Self-Report	48	1,47	8.82	.005
MFS Parent-Report	54	1,53	4.91	.031
PedsQL Self-Report	54	1,53	10.44	.002
PedsQL Parent-Report	55	1,54	1.53	.221
BASC-2 Externalizing	66	1,65	0.14	.709

Race. Race did not have a significant effect on any of the outcome variables, including the Trail Making Test [$F(5, 59) = 0.04$, $p = .999$], Verbal Fluency Test [$F(5, 40) = 1.15$, $p = 0.35$], BRIEF Self-Report [$F(5, 42) = 0.93$, $p = .469$], BRIEF Parent-Report [$F(5, 57) = 1.97$, $p = .097$], MFS Self-Report [$F(5, 43) = 1.99$, $p = 0.10$], MFS

Other-Report [$F(5, 49) = 1.64$, $p = 0.17$], PedsQL Self-Report [$F(5, 49) = 1.64$, $p = .167$], PedsQL Parent-Report [$F(5, 50) = 0.61$, $p = .691$], or BASC-2 Externalizing Problems [$F(5, 61) = 1.25$, $p = .297$]. Thus, race was not included as a covariate in the main analyses.

Table 21

Analysis of Variance (ANOVA) Between Race and Outcome Variables

Variable	*n*	*df*	*F*	*p*
D-KEFS Trail Making Test	64	5,59	0.04	.999
D-KEFS Verbal Fluency	45	5,40	1.15	.350
BRIEF Self-Report	47	5,42	0.93	.469
BRIEF Parent-Report	62	5,57	1.97	.097
MFS Self-Report	48	5,43	1.99	.100
MFS Parent-Report	54	5,49	1.64	.167
PedsQL Self-Report	54	5,49	0.73	.602
PedsQL Parent-Report	55	5,50	0.61	.691
BASC-2 Externalizing	66	5,61	1.25	.297

Mother education level. Mother education level was not significantly correlated with any of the outcome variables, including the Trail Making Test ($r = -.09$, $p = .456$), Verbal Fluency Test ($r = .07$, $p = .664$), BRIEF Self-Report ($r = .10$, $p = .491$), BRIEF Parent-Report ($r = -.12$, $p = .367$), MFS Self-Report ($r = -.03$, $p = .831$), MFS Other-Report ($r = .07$, $p = .627$), PedsQL Self-Report ($r = .00$, $p = .997$), PedsQL Parent-Report

(r = .24, p = .073), or BASC-2 Externalizing Problems (r = -.11, p = .396). Thus, mother education level was not included as a covariate in the main analyses.

Father education level. Father education level was not significantly correlated with any of the outcome variables, including the Trail Making Test (r = .02, p = .901), Verbal Fluency Test (r = .04, p = .773), BRIEF Self-Report (r = .14, p = .341), BRIEF Parent-Report (r = -.22, p = .091), MFS Self-Report (r = -.11, p = .442), MFS Other-Report (r = .01, p = .950), PedsQL Self-Report (r = -.07, p = .610), PedsQL Parent-Report (r = .08, p = .557), or BASC-2 Externalizing Problems (r = -.08, p = .538). Thus, father education level was not included as a covariate in the main analyses.

Age at testing. Age at testing significantly correlated with the Trail Making Test (r = -.60, p < .001) and the Verbal Fluency Test (r = .47, p = .001). These correlations were in the expected direction, with younger age at neuropsychological evaluation associated with poorer performance on executive function measures. No significant correlations were found between age at testing and BRIEF Self-Report (r = .01, p = .939), BRIEF Parent-Report (r = .03, p = .818), MFS Self-Report (r = .14, p = .347), MFS Parent-Report (r = .07, p = .625), PedsQL Self-Report (r = .12, p = .387), PedsQL Parent-Report (r = .11, p = .443), or BASC-2 Externalizing Problems (r = .00, p = .976). Thus, for regressions that involve the Trail Making Test and Verbal Fluency Test, age at testing was included as a covariate at Step 1 of the regression.

Age of onset. Results indicated that age of onset was significantly correlated with the Trail Making Test (r = -.47, p < .001) and Verbal Fluency Test (r = .57, p < .001). These correlations were in the expected direction, where younger age of onset was associated with poorer performance on executive function measures. No significant

correlations were found between age of onset and BRIEF Self-Report (r = -.00, p = .988), BRIEF Parent-Report (r = -.06, p = .670), MFS Self-Report (r = .02, p = .919), MFS Parent-Report (r = .01, p = .950), PedsQL Self-Report (r = .05, p = .712), PedsQL Parent-Report (r = .23, p = .085), and BASC-2 Externalizing Problems (r = -.09, p = .479). Thus, for regressions that involve the Trail Making Test and the Verbal Fluency Test, age of onset was included as a covariate at Step 1 of the regression.

Disease duration. Results indicated that disease duration was negatively correlated with the Verbal Fluency Test (r = -.36, p = .014). These correlations were consistent with expectations. Longer disease duration was associated with poorer performance on the Verbal Fluency Test. No significant correlations were found between disease duration and the Trail Making Test (r = .05, p = .703), BRIEF Self-Report (r = .01, p = .951), BRIEF Parent-Report (r = .13, p = .310), MFS Self-Report (r = .11, p = .441), MFS Parent-Report (r = .07, p = .627), PedsQL Self-Report (r = .04, p = .771), PedsQL Parent-Report (r = -.24, p = .076), and BASC-2 Externalizing Problems (r = .14, p = .257). Thus, for regressions that involve the Verbal Fluency Test, disease duration was included as a covariate at Step 1 of the regression.

Disease severity. Disease severity was negatively correlated with the MFS Parent-Report (r = -.31, p = .022), which was in the expected direction. More severe disease was associated with greater parent-reported fatigue. No significant correlations were found between disease severity and the Trail Making Test (r = .05, p = .715), Verbal Fluency Test (r = .04, p = .796), BRIEF Self-Report (r = .07, p = .629), BRIEF Parent-Report (r = .12, p = .368), MFS Self-Report (r = -.26, p = .073), PedsQL Self-Report (r = -.23, p = .098), PedsQL Parent-Report (r = -.16, p = .239), and BASC-2

Externalizing Problems (r = .07, p = .554). Thus, for regressions that involve the MFS Parent-Report, disease severity was included as a covariate.

IQ. Results demonstrated significant correlations between IQ and the Verbal Fluency Test (r = .49, p = .001). No significant correlations were found between IQ and the Trail Making Test (r = -.12, p = .368), BRIEF Self-Report (r = .24, p = .121), BRIEF Parent-Report (r = -.16, p = .216), MFS Self-Report (r = .07, p = .628), MFS Parent-Report (r = -.00, p = .980), PedsQL Self-Report (r = -.09, p = .523), PedsQL Parent-Report (r = -.05, p = .726), and BASC-2 Externalizing Problems (r = -.01, p = .942). Thus, for regressions that involve the Verbal Fluency Test and Digit Span Backward, IQ was included as a covariate at Step 1 of the regression.

Table 22

Two-Tailed Pearson and Spearman Correlations Between Covariates and Outcome Variables

Variable	Mother Ed[a]	Father Ed[a]	Age at Testing	Age of Onset	Disease Duration	Disease Severity[a]	IQ
TMT	-.09	.01	-.60***	-.47***	.05	.05	-.12
VF	.07	.04	.48**	.57***	-.36*	.04	.49***
BRIEF SR	.10	.14	.01	-.00	.01	.07	.24
BRIEF PR	-.12	-.22	.03	-.06	.13	.12	-.16
MFS SR	-.03	-.11	.14	.02	.11	-.26	.07
MFS PR	.07	-.01	.07	.01	.07	-.31*	-.00
PedsQL SR	.00	-.07	.12	.05	.04	-.23	-.09
PedsQL PR	.24	.08	.11	.23	-.24	-.16	-.05
BASC-2 Externalizing	-.11	-.08	.00	-.09	.14	.07	-.01

Note. BASC-2 – Behavior Assessment System for Children, Second Edition; BRIEF – Behavior Rating Inventory of Executive Function; Ed – Education Level; MFS – PedsQL Multidimensional Fatigue Scale; PedsQL – Pediatric Quality of Life Inventory; PR – Parent-Report; SR – Self-Report; TMT – Trail Making Test; VF – Verbal Fluency Test.

[a] Correlations conducted using Spearman rank correlation coefficient.

* $p < .05$. ** $p < .01$. *** $p < .001$.

Correlations between predictors and outcome variables. The zero-order correlations between the outcome variables and their possible predictor variables are shown in Tables 23-26. If correlations were not found to be significant, the respective independent variables were excluded from the subsequent multiple regression analyses.

Correlations between anxiety, depression, and executive functioning. The Trail Making Test was significantly correlated with BASC-2 Parent-Report Anxiety ($r = .36$, $p = .008$). This correlation was in the expected direction, with slower performance on the Trail Making Test associated with higher levels of parent-reported anxiety. The Trail Making Test was not correlated with BASC-2 Self-Report Anxiety ($r = .09$, $p = .521$), BASC-2 Self-Report Depression ($r = .06$, $p = .699$), or BASC-2 Parent-Report Depression ($r = .11$, $p = .446$). Thus, these independent variables were not included in the subsequent multiple regression analyses.

