Neuropsychological correlates of multiple sclerosis across the lifespan

Julia Nunan-Saah, Selvi R Paulraj, Emmanuelle Waubant, Lauren B Krupp and Rowena G Gomez

Abstract: Multiple sclerosis can adversely affect cognitive functioning whether the disease has an adult or pediatric onset. The research thus far suggests that pediatric MS shares many features with adult MS but is also unique in several respects. One particular characteristic of pediatric MS is that, while physical disability develops more slowly as compared with adult patients, the impact of cognitive deficits in children may be more substantial as they are in a period of life during which they acquire many skills that are needed to transition into independently functioning adults. Our review takes a lifespan approach to MS, comparing and contrasting the neuropsychology (i.e., cognitive, psychological, and psychosocial factors) of these two populations. Understanding how MS manifests across the lifespan has important implications for tailoring assessment and treatment for individuals with MS as they transition from childhood to adulthood, and later life.

Keywords: Multiple sclerosis, pediatric, neuropsychology, psychosocial

Date received: 13 March 2015; accepted: 13 April 2015

Introduction

The vast majority of 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).1–3 Fewer than 1% of all MS cases have an onset before the age of 10.4 Unlike adult MS, over 95% of pediatric MS patients (under age 18) initially have a relapsing-remitting course.5–7 Pediatric MS appears to convert to secondary progressive phase MS 10 years later than the adult disease, as measured from time of onset.7 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.1,8 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.3

This past decade has witnessed a growing literature on pediatric MS, which has revealed fundamental differences in the presentation of this disease in children that distinguish it from the adult disease. To that end, this review takes a lifespan approach to MS by comparing and contrasting the neuropsychology of the disease from childhood to adulthood. We used PubMed, EBSCOhost, and Google Scholar to search for articles using the terms ‘multiple sclerosis’, ‘pediatric’, ‘cognition’, ‘neuropsychology’, ‘psychosocial’, ‘psychological’, ‘fatigue’, ‘quality of life’, ‘anxiety’, and ‘depression’. We also reviewed reference lists from these papers. Due to space limitations, we did not include all papers found but attempted to highlight key papers. Understanding what is known about this disease across the lifespan may help to tailor assessment and treatment of these individuals.

Neurobiology of pediatric and adult MS

The few pathological studies of pediatric MS suggest that it shares many features with the adult disease. As in adult MS, myelin and axonal damage have also been found in normal-appearing intrahemispheric, interhemispheric, and projection white matter tracts.9 Despite some remyelination after an attack, over time neurological functioning is permanently decreased due to irreversible axonal injury, depletion of oligodendrocytes, and gliosis.10 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.11 This finding may provide some explanation for the often observed severe onset in pediatric MS.
In pediatric MS compared to adults with the disease, infratentorial lesions (e.g., brainstem, pons, cerebellum), particularly in the pons, are more frequent and less well defined.\textsuperscript{12,13} 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.\textsuperscript{14,15} These findings suggest increased inflammation and a more active disease process in children. 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.\textsuperscript{3,16} Pediatric MS has also been associated with early gray matter atrophy in the thalamus, with sparing of the cortex, suggestive of Wallerian degeneration.\textsuperscript{17} Relative to healthy controls, pediatric patients also have lower total brain volume, thalamic volume, and gray matter volume.\textsuperscript{17,18} While in adult MS gray matter atrophy correlates with degree of disability, this association has not been found in pediatric MS.\textsuperscript{17,19,20}

<table>
<thead>
<tr>
<th>Neuropathology</th>
<th>Pediatric onset MS</th>
<th>Adult onset MS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White matter plaque, axonal demyelination in lesions and normal-appearing white matter, gliosis</td>
<td>White matter plaque, axonal demyelination in lesions and normal-appearing white matter, gliosis</td>
</tr>
<tr>
<td></td>
<td>More pronounced acute axonal damage in early active demyelinating lesions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lower axonal density in lesions</td>
<td></td>
</tr>
<tr>
<td>Anatomical location</td>
<td>More infratentorial lesions, especially pons, also in brainstem and cerebellum</td>
<td>Lesions in spinal cord, optic nerves, corpus callosum, periventricular region, white matter of cerebellum, brain stem</td>
</tr>
<tr>
<td>Neuroimaging</td>
<td>Greater T2 lesion volume and increased number of lesions at time of first demyelinating event</td>
<td>Lower T2 lesion volume and fewer lesions at time of first demyelinating event</td>
</tr>
<tr>
<td></td>
<td>Decreased total brain, thalamic, and gray matter volume relative to controls</td>
<td>Decreased thalamic and gray matter volume relative to controls</td>
</tr>
<tr>
<td></td>
<td>Thalamic gray matter atrophy in early stages</td>
<td>Thalamic gray matter atrophy in early stages</td>
</tr>
</tbody>
</table>