The Verbal Fluency Test was also significantly correlated with BASC-2 Parent-Report Anxiety ($r = -.33$, $p = .047$). This correlation was in the expected direction, with reduced verbal fluency associated with higher levels of parent-reported anxiety. The Verbal Fluency Test was not correlated with BASC-2 Self-Report Anxiety ($r = .09$, $p = .621$), BASC-2 Self-Report Depression ($r = -.00$, $p = .990$), or BASC-2 Parent-Report Depression ($r = -.14$, $p = .396$). Thus, these independent variables were not included in the subsequent multiple regression analyses.

The BRIEF Self-Report was significantly correlated with BASC-2 Self-Report Anxiety ($r = .52$, $p < .001$), BASC-2 Self-Report Depression ($r = .61$, $p < .001$), and BASC-2 Parent-Report Depression ($r = .48$, $p = .001$). All of these correlations were in the expected direction. Greater self-reported executive functioning problems were

associated with higher self-reported anxiety and depression, and higher parent-reported depression. The BRIEF Self-Report was not significantly associated with BASC-2 Parent-Report Anxiety ($r = .04$, $p = .789$). Thus, this independent variable was excluded from subsequent multiple regression analyses.

The BRIEF Parent-Report was significantly correlated with BASC-2 Parent-Report Anxiety ($r = .33$, $p = .009$) and BASC-2 Parent-Report Depression ($r = .71$, $p < .001$). These correlations were in the expected direction, with greater parent-reported executive functioning problems associated with higher parent-reported anxiety and depression. The BRIEF Parent-Report was not significantly associated with BASC-2 Self-Report Anxiety ($r = .28$, $p = .063$) or BASC-2 Self-Report Depression ($r = .10$, $p = .505$). Thus, these independent variables were excluded from subsequent multiple regression analyses.

Table 23

Two-Tailed Pearson Correlations Between Anxiety, Depression, and Executive Functioning

Outcome Variable	Anxiety		Depression	
	Self-Report	Parent-Report	Self-Report	Parent-Report
Trail Making Test	.09	.36**	.06	.11
Verbal Fluency Test	.09	-.33*	-.00	-.14
BRIEF Self-Report	.52***	.04	.61***	.48**
BRIEF Parent-Report	.28	.33**	.10	.71***

Note. BRIEF – Behavior Rating Inventory of Executive Function.

* $p < .05$. ** $p < .01$. *** $p < .001$.

Correlations between anxiety, depression, and psychosocial functioning. The MFS Self-Report was associated with BASC-2 Self-Report Anxiety ($r = -.66$, $p < .001$), BASC-2 Self-Report Depression ($r = -.51$, $p < .001$), and BASC-2 Parent-Report Depression ($r = -.46$, $p = .002$). These correlations were in the expected direction. Greater self-reported fatigue was associated with greater self-reported depression and anxiety, and greater parent-reported depression. The MFS was not significantly correlated with BASC-2 Parent-Report Anxiety ($r = -.16$, $p = .304$). Thus, this independent variable was not included in subsequent multiple regression analyses.

The MFS Parent-Report was significantly correlated with BASC-2 Self-Report Anxiety ($r = -.49$, $p = .001$), BASC-2 Self-Report Depression ($r = -.39$, $p = .011$), BASC-2 Parent-Report Anxiety ($r = -.27$, $p = .048$), and BASC-2 Parent-Report Depression ($r =$

-.51, $p < .001$). These correlations were in the expected direction. Greater parent-reported fatigue was associated with greater depression and anxiety, measured by both self- and parent-report.

Mirroring the MFS Self-Report, the PedsQL Self-Report was significantly correlated with BASC-2 Self-Report Anxiety ($r = -.63$, $p < .001$), BASC-2 Self-Report Depression ($r = -.59$, $p < .001$), and BASC-2 Parent-Report Depression ($r = -.44$, $p = .002$). As expected, worse self-reported quality of life was associated with greater self-reported depression and anxiety, and greater parent-reported depression. The PedsQL Self-Report was not significantly correlated with BASC-2 Parent-Report Anxiety ($r = -.26$, $p = .077$). Thus, this independent variable was not included in subsequent multiple regression analyses.

The PedsQL Parent-Report was significantly correlated with BASC-2 Self-Report Anxiety ($r = -.39$, $p = .011$), BASC-2 Parent-Report Anxiety ($r = -.27$, $p = .043$), and BASC-2 Parent-Report Depression ($r = -.47$, $p < .001$). These correlations were in the expected direction. Worse parent-reported quality of life was associated with greater parent-reported depression and anxiety, and greater self-reported anxiety. The PedsQL Parent-Report was not significantly correlated with BASC-2 Self-Report Depression ($r = -.31$, $p = .052$). Thus, this independent variable was not included in subsequent multiple regression analyses.

Lastly, the BASC-2 Parent-Report Externalizing Problems was significantly correlated with BASC-2 Parent-Report Depression ($r = .53$, $p < .001$). Parent-reported externalizing behavior was associated with greater parent-reported depression. The BASC-2 Parent-Report Externalizing Problems was not significantly correlated with

BASC-2 Self-Report Anxiety (r = .18, p = .218), BASC-2 Self-Report Depression (r = -.10, p = .513), or BASC-2 Parent-Reported Anxiety (r = .20, p = .105). Thus, these independent variables were not included in subsequent multiple regression analyses for externalizing symptoms.

Table 24

Two-Tailed Pearson Correlations Between Anxiety, Depression, and Psychosocial Functioning

Outcome Variable	Anxiety		Depression	
	Self-Report	Parent-Report	Self-Report	Parent-Report
MFS Self-Report	-.66***	-.16	-.51***	-.46**
MFS Parent-Report	-.49**	-.27*	-.39*	-.51***
PedsQL Self-Report	-.63***	-.26	-.59***	-.44**
PedsQL Parent-Report	-.39*	-.27*	-.31	-.47***
BASC-2 Externalizing	.18	.20	-.10	.53***

Note. BASC-2 – Behavior Assessment System for Children, Second Edition; MFS – PedsQL Multidimensional Fatigue Scale; PedsQL – Pediatric Quality of Life Inventory. * p < .05. ** p < .01. *** p < .001.

Correlations between executive and psychosocial functioning. The Trail Making Test and Verbal Fluency Test were not significantly correlated with any psychosocial variables. For the Trail Making Test, these insignificant correlations included: the MFS Self-Report (r = -.60, p = .076), MFS Parent-Report (r = -.15, p =

.323), PedsQL Self-Report (r = -.14, p = .356), PedsQL Other Report (r = -.21, p = .178), and BASC-2 Externalizing Problems (r = .05, p = .739). Insignificant correlations for the Verbal Fluency Test were as follows: MFS Self-Report (r = .04, p = .844), MFS Parent-Report (r = -.02, p = .936), PedsQL Self-Report (r = -.02, p = .900), PedsQL Other Report (r = -.02, p = .904), and BASC-2 Externalizing Problems (r = -.08, p = .654).

The BRIEF Self-Report was correlated with the MFS Self-Report (r = -.60, p < .001) and the PedsQL Self-Report (r = -.61, p < .001), such that worse self-reported executive functioning was associated with greater levels of self-reported fatigue and worse self-reported quality of life. The BRIEF Self-Report demonstrated weaker but still significant correlations with the MFS Parent-Report (r = -.37, p = .021) and the PedsQL Parent-Report (r = -.39, p = .017), such that worse self-reported executive functioning was associated with greater levels of parent-reported fatigue and worse parent-reported quality of life. The BRIEF Self-Report was not significantly correlated with BASC-2 Externalizing Problems (r = .22, p = .151).

The BRIEF Parent-Report was negatively correlated with the MFS Self-Report (r = -.48, p = .002), MFS Parent-Report (r = -.59, p < .001), PedsQL Self-Report (r = -.31, p = .043), PedsQL Parent-Report (r = -.50, p < .001), and BASC-2 Externalizing Problems (r = .79, p < .001). Thus, parent-reported executive functioning problems correlated with increased parent- and child-reported fatigue, worse quality of life, and greater externalizing symptoms.

Table 25

Two-Tailed Pearson Correlations Between Executive Functioning and Psychosocial Functioning

			BRIEF	
Outcome Variable	TMT	VF	Self-Report	Parent-Report
MFS Self-Report	-.28	-.04	-.60***	-.48**
MFS Parent-Report	-.15	-.02	-.37*	-.59***
PedsQL Self-Report	-.14	-.02	-.61***	-.31*
PedsQL Parent-Report	-.21	-.02	-.39*	-.50***
BASC-2 Externalizing	.05	-.08	.22	.79***

Note. BASC-2 – Behavior Assessment System for Children, Second Edition; BRIEF – Behavior Rating Inventory of Executive Functioning; MFS – PedsQL Multidimensional Fatigue Scale; PedsQL – Pediatric Quality of Life Inventory; TMT – Trail Making Test; VF – Verbal Fluency Test.

* $p < .05$. ** $p < .01$. *** $p < .001$.

Correlations between working memory and psychosocial functioning. Digit Span Backward was not significantly correlated with any psychosocial variables, including MFS Self-Report ($r = .15$, $p = .343$), MFS Parent-Report ($r = .05$, $p = .741$), PedsQL Self-Report ($r = -.05$, $p = .751$), PedsQL Parent-Report ($r = .16$, $p = .260$), or BASC-2 Parent-Report Externalizing Problems ($r = -.04$, $p = .769$). Given that these correlations were not found to be significant, the regression analyses for Hypothesis 4 and 5 were not conducted.

Table 26

Two-Tailed Pearson Correlations Between Working Memory and Psychosocial Functioning

Outcome Variable	Digit Span Backward
MFS Self-Report	.15
MFS Parent-Report	.05
PedsQL Self-Report	-.05
PedsQL Parent-Report	.16
BASC-2 Externalizing Problems	-.04

Note. BASC-2 – Behavior Assessment System for Children, Second Edition; MFS – PedsQL Multidimensional Fatigue Scale; PedsQL – Pediatric Quality of Life Inventory.

Conclusion

Preliminary analyses resulted in a reduction in the number of variables to be used in the main analyses. In order to further simplify the multiple regressions and avoid the problem of shrinkage, this study used only the summary scores from each measure. This resulted in the following 13 final variables: Executive Functioning (Trail Making Test, Verbal Fluency Test, BRIEF Self-Report, BRIEF Parent-Report), Psychological Functioning (BASC-2 Self-Report Anxiety, BASC-2 Self-Report Depression, BASC-2 Parent-Report Anxiety, BASC-2 Parent-Report Depression), and Psychosocial Functioning (MFS Self-Report, MFS Parent-Report, PedsQL Self-Report, PedsQL Parent-Report, and BASC-2 Externalizing Problems).

In addition, given the results of the correlations between possible covariates and outcome variables, the following variables were selected to be covariates: sex, age at testing, age of onset, disease duration, disease severity, and IQ.

Main Analyses

Hierarchical and simultaneous regressions were conducted for each predictor that had significant correlations with each outcome variable. Note that only if the covariates had significant correlations with the dependent variable were they included in the regression model for that dependent variable.

Hypothesis 1. Anxiety and depression will predict executive functioning.

Two hierarchical regression analyses were conducted with each applicable measure of executive functioning (Trail Making Test, Verbal Fluency Test) as the dependent variable, appropriate covariates (sex, age at testing, age of onset, disease duration, disease severity, IQ) as entered at Step 1, and anxiety and depression (BASC-2 Self-Report and Parent-Report) entered at Step 2. In addition, two simultaneous regression analyses were conducted with each applicable executive functioning variable (BRIEF Self-Report, BRIEF Parent-Report) as the dependent variable and anxiety and depression (BASC-2 Self-Report and Parent-Report) entered at Step 1. None of the covariates (sex, age at testing, age of onset, disease duration, disease severity, IQ) had significant correlations with the BRIEF Self-Report and BRIEF Parent-Report; thus, these were not included in the regression model for those variables.

Table 27 illustrates the results of the multiple regression analysis for performance on the Trail Making Test, a measure of executive functioning. In Step 1, the covariates age at testing and age of onset significantly explained 39.5% of the variance on

performance for the Trail Making Test ($p < .001$). However, only age at testing had a significant regression coefficient at the first step ($\beta = -.63$, $p < .001$), while age of onset did not ($\beta = -.05$, $p = .759$). When BASC-2 Parent-Report Anxiety was added to the model at Step 2, an additional 7.7% of the variance on the Trail Making Test was explained ($p = .010$). BASC-2 Parent-Report Anxiety ($\beta = .29$, $p = .010$) significantly contributed to the model. Age of testing remained a significant contributor to model 2 in explaining variance on the Trail Making Test.

Table 27

Hierarchical Regression Analysis of Anxiety and Depression on the Trail Making Test

Variable	*B*	SE_B	β	Increment in R^2
Step 1				.40***
Age at Testing	-10.87**	3.00	-.59**	
Age at Symptom Onset	-.68	2.19	-.05	
Step 2				.08*
Age at Testing	-11.51***	2.84	-.63***	
Age at Symptom Onset	.64	2.12	.05	
BASC-2 Parent-Report Anxiety	1.41*	.52	.29*	

Note. BASC-2 – Behavior Assessment System for Children, Second Edition.

*$p < .05$. **$p < .01$. ***$p < .001$.

Table 28 illustrates the results of the multiple regression analysis for performance on the Verbal Fluency Test, a measure of executive functioning. Due to

multicollinearity, the regression analysis excluded age of onset as a covariate. In Step 1, the three remaining covariates (age at testing, disease duration, and IQ) significantly explained 55.7% of the variance on performance for the Verbal Fluency Test ($p < .001$). However, only age at testing ($\beta = .47$, $p < .001$) and IQ ($\beta = .53$, $p < .001$) had significant regression coefficients. When BASC-2 Parent-Report Anxiety was added to the model at Step 2, no additional variance on the Verbal Fluency Test was explained ($p = .905$). BASC-2 Parent-Report Anxiety ($\beta = -.02$, $p = .905$) did not significantly contribute to the model. Age of testing and IQ remained significant contributors to model 2.

Table 28

Hierarchical Regression Analysis of Anxiety and Depression on Verbal Fluency

Variable	*B*	SE_B	β	Increment in R^2
Step 1				.56***
Age at Testing	.61***	.16	.47***	
Disease Duration	-.07	.20	.05	
IQ	.20***	.05	.53***	
Step 2				.00
Age at Testing	.61**	.16	.47**	
Disease Duration	-.07	.20	-.05	
IQ	.19**	.06	.52**	
BASC-2 Parent-Report Anxiety	-.01	.06	-.02	

Note. BASC-2 – Behavior Assessment System for Children, Second Edition.

**$p < .01$. ***$p < .001$.

Table 29 illustrates the results of the simultaneous regression analysis for the BRIEF Self-Report, a self-report measure of executive functioning. The three predictors (BASC-2 Self-Report Anxiety, BASC-2 Self-Report Depression, and BASC-2 Parent-Report Depression) significantly explained 58.4% of the variance on the BRIEF Self-Report ($p < .001$). However, only BASC-2 Self-Report Depression ($\beta = .54$, $p < .001$) had a significant regression coefficient at the first step. BASC-2 Self-Report Anxiety ($\beta = .13$, $p = .350$) and BASC-2 Parent-Report Depression ($\beta = .24$, $p = .054$) were not significant predictors and did not significantly explain additional variance for the BRIEF Self-Report.

Table 29

Simultaneous Regression Analysis of Anxiety and Depression on Self-Reported Executive Functioning

Variable	*B*	SE_B	β	Increment in R^2
Step 1				.58***
BASC-2 Self-Report Anxiety	.16	.16	.13	
BASC-2 Self-Report Depression	.62***	.15	.54***	
BASC-2 Parent-Report Depression	.36	.18	.24	

Note. BASC-2 – Behavior Assessment System for Children, Second Edition.

***$p < .001$.

Table 30 illustrates the results of the simultaneous regression analysis for the BRIEF Parent-Report, a parent-report measure of executive functioning. The two

predictors (BASC-2 Parent-Report Anxiety and BASC-2 Parent-Report Depression) significantly explained 52.6% of the variance on the BRIEF Parent-Report ($p < .001$). However, only BASC-2 Parent-Report Depression ($\beta = .82$, $p < .001$) had a significant regression coefficient at the first step. BASC-2 Parent-Report Anxiety ($\beta = -.17$, $p = .139$) did not significantly contribute to the model.

Table 30

Simultaneous Regression Analysis of Anxiety and Depression on Parent-Reported Executive Functioning

Variable	*B*	SE_B	β	Increment in R^2
Step 1				.53***
BASC-2 Parent-Report Anxiety	-.15	.10	-.17	
BASC-2 Parent-Report Depression	.93***	.13	.82***	

Note. BASC-2 – Behavior Assessment System for Children, Second Edition.

***$p < .001$.

In summary, results partially supported Hypothesis 1 that anxiety and depression would predict executive functioning. After controlling for age at testing, BASC-2 Parent-Report Anxiety was a significant predictor of performance on the Trail Making Test. However, for the Verbal Fluency Test, after controlling for age at testing, disease duration, and IQ, BASC-2 Parent-Report Anxiety did not remain a significant predictor. In contrast to performance-based measures of executive functioning, self-report measures of executive functioning showed significant relationships with depression but not anxiety.

BASC-2 Self-Report Depression was a significant predictor of the BRIEF Self-Report, while BASC-2 Parent-Report Depression was a significant predictor of the BRIEF Parent-Report.

Hypothesis 2. Anxiety and depression will predict psychosocial functioning.

Three hierarchical regression analyses were conducted with the relevant psychosocial variables (MFS Self-Report, MFS Parent-Report, PedsQL Self-Report) as the dependent variable, appropriate covariates (sex, age at testing, age of onset, disease duration, disease severity, IQ) entered at Step 1, and anxiety and depression (BASC-2 Self-Report and Parent-Report) entered at Step 2. In addition, two simultaneous regression analyses were conducted with the appropriate psychosocial variables (PedsQL Other-Report, BASC-2 Externalizing Problems) as the dependent variable and anxiety and depression (BASC-2 Self-Report and Parent-Report) entered at Step 1. None of the covariates (sex, age at testing, age of onset, disease duration, disease severity, IQ) had significant correlations with the PedsQL Parent-Report or BASC-2 Externalizing Problems; thus, they were not included in the regression model for these variables.

Table 31 illustrates the results of the hierarchical regression analysis for the MFS Self-Report, a self-report measure of fatigue. In Step 1, the covariate sex significantly explained 12.7% of the variance on the MFS Parent-Report ($p = .026$) and had a significant regression coefficient at the first step ($\beta = -.36$, $p = .026$). When the three predictors (BASC-2 Self-Report Anxiety, BASC-2 Self-Report Depression, and BASC-2 Parent-Report Depression) were added to the model at Step 2, they significantly explained an additional 38.3% of the variance on the MFS Self-Report ($p < .001$). However, only BASC-2 Self-Report Anxiety ($\beta = -.33$, $p = .048$) significantly

contributed to the model. BASC-2 Self-Report Depression (β = -.26, p = .081) and BASC-2 Parent-Report Depression (β = -.22, p = .116) did not significantly contribute to the model. Sex did not remain a significant contributor to model 2 in explaining variance on the MFS Self-Report.

Table 31

Hierarchical Regression Analysis of Anxiety and Depression on Self-Reported Fatigue

Variable	B	SE_B	β	R^2
Step 1				.13*
Sex	-12.63*	5.45	-.36*	
Step 2				.38***
Sex	-5.98	4.71	-.17	
BASC-2 Self-Report Anxiety	-.52*	.25	-.33*	
BASC-2 Self-Report Depression	-.43	.24	-.26	
BASC-2 Parent-Report Depression	-.40	.25	-.22	

Note. BASC-2 – Behavior Assessment System for Children, Second Edition.

*p < .05. ***p < .001.

Table 32 illustrates the results of the hierarchical regression analysis for the MFS Parent-Report, a parent-report measure of fatigue. In Step 1, the covariates sex and disease severity significantly explained 26.1% of the variance on the MFS Parent-Report (p = .004). However, only sex had a significant regression coefficient at the first step (β = -.42, p = .006), while disease severity did not (β = -.24, p = .106). When the four

predictors (BASC-2 Self-Report Anxiety, BASC-2 Self-Report Depression, BASC-2 Parent-Report Anxiety, and BASC-2 Parent-Report Depression) were added to the model at Step 2, an additional 27.5% of the variance on the MFS Parent-Report was explained (p = .003). However, only BASC-2 Parent-Report Depression (β = -.55, p = .004) significantly contributed to the model. BASC-2 Self-Report Anxiety (β = .02, p = .905), BASC-2 Self-Report Depression (β = -.16, p = .313), and BASC-2 Parent-Report Anxiety (β = .16, p = .335) did not significantly contribute to the model. Sex and disease severity both remained significant contributors to model 2 in explaining variance on the MFS Parent-Report.

Table 32

Hierarchical Regression Analysis of Anxiety and Depression on Parent-Reported Fatigue

Variable	*B*	SE_B	β	Increment in R^2
Step 1				.26**
Sex	-17.24**	5.93	-.42**	
Disease Severity (EDSS Score)	-3.74	2.26	-.24	
Step 2				.28**
Sex	-13.89*	5.69	-.34*	
Disease Severity (EDSS Score)	-4.18*	1.99	-.27*	
BASC-2 Self-Report Anxiety	-.04	.32	.02	
BASC-2 Self-Report Depression	-.30	.29	-.16	
BASC-2 Parent-Report Anxiety	.29	.30	.16	
BASC-2 Parent-Report Depression	-1.15**	.37	-.55**	

Note. BASC-2 – Behavior Assessment System for Children, Second Edition; EDSS – Expanded Disability Status Scale.

*$p < .05$. **$p < .01$.

Table 33 illustrates the results of the hierarchical regression analysis for the PedsQL Self-Report, a self-report measure of quality of life. In Step 1, the covariate sex significantly explained 17.3% of the variance on the PedsQL Self-Report ($p = .006$) and had a significant regression coefficient at the first step ($\beta = -.42$, $p = .006$). When the three predictors (BASC-2 Self-Report Anxiety, BASC-2 Self-Report Depression, BASC-2 Parent-Report Depression) were added to the model at Step 2, they significantly

explained 39.1% of the variance on the PedsQL Self-Report ($p < .001$). However, only BASC-2 Self-Report Depression ($\beta = -.37$, $p = .011$) significantly contributed to the model. BASC Self-Report Anxiety ($\beta = -.24$, $p = .106$) and BASC-2 Parent-Report Depression ($\beta = -.17$, $p = .178$) did not significantly contribute to the model. Sex remained a significant contributor to model 2 in explaining variance on the PedsQL Self-Report.

Table 33

Hierarchical Regression Analysis of Anxiety and Depression on Self-Reported Quality of Life

Variable	*B*	SE_B	β	R^2
Step 1				.17**
Sex	-15.70**	5.36	-.42**	
Step 2				.39***
Sex	-10.43*	4.39	-.28*	
BASC-2 Self-Report Anxiety	-.39	.23	-.24	
BASC-2 Self-Report Depression	-.62*	.23	-.37*	
BASC-2 Parent-Report Depression	-.34	.24	-.17	

Note. BASC-2 – Behavior Assessment System for Children, Second Edition.

*$p < .05$. **$p < .01$. ***$p < .001$.

Table 34 illustrates the results of the simultaneous regression analysis for the PedsQL Parent-Report, a parent-report measure of quality of life. The three predictors

(BASC-2 Self-Report Anxiety, BASC-2 Parent-Report Anxiety, and BASC-2 Parent-Report Depression) significantly explained 37.0% of the variance on the PedsQL Parent-Report (p = .001). Only BASC-2 Parent-Report Depression (β = -.57, p = .004) significantly contributed to the model. BASC-2 Self-Report Anxiety (β = -.09, p = .571) and BASC-2 Parent-Report Anxiety (β = .01, p = .955) did not significantly contribute to the model.

Table 34

Simultaneous Regression Analysis of Anxiety and Depression on Parent-Reported Quality of Life

Variable	B	SE_B	β	R^2
Step 1				.37**
BASC-2 Self-Report Anxiety	-.15	.26	-.09	
BASC-2 Parent-Report Anxiety	.02	.30	.01	
BASC-2 Parent-Report Depression	-1.20**	.38	-.57**	

Note. BASC-2 – Behavior Assessment System for Children, Second Edition.

**p < .01.

Lastly, Table 35 illustrates the results of the simultaneous regression analysis for BASC-2 Parent-Report Externalizing Problems, a subscale on the BASC-2 measuring disruptive and externalizing behaviors. BASC-2 Parent-Report Depression explained 28.0% of the variance on BASC-2 Parent-Report Externalizing Problems (p < .001) and was a significant contributor to the model (β = .53, p < .001).

Table 35

Simultaneous Regression Analysis of Anxiety and Depression on Externalizing Symptoms

Variable	*B*	SE_B	β	R^2
Step 1				.27***
BASC-2 Parent-Report Depression	.45***	.09	.53***	

Note. BASC-2 – Behavior Assessment System for Children, Second Edition.

***$p < .001$.

In summary, these results provide full support for Hypothesis 2 that anxiety and depression predict psychosocial functioning in pediatric multiple sclerosis (MS). BASC-2 Self-Report Anxiety significantly predicted the MFS Self-Report while BASC-2 Parent-Report Depression significantly predicted the MFS Parent-Report. Regarding quality of life, BASC-2 Self-Report Depression significantly explained variance for the PedsQL Self-Report, while BASC-2 Parent-Report Depression significantly predicted the PedsQL Parent-Report. Lastly, BASC-2 Parent-Report Depression explained 27% of the variance for BASC-2 Parent-Report Externalizing Problems.

Hypothesis 3. Executive functioning will predict psychosocial functioning.

Three hierarchical regression analyses were conducted with each applicable measure of psychosocial functioning (MFS Self-Report, MFS Parent-Report, PedsQL Self-Report) as the dependent variable, appropriate covariates (sex, age at testing, age of onset, disease duration, disease severity, IQ) entered at Step 1, and measures of executive functioning (Trail Making Test, Verbal Fluency, BRIEF Self-Report, BRIEF Parent-Report) entered at Step 2. In addition, two simultaneous regression analyses were

conducted with the appropriate psychosocial variables (PedsQL Other-Report, BASC-2 Externalizing Problems) as the dependent variable and measures of executive functioning (Trail Making Test, Verbal Fluency, BRIEF Self-Report, BRIEF Parent-Report) entered at Step 1. None of the covariates (sex, age at testing, age of onset, disease duration, disease severity, IQ) had significant correlations with the PedsQL Other-Report or BASC-2 Externalizing Problems; thus, they were not included in the regression model for these variables.

Table 36 illustrates the results of the hierarchical regression analysis for the MFS Self-Report, a self-report measure of fatigue. In Step 1, the covariate sex significantly explained 15.0% of the variance on the MFS Self-Report ($p = .021$). Sex had a significant regression coefficient at the first step ($\beta = -.39$, $p = .004$). When the two predictors (BRIEF Self-Report and BRIEF Parent-Report) were added to the model at Step 2, they significantly explained 43.3% of the variance on the MFS Self-Report ($p < .001$). Both the BRIEF Self-Report ($\beta = -.45$, $p = .001$) and the BRIEF Parent-Report ($\beta = -.32$, $p = .018$) were significant contributors to the model. Sex remained a significant contributor to model 2 in explaining variance on the MFS Self-Report.

Table 36

Hierarchical Regression Analysis of Executive Functioning on Self-Reported Fatigue

Variable	*B*	SE_B	*β*	R^2
Step 1				.15*
Sex	-14.82*	6.13	-.39*	
Step 2				.43***
Sex	-13.82**	4.43	-.36**	
BRIEF Self-Report	-.60**	.17	-.45**	
BRIEF Parent-Report	-.49*	.20	-.32*	

Note. BRIEF – Behavior Rating Inventory of Executive Function.

*$p < .05$. **$p < .01$. ***$p < .001$.

Table 37 illustrates the results of the hierarchical regression analysis for the MFS Parent-Report, a parent-report measure of fatigue. In Step 1, the covariates sex and disease severity significantly explained 17.5% of the variance on the MFS Parent-Report ($p = .038$). Sex had a significant regression coefficient at the first step ($\beta = -.33$, $p = .048$), while disease severity did not ($\beta = -.18$, $p = .278$). When the two predictors (BRIEF Self-Report and BRIEF Parent-Report) were added to the model at Step 2, an additional 44.3% of the variance on the MFS Parent-Report was explained ($p < .001$). Only the BRIEF Parent-Report ($\beta = -.64$, $p < .001$) significantly contributed to the model, while the BRIEF Self-Report ($\beta = -.08$, $p = .542$) was not a significant contributor. Sex and disease severity remained significant contributors to model 2 in explaining variance on the MFS Parent-Report.

Table 37

Hierarchical Regression Analysis of Executive Functioning on Parent-Reported Fatigue

Variable	*B*	SE_B	β	R^2
Step 1				.18*
Sex	-13.89*	6.78	-.33*	
Disease Severity (EDSS Score)	-3.22	2.92	-.18	
Step 2				.44***
Sex	-11.80*	4.77	-.28*	
Disease Severity (EDSS Score)	-5.51*	2.09	-.31*	
BRIEF Self-Report	-.11	.18	-.10	
BRIEF Parent-Report	-1.10***	.21	-.64***	

Note. BRIEF – Behavior Rating Inventory of Executive Function; EDSS – Expanded Disability Status Scale.

* $p < .05$. ***$p < .001$.

Table 38 illustrates the results of the hierarchical regression analysis for the PedsQL Self-Report, a self-report measure of quality of life. In Step 1, the covariate sex significantly explained 18.7% of the variance for the PedsQL Self-Report ($p = .008$) and had a significant regression coefficient at the first step ($\beta = -.43$, $p = .001$). When the two predictors (BRIEF Self-Report and BRIEF Parent-Report) were added to the model at Step 2, they significantly explained an additional 39.5% of the variance for the PedsQL Self-Report ($p < .001$). Only the BRIEF Self-Report ($\beta = -.60$, $p < .001$) significantly contributed to the model, while the BRIEF Parent-Report ($\beta = -.07$, $p = .612$) was not a

significant contributor. Sex remained a significant contributor to model 2 in explaining variance on the PedsQL Self-Report.

Table 38

Hierarchical Regression Analysis of Executive Functioning on Self-Reported Quality of Life

Variable	*B*	SE_B	β	R^2
Step 1				.19**
Sex	-16.60**	5.94	-.43**	
Step 2				.40***
Sex	-15.97**	4.39	-.42**	
BRIEF Self-Report	-.81***	.17	-.60***	
BRIEF Parent-Report	-.10	.20	-.07	

Note. BRIEF – Behavior Rating Inventory of Executive Function.

**$p < .01$. ***$p < .001$.

Table 39 illustrates the results of the simultaneous regression analysis for the PedsQL Parent-Report, a parent-report measure of quality of life. The two predictors (BRIEF Self-Report and BRIEF Parent-Report) significantly explained 37.3% of the variance for the PedsQL Self-Report ($p = .001$). However, only the BRIEF Parent-Report ($\beta = -.53$, $p = .001$) significantly contributed to the model, while the BRIEF Self-Report ($\beta = -.15$, $p = .335$) was not a significant contributor.

Table 39

Simultaneous Regression Analysis of Executive Functioning on Parent-Reported Quality of Life

Variable	*B*	SE_B	β	R^2
Step 1				.37**
BRIEF Self-Report	-.21	.22	-.15	
BRIEF Parent-Report	-.87**	.25	-.53**	

Note. BRIEF – Behavior Rating Inventory of Executive Function.

**$p < .01$.

Lastly, Table 40 illustrates the results of the simultaneous regression analysis for the BASC-2 Parent-Report Externalizing Problems, a composite score on the BASC-2 measuring disruptive and externalizing behaviors. The BRIEF Parent-Report ($\beta = .79$, $p < .001$) significantly explained 62.4% of the variance for the BASC-2 Externalizing Problems ($p < .001$) and was a significant contributor to the model.

Table 40

Simultaneous Regression Analysis of Executive Functioning on Externalizing Symptoms

Variable	*B*	SE_B	β	R^2
Step 1				.62***
BRIEF Parent-Report	.59***	.06	.79***	

Note. BRIEF – Behavior Rating Inventory of Executive Function.

***$p < .001$.

Overall, results provide partial support for Hypothesis 3 that executive functioning would predict psychosocial functioning. Psychosocial functioning was significantly predicted by self-report but not performance-based measures of executive functioning. The BRIEF Parent-Report significantly explained variance for the MFS Parent-Report, PedsQL Parent-Report, and BASC-2 Parent-Report Externalizing Problems. In addition, the BRIEF Self- and Parent-Reports were significant predictors of self-reported fatigue (MFS Self-Report), and the BRIEF Self-Report was a significant predictor of self-reported quality of life (PedsQL Self-Report).

Hypothesis 4. Working memory will predict psychosocial functioning.

As revealed in the preliminary analyses, working memory (Digit Span Backward) did not show significant zero-order correlations with any psychosocial variables (MFS Self- and Parent-Report, PedsQL Self- and Parent-Report, BASC-2 Externalizing Problems). Thus, hierarchical regressions for this hypothesis were not conducted.

Hypothesis 5. Working memory and executive functioning will have unique predictive value for psychosocial functioning.

Given that Hypothesis 4 was not supported, hierarchical regressions for Hypothesis 5 were not conducted.

CHAPTER V

DISCUSSION

Overview

The purpose of the current study was to characterize the relationships among the psychological, psychosocial, and cognitive factors in pediatric multiple sclerosis (MS) in an attempt to lay the groundwork for our neuropsychological understanding of this disorder. Specifically, this research aimed to determine the contribution of (1) psychological variables to executive functioning, (2) psychological variables to psychosocial functioning, and (3) executive functioning to psychosocial functioning. The first section of this chapter will summarize and interpret the findings related to the preliminary analyses and main hypotheses of this study in light of the current literature on pediatric MS. Next, strengths and limitations of the present study will be discussed as well as recommendations for future research. Lastly, the chapter will conclude by discussing clinical implications of the findings.

Findings of the Preliminary Analyses

Clinical Correlates of Executive and Psychosocial Functioning

Clinical variables including age at testing, age of onset, disease duration, and IQ were significantly correlated with performance-based measures of executive functioning. However, they were not correlated with any self-report measures of executive functioning or psychosocial measures. Specifically, the Trail Making Test demonstrated significant correlations with age at testing and age of onset, such that younger age of onset and younger age at testing were associated with worse performance on the Trail Making Test. The Verbal Fluency Test demonstrated significant correlations with age at testing, age of

onset, disease duration, and IQ. Those with younger age at MS onset, longer disease duration, and lower IQ appear to be at greater risk for deficits on the Verbal Fluency Test. In addition, disease severity as measured by Expanded Disability Status Scale (EDSS) score was significantly correlated with parent-reported fatigue but no other measures of executive or psychosocial functioning.

These findings are consistent with some prior research (Amato et al., 2008; Banwell & Anderson, 2005; MacAllister et al., 2005; Till, Udler et al., 2012) and inconsistent with other studies (Holland et al., 2012; Till, Ho et al., 2012). Discrepancies in the literature have been noted with regard to the prognostic value of age of onset in pediatric MS (Ness et al., 2007). Till, Ho et al. (2012) noted that younger age at disease onset was significantly correlated with outcomes on the BRIEF Parent-Report, including Working Memory, Plan/Organize, and the GEC, while it was not correlated with any performance-based measures of executive functioning. This contrasts with the findings from the current study, which found significant correlations between age of onset and performance-based measures of executive functioning, but not with any subscales of the BRIEF. In Till and colleagues' (2012) sample, the disease duration was nearly 2 years longer than in the present study. The lack of a strong relationship between age of onset and the BRIEF in the present study may therefore reflect a restriction in disease length. In addition, differences in study findings may be due to the use of different measures of executive functioning (Till and colleagues used the Delis-Kaplan Executive Function System [D-KEFS] Verbal Fluency Condition 1: Letter Fluency and Trail Making Test Part B).

The current study found an association between disease severity (EDSS score) and fatigue. While several studies in the adult MS population have reported a correlation between disease severity and fatigue (Bergamaschi, Romani, Versino, Poli, & Cosi, 1997; Kroenke, Lynch, & Denney, 2000), another study reported that after controlling for depression, disease severity and fatigue were no longer associated (Bakshi et al., 2000). It is possible that the same effect would be found in our sample after controlling for depression. In addition, our findings suggest that disease severity was not associated with any measures of executive functioning. While one previously published study reported significant relationships between cognitive functioning and EDSS score, number of relapses, and disease duration (MacAllister et al., 2005), the current findings are in line with other studies of pediatric MS patients as well as several adult studies that have shown a poor relationship between cognitive functioning and disability levels (Achiron & Barak, 2003; Amato et al., 2004; Rao, Leo, Bernardin et al., 1991).

With regard to clinical correlates of psychosocial functioning, the current study's findings are in line with Till, Udler et al. (2012), which reported no significant associations between psychosocial outcomes (including externalizing symptoms) and number of relapses, EDSS score, disease duration, brain lesion volume, or IQ. Together with the present study, this emphasizes that some clinical and disease features may be poor prognostic indicators of self-reported executive functioning and psychosocial functioning. Future research should strive to find other indicators that may be more helpful in predicting these outcomes.

Findings of the Main Analyses

Hypothesis 1

The first hypothesis—that anxiety and depression will predict executive functioning—was partially upheld. Anxiety was found to predict only one performance-based measure of executive functioning (Trail Making Test), while it did not predict any self-report measures of executive functioning (BRIEF Self- and Parent-Report). By contrast, depression was predictive of self-report measures of executive functioning but not performance-based measures.

Regarding findings on performance-based measures of executive functioning, the current study is generally consistent with previous research. This includes Holland and colleagues' (2012) study, which found that parent-reported anxiety significantly correlated with the Trail Making Test A and B but not the D-KEFS Verbal Fluency Test. However, they also found that parent-reported depression significantly correlated with the Trail Making Test A and B, which the current study did not find. This discrepancy may be due to the use of different Trail Making Tests, as well as differences in sample characteristics. The lack of relationship between depression and executive functioning measures in the current study is also consistent with Goretti and colleagues' (2012) research, which found that depression was not related to number of tests failed or overall cognitive impairment. Taken together, the findings of the current study suggest that anxiety is more predictive of performance on executive functioning tasks than is depression. Specifically, higher levels of parent-reported anxiety are associated with slower performance on a task of visual-motor sequencing requiring "set-shifting" or mental flexibility.

In contrast with performance-based measures of executive functioning, self-report measures of executive functioning (BRIEF Self- and Parent-Report) showed significant relationships with depression but not anxiety. To the author's knowledge, no study has yet examined the relationship between anxiety, depression, and self-reported executive functioning deficits in pediatric MS. However, the general literature on depression and executive functioning provides support for these findings. Depressive symptoms have been found to be associated with increased symptom reporting in individuals with medical disorders (Ciechanowski, Katon, Russo, & Hirsch, 2003). Thus, in the current study, the presence of depressive symptoms could have resulted in an increased perception and/or reporting of executive function deficits, even if these deficits are fairly mild from an objective viewpoint. On the other hand, it is possible that depressive symptoms are more strongly predictive of executive dysfunction in a real-world setting (such as task monitoring, planning, and organization) than on measures given in a neuropsychological testing environment. From a neurobiological perspective, abnormal functioning of the hypothalamic-pituitary-adrenal axis plays a role in depressive symptomatology, and it is also associated with structural changes in the frontal cortex (Weinstock, 2008). Thus, it is possible that depression could impact executive functions mediated by the frontal cortex (Schmitt, Miller, & Long, 2012), which may manifest more strongly in a real world setting than on neuropsychological measures in a testing setting.

Hypothesis 2

Consistent with what was hypothesized, depression and anxiety predicted aspects of psychosocial functioning including fatigue, quality of life, and externalizing

symptoms. In particular, the findings emphasized the role of depression in predicting these psychosocial outcomes. Specifically, self-reported anxiety was associated with self-reported fatigue, while parent-reported depression predicted greater parent-reported fatigue. In addition, depression was associated with both self- and parent-reported quality of life. Lastly, parent-reported depression significantly explained 27% of the variance for parent-reported externalizing symptoms.

The current study's findings on fatigue are consistent with the substantial body of literature on emotional functioning and fatigue in adult MS (Brown et al., 2009; Induruwa et al., 2012; Iriarte et al., 2000; Kroencke et al., 2000; Mills & Young, 2011; Trojan et al., 2007), as well as several studies in pediatric MS (Goretti et al., 2012; Holland et al., 2012; MacAllister et al., 2009; Till, Udler, et al., 2012). Depression and fatigue are highly correlated in adult MS, although due to the significant overlap of symptoms between depression and fatigue, these two are difficult to tease apart (Induruwa et al., 2012; Kroencke et al., 2000; Mills & Young, 2011). In addition, fatigue and anxiety have also shown a consistent relationship in the adult MS literature (Chwastiak et al., 2005; Ford et al., 1998; Iriarte et al., 2000; Skerrett & Moss-Morris, 2006; Trojan et al., 2007). However, due to the significant overlap of anxiety and depression in MS (depression in MS often involves symptoms common to anxiety such as irritability and worry, rather than apathy and social withdrawal), the relationship between anxiety and fatigue may also be difficult to distinguish (Minden et al., 1987; Ron & Logsdail, 1989).

In the pediatric literature, findings on psychological correlates of fatigue have been somewhat more inconsistent. Goretti and colleagues (2012) found that self- and

parent-reported fatigue on the MFS was associated with self-reported depressive symptoms on the Children's Depression Inventory. This is consistent with the zero-order correlations conducted in the present study, which suggest that both self- and parent-reported fatigue are correlated with depressive symptoms. Goretti et al. (2012) did not examine anxiety. Till, Udler et al. (2012) also found that patient-reported fatigue approached significance with problems related to anxiety and depression. The present study adds to this growing body of literature on anxiety, depression, and fatigue in MS in suggesting that higher anxiety and depression are both predictors of fatigue, depending on the reporter (i.e., self or parent).

Regarding quality of life, the current study found that only depression had a significant effect on both self- and parent-reported quality of life. To the author's knowledge, this is the first study to examine the relationship between quality of life and emotional functioning in pediatric MS. However, in the adult MS literature both depression (McIvor et al., 1984; Wang et al., 2000) and anxiety (Dubayova et al., 2013) have been linked to reduced quality of life. A recent study found that in adults with MS, both anxiety and depression were strongly associated with lower scores on the physical and mental subscales of a quality of life inventory (Dubayova et al., 2013). The results of the present study provide preliminary evidence of a relationship between depression and quality of life in a pediatric MS sample. In addition, the current results suggest that anxiety may not be related to quality of life in children with MS, contrary to what has been found in the adult MS population.

Lastly, depression was found to be predictive of externalizing symptoms in the current study. Although previous literature has found cognitive impairment to be linked

to greater externalizing symptoms (Till, Udler et al., 2012), no study has yet examined anxiety and depression as it relates to externalizing behavior in MS. Nevertheless, outside literature does suggest some comorbidity between depression and certain externalizing disorders such as attention deficit hyperactivity disorder (ADHD; Wilens et al., 2002), which provides support for this finding.

Hypothesis 3

It was hypothesized that executive functioning would predict psychosocial functioning, including fatigue, quality of life, and externalizing symptoms. This claim was partially supported by our findings. The most notable exception to this hypothesis was that performance-based measures of executive functioning (Trail Making Test, Verbal Fluency Test) did not significantly predict measures of psychosocial functioning. By contrast, self-report measures of executive functioning (BRIEF Self- and Parent-Report) were predictive of all measures of self- and parent-reported fatigue, quality of life, and externalizing symptoms.

The lack of a relationship between performance-based measures of executive functioning and psychosocial functioning adds to a growing trend in the pediatric MS literature, although findings remain uncertain. With regard to fatigue, several studies have found that higher levels of parent- and self-reported cognitive and general fatigue were associated with impaired performance on the Trail Making Test B (Goretti et al., 2012; Holland et al., 2012) but not on the Verbal Fluency Test. The choice of which MFS subscales to use in analyses may explain why these findings partially conflict with the current study, as we measured fatigue using the fatigue total score rather than the general or cognitive fatigue subscales. It is also possible that the lack of a strong relation

between fatigue and executive functioning tests in the current study may reflect a restriction in the severity of the study population.

Nevertheless, results of the current study are consistent with several other studies in pediatric MS (Amato et al., 2008; MacAllister et al., 2005) as well as findings in adult MS (Krupp & Elkins, 2000; Morrow et al., 2009; Paul et al., 1998; Schwartz et al., 1996). These studies have shown that fatigue does not appear to be strongly correlated with neuropsychological test performance in either pediatric or adult patients.

Existing studies of pediatric MS have not yet directly examined the relationship between performance-based executive function measures and other psychosocial variables such as quality of life and externalizing symptoms. The studies to date have broadly suggested that overall cognitive impairment may be linked to difficulties in daily living and increased disruptive behavior (Amato et al., 2008; Amato et al., 2010; Till, Udler, et al., 2012). However, the findings of this study specifically demonstrate that impairment on tests of executive functioning are not linked to worse quality of life or increased externalizing behaviors.

By contrast, the current study supports a relationship between report-based measures of executive functioning and psychosocial functioning, which has not yet been examined in the research to date. One explanation for this association is that report-based measures are affected by issues of recall and response bias, and they may be more likely to show correlations with one another (Prince et al., 2008). This explanation is supported by the fact that the BRIEF Self-Report tended to correlate most highly with self-report measures of psychosocial functioning, while the BRIEF Parent-Report correlated most often with parent questionnaires of psychosocial functioning.

Despite these caveats, the current findings make sense in light of the fact that the BRIEF represents multiple aspects of executive functioning and is more applicable to a real world setting than the performance-based measures of executive functioning (Trail Making Test, Verbal Fluency Test) used in this study. Given the broad scope of the BRIEF, it is logical that it would be an important predictor of psychosocial functioning, (i.e., how a child functions within his/her social environment). More specifically, it makes sense that aspects of executive functioning in daily life—including the ability to plan, organize, and complete tasks, shift from one task to another, and regulate emotional responses appropriately—would be related to an individual's fatigue, quality of life, and externalizing behaviors.

In addition, in the standardization sample for the Behavior Assessment System for Children, Second Edition (BASC-2), the authors found high correlations between the BASC-2 Externalizing Problems Composite and the BRIEF Global Executive Composite. The findings of the current study confirm that the relationship between self-reported executive functioning and externalizing symptoms reported in the BASC-2 normative population is also present in pediatric MS.

The present results do not give information with regards to directionality of these associations, but it is hypothesized that higher levels of fatigue would negatively affect executive functioning, and that executive dysfunction would have a negative impact on quality of life. In addition, poor executive functioning skills may lead to increased disruptive behaviors, as has been suggested in the literature on ADHD (Tannock & Schachar, 1996; Wahlstedt, Thorell, & Bohlin, 2008). These hypotheses will be important questions to examine in future research.

Overall, the current results suggest that while tests of executive functioning have limited applicability in predicting how a child will function in his/her daily life, self-report measures are more predictive of psychosocial functioning. The strong association of the BRIEF with psychosocial functioning (particularly for externalizing symptoms) should be taken into account when designing a neuropsychological battery for children with MS, especially when areas of psychosocial functioning are of concern.

Hypotheses 4 and 5

It was hypothesized that working memory would predict psychosocial functioning, and that working memory and executive functioning would have unique predictive value for psychosocial functioning. These hypotheses were not supported by the present study. Preliminary analyses demonstrated that there were no significant zero-order correlations between a measure of working memory and measures of psychosocial functioning, including fatigue, quality of life, and externalizing behaviors. Thus, psychosocial functioning was better predicted by self-report measures of executive functioning than measures of working memory.

One possible explanation for insignificant correlations between working memory and psychosocial functioning is that deficits in working memory in our population may not have been severe enough to reflect significant results. While some studies of pediatric MS have found significant deficits on the Digit Span subtest (Charvet, O'Donnell et al., 2014), others have reported either average performance or only mild impairment on this measure (Holland et al., 2012; Julian et al., 2012). Some studies that have reported deficits in working memory have generally used measures other than Digit Span, including the Concepts and Directions and Listening to Paragraphs subtests of the

Clinical Evaluation of Language Fundamentals (Banwell & Anderson, 2005). It remains unclear whether correlations between working memory and psychosocial functioning would emerge with a more severe population.

Although the hypotheses were not supported, the findings are consistent with the research to date, which has also failed to find correlations between working memory and measures of psychosocial functioning. For example, Holland et al. (2012) found that although fatigue was related to measures of executive functioning, it was not related to performance on Digit Span. Therefore, the current investigation is consistent with previous studies, and it implies that working memory does not play a significant role in determining psychosocial functioning. Despite this, it is important to note that the current research is very limited, and more research is needed to bolster the lack of association between working memory and psychosocial functioning.

Summary of Findings

Results of the study (summarized in Tables 41 and 42) generally demonstrated support for the first three hypotheses. Higher levels of anxiety and depressive symptoms were associated with executive dysfunction, both on performance-based as well as self-report measures. In addition, anxiety, depression, and report-based executive dysfunction were predictive of psychosocial difficulties, including higher levels of fatigue, worse quality of life, and more severe externalizing symptoms. Working memory was not related to psychosocial functioning, disconfirming the latter two hypotheses. In addition, clinical variables such as age of onset, disease duration, and IQ significantly correlated with performance-based measures of executive functioning, but they did not correlate with measures of psychosocial functioning.

Table 41

Summary of Main Hypothesis Regression Analysis Results – Predictors of Executive Functioning

Variable	Trail Making Test	Verbal Fluency Test	Self-Report Executive Functioning	Parent-Report Executive Functioning
Self-Report Anxiety				
Self-Report Depression			✓+	
Parent-Report Anxiety	✓+			
Parent-Report Depression				✓+

✓ denotes a significant relationship between predictor and outcome variable.

+ denotes a positive β value.

− denotes a negative β value.

Table 42

Summary of Main Hypothesis Regression Analysis Results – Predictors of Psychosocial Functioning

Variable	Self-Report Fatigue	Parent-Report Fatigue	Self-Report Quality of Life	Parent-Report Quality of Life	Externalizing Symptoms
Self-Report Executive Functioning	✓−		✓−		
Parent-Report Executive Functioning	✓−	✓−		✓−	✓+
Self-Report Anxiety	✓−				
Self-Report Depression			✓−		
Parent-Report Anxiety					
Parent-Report Depression		✓−		✓−	✓+

✓ denotes a significant relationship between predictor and outcome variable.

+ denotes a positive β value.

− denotes a negative β value.

Limitations of the Study

There are several limitations to the present study. Because this was an outpatient sample with a relatively short disease duration (mean = 2.37 years), test scores were somewhat restricted in range. Patients showed less severe cognitive, psychosocial, and psychological functioning than might be seen in a more severe outpatient population or

an inpatient sample. It is possible that this restriction of range affected the correlations between executive functioning, psychological functioning, and psychosocial functioning. For example, performance-based measures of executive functioning did not significantly predict measures of psychosocial functioning. These insignificant findings could be due to the restriction in range of the current pediatric MS sample, particularly for performance on neuropsychological tests of executive function. However, many studies have shown that cognitive dysfunction and fatigue can be present quite early in the disease course (Achiron & Barak, 2003; Deloire et al., 2006; Glanz et al., 2007); therefore, this study may provide an accurate representation of the associations that would be found even in a sample with a longer disease duration.

Although the study sample was large (N = 79), the sample sizes for each neuropsychological measure and self-report questionnaire were relatively smaller, particularly for the Verbal Fluency Test (n = 46), BRIEF Self-Report (n = 48), and Pediatric Quality of Life Inventory (PedsQL) Multidimensional Fatigue Scale (MFS) Self-Report (n = 49). Power of the data would have been increased if all participants completed all measures. In addition, it is possible that the variations in battery content, order, and length may have differentially affected test performance. Future research should administer a fixed battery to all subjects to control for these effects.

Additionally, the use of self-report measures in this study is a limitation. Self-report measures are affected by threats to validity from interpersonal, intrapersonal, and situational factors. Consequently, the correlations between self-report measures may simply be an artifact of response bias. For example, the finding that parent-reported depression was predictive of externalizing symptoms may simply suggest that parents

who are having difficulties with their children report problems across domains, including increased depressive symptoms and increased disruptive behavior.

This study examined numerous regression analyses, which may have increased the likelihood of incorrectly rejecting the null hypothesis (Type I error). However, the ability to conduct these exploratory analyses could be considered to outweigh the risk of Type I error given that there is limited knowledge about pediatric MS, particularly in a sample this large. In addition, the hypotheses in the current study were empirically derived, which also decreases the likelihood of false positives.

Additionally, the analyses did not include certain sociodemographic and clinical variables that may influence neuropsychological performance in children, including parent language status, disease-modifying therapies, glucocorticoid treatment, presence of non-neurological medical problems, and aspects of disease burden as measured by magnetic resonance imaging (MRI). These variables may have affected the relationships among the variables of interest in the study. The lack of a control group in the present study is also a significant limitation, which further emphasizes the importance of controlling for these additional sociodemographic and clinical variables.

Finally, this study is cross-sectional. Thus the associations that were found among psychological and psychosocial variables in relation to executive functioning cannot be interpreted as causal relationships. It remains unknown what other mediating variables might be playing a role in these relationships.

Despite these limitations, this is the largest study to date that has examined cognitive, psychological, and psychosocial factors in a pediatric MS population. Although the UCSF Regional Pediatric Multiple Sclerosis Center is a tertiary referral

center (potentially resulting in a sample with more severe disease), the findings are nevertheless generalizable to the pediatric MS population as a whole due to the wide age range (mean = 14.25, range = 6.5-18), ethnic diversity, and range of socioeconomic statuses represented in the participants. In addition, this study describes relationships among important clinical variables, not only for pediatric MS patients but for adult patients as well.

Directions for Future Research

The study sample consisted of children and adolescents seen at an academic medical center outpatient clinic. The study could be replicated in the future with a more severe outpatient population, perhaps with a longer disease duration. This could reveal stronger associations between psychosocial and psychological factors and neuropsychological performance.

In addition, the present study utilized existing data, and therefore neuropsychological measures were limited to those administered in the original study. Although the neuropsychological battery used was quite comprehensive, including additional executive functioning measures would have allowed for more sensitivity in detecting cognitive deficits in this domain. For example, in previous literature children with MS have shown deficits in the Rey-Osterreith Complex Figure Copy (Banwell & Anderson, 2005) and the Modified Card Sorting Test (Amato et al., 2008), which measure additional aspects of executive functioning not captured by the measures used in this study. Additionally, although pediatric studies have not yet included the D-KEFS Color-Word Interference/Stroop Test, adult MS studies have demonstrated deficits on this measure (Drew, Tippett, Starkey, & Isler, 2008; Foong et al., 1997). Thus, it could

serve as an additional sensitive measure for examining executive functioning in children. The addition of tests measuring other aspects of executive functioning may have allowed the study to make more specific conclusions about which aspects of executive functioning are related to psychological and psychosocial functioning, including inhibition, visual-motor planning, problem solving, and abstraction.

Participants in this study also varied in terms of the presence and type of disease-modifying therapy being prescribed. In adult MS, interferon β-1a has been shown to improve cognitive performance over a two-year period in the domains of information processing, learning, and memory (Fischer et al., 2000). Therefore, it is possible that disease-modifying therapies could affect aspects of cognition in children, and future studies should aim to control for this factor. Future research may also consider controlling for additional sociodemographic and clinical variables mentioned in the section on limitations (e.g., disease-modifying therapies, glucocorticoid treatment, etc.) as well as the presence of non-neurological medical problems. These factors have the potential to influence cognitive, psychological, and psychosocial factors.

Finally, future research should examine these hypotheses over time in a pediatric MS sample. A longitudinal design would allow a detailed description of how psychological, psychosocial, and executive functioning change over the course of the disease. Grover and colleagues (2014) have been among the first groups to examine academic functioning over time in pediatric MS, and their research suggests a downward educational trajectory involving declining grades and increased need for special education services. Academic functioning is an important component of quality of life in

this population, and it is likely linked to aspects of cognitive and emotional functioning as well.

A longitudinal design would also allow for causal mechanisms to be outlined that would enhance our understanding of which factors influence each other and would serve best as targets of intervention. For example, executive functioning difficulties may contribute to increased psychiatric and psychosocial difficulties just as these emotional and psychosocial difficulties may contribute to increased executive dysfunction. Longitudinal research would allow for the development of strategies for prompt identification of children at risk for cognitive, psychosocial, and psychiatric symptoms so that treatment can be initiated and interventions put in place early in the disease course.

Clinical Implications

The findings of this study suggest several clinical implications. In an attempt to better characterize the nature of pediatric MS and provide a baseline on which future research can build, this study is the first to examine relationships between executive function, anxiety, depression, fatigue, quality of life, and externalizing symptoms within the same pediatric MS sample. We present the novel findings that higher levels of anxiety and depressive symptoms are associated with self-reported executive dysfunction in daily life, worse quality of life, and increased externalizing behaviors. In addition, the findings corroborate previous research showing that anxiety and depression are related to fatigue and certain neuropsychological measures of executive functioning.

These findings warrant further examination of cognitive, psychological, and psychosocial outcomes in pediatric MS to inform appropriate interventions. Specifically, this study suggests that interventions targeting depression, anxiety, fatigue, and

improvements in quality of life have the potential to contribute to improvements in executive functioning (and vice versa) in pediatric MS. This lays the groundwork for future intervention-focused research.

In addition, the current findings emphasize the need for regular monitoring by neuropsychology as part of a multidisciplinary team. Neuropsychologists should strive to detect psychological and psychosocial difficulties and understand their impact on executive functioning (and vice versa) in order to make appropriate recommendations. This study's finding that the BRIEF Self- and Parent-Report are strong predictors of psychosocial difficulties suggest that this may be a useful measure to use in this population, not only in evaluating executive dysfunction but in understanding the broader impact this has on the child's daily life.

While clinical information easily gleaned from a medical chart (such as age of onset, disease duration, and disease severity) may relate to certain aspects of cognitive functioning, the findings of this study suggest that this information will not necessarily provide accurate predictions about how the child may be functioning on a psychosocial level. This, too, emphasizes the importance of regular use of screens for detecting psychosocial difficulties, including the MFS and PedsQL.

Detection of impairments in psychological, psychosocial, and executive functioning can be used to inform development of educational planning (e.g., school accommodations, school placement) that will help maximize educational opportunities. In addition, awareness of the psychosocial effects of pediatric MS can help guide interventions in the home and community to maintain a positive developmental trajectory.

Lastly, this study furthers our clinical understanding of the ways in which pediatric MS is similar and distinct from the adult disease. In pediatric MS, demyelination and inflammation occur during key formative years, and therefore have the unique result of disrupting normal development. Thus, the disease has profound impacts on cognitive development and psychosocial functioning in childhood that are unique to pediatric MS. This study contributes to our understanding of MS throughout the lifespan, suggesting that relationships among executive, psychosocial, and psychological functioning that have been found in adults may also be found in children with the disease. However, it remains unknown how these relationships may change as these children age, and further studies are needed to characterize the functioning of pediatric MS patients once they reach adulthood.

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APPENDIX A

LETTER OF PERMISSION FROM PRINCIPAL INVESTIGATOR

TO USE ARCHIVAL DATA

UCSF
University of California
San Francisco

September 21, 2014

To Whom It May Concern,

I am a member of the Pediatric MS Centers of Excellence, a nationwide network that provides comprehensive evaluation and care to children and adolescents with MS and other demyelinating disorders. Fourteen members of this network are currently engaged in research to understand the causes and characteristics of MS in children and to improve treatment of this disorder.

I give Julia Nunan-Saah permission to use the database originally created for the manuscript entitled "Cognitive Impairment Occurs in Children and Adolescents with Multiple Sclerosis: Results From a United States Network." She may use this data for her dissertation titled "Psychological and Psychosocial Correlates of Executive Functioning in Pediatric Multiple Sclerosis" and any associated presentations and publications.

Sincerely,

Emmanuelle Waubant, M.D., Ph.D.
Professor of Neurology

UCSF School of Medicine
675 Nelson Rising Lane
San Francisco, CA 94143
emmanuelle.waubant@ucsf.edu

APPENDIX B

APPROVAL LETTER FROM INSTITUTIONAL REVIEW BOARD

INSTITUTIONAL REVIEW BOARD

Assurance Number: FWA00010885

Julia Nunan-Saah
Rowena Gomez, PhD
Palo Alto University
1791 Arastradero Road
Palo Alto, CA 94304

April 13, 2015

FULL APPROVAL: 15-026 - H: "Psychological and psychosocial correlates of executive functioning in pediatric multiple sclerosis"

Dear Ms. Nunan-Saah:

You have requested Expedited Review of the above-entitled protocol by the PAU IRB. You have provided necessary documentation including approval from the UCSF CHR, and certificates of completion of human subjects research training. The PAU IRB has reviewed and approved this application to involve humans as research participants.

Approval Date: 04/13/2015

Expiration Date: 04/13/2016
If the project is to continue, it must be renewed by the expiration date.

Modifications: Any changes to the protocol must be approved, in advance, by the IRB prior to being implemented.

Please print and retain this letter for your files.

Sincerely,

Wendy Packman, JD, PhD
Professor and Chair, PAU IRB

cc: Project File, Correspondence File

1791 ARASTRADERO ROAD • PALO ALTO, CA • 94304
PHONE: 650-433-3827 • FAX: 650-433-3888