Neuropsychology of pediatric and adult MS

Cognitive factors affected by MS

Given the neurobiological characteristics of MS, it is not unexpected that there are significant effects of MS on cognition. It is estimated that approximately one third of children with MS experience cognitive impairment,\textsuperscript{21–23} while cognitive impairment occurs in approximately 40–60% of adults with MS.\textsuperscript{24} 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. In addition, the often shorter disease duration for pediatric MS at the time of cognitive testing, as compared with adult studies, makes direct comparison difficult.

Attention, processing speed, and working memory

Slowed information processing is one of the most commonly observed deficits in both adult and pediatric MS.\textsuperscript{23,25,26} A study measuring processing speed using the WISC-IV and WAIS-IV Coding subtests and the D-KEFS Trail Making Test found that children with MS were significantly impaired in these tasks, confirming that this cognitive domain is susceptible to impairment across the lifespan.\textsuperscript{23} Several other studies have reported similar findings when measuring processing speed using the WISC-IV.\textsuperscript{21,27} Longitudinally, visual-motor speed demonstrated the most pronounced decline in performance over time among children.\textsuperscript{28} Several studies have also suggested that working memory functions are deficient in children with MS.\textsuperscript{21,29,30} These deficits are likely in part related to slow processing speed, although more research is needed to clarify this relationship.

In adult MS, impaired processing speed is a common finding and appears to partially account for other deficits, such as in attention and working memory.\textsuperscript{25,26,31} A meta-analysis of 57 studies of adult MS found the greatest cognitive deficits on measures of processing speed and selective/focused attention.\textsuperscript{31} Deficits in processing speed and working memory play an important role in contributing to deficits in verbal and nonverbal...
In one study, MS patients performed worse than controls on a spatial working memory task, and this performance could not be explained by poor immediate recall or less efficient use of strategy. This finding indicated a specific impairment in working memory. Other studies have also documented deficits in verbal working memory in adult MS patients. 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, receptive language, sentence comprehension, and crystallized knowledge, while other language abilities remain intact. There are mixed findings in regard to confrontation naming, with some studies finding impairment in pediatric MS, whereas others have not. The fact that deficits in

<table>
<thead>
<tr>
<th>Cognitive</th>
<th>Pediatric onset MS</th>
<th>Adult onset MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention &amp; processing speed</td>
<td>• Relatively intact simple attention/short-term memory • Slowed information processing</td>
<td>• Impaired attention • Slowed information processing</td>
</tr>
<tr>
<td>Working memory</td>
<td>• Impaired working memory</td>
<td>• Impaired working memory</td>
</tr>
<tr>
<td>Language</td>
<td>• Deficits in verbal fluency, receptive language, sentence comprehension, and crystallized knowledge • Relatively intact expressive language abilities; mixed evidence for confrontation naming</td>
<td>• Relatively intact, with exception of confrontation naming and timed language tasks</td>
</tr>
<tr>
<td>Visual spatial</td>
<td>• Impaired visual perceptual skills, especially involving fine motor tasks</td>
<td>• Impaired visual perceptual skills, including visual form, facial, and spatial perception</td>
</tr>
<tr>
<td>Motor &amp; psychomotor</td>
<td>• Impaired fine motor speed and coordination</td>
<td>• Impaired fine motor speed and coordination</td>
</tr>
<tr>
<td>Learning &amp; memory</td>
<td>• Impaired verbal learning and memory • Limited evidence of nonverbal deficits</td>
<td>• Impaired verbal learning and memory, especially for delayed recall • Impaired nonverbal memory</td>
</tr>
<tr>
<td>Executive functions</td>
<td>• Impaired in rapid set-shifting and organizational ability • Mixed findings on card sorting</td>
<td>• Impaired problem-solving, strategy, planning, sequencing, inhibition, and cognitive estimation</td>
</tr>
<tr>
<td>Psychosocial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>• 6−50% prevalence rates, may be lower than adult MS • Higher rates reported by parents than their children</td>
<td>• 27−54% prevalence rates, may be higher than pediatric MS</td>
</tr>
<tr>
<td>Anxiety</td>
<td>• Limited studies on anxiety</td>
<td>• 25−41% prevalence rates • Often comorbid with depression</td>
</tr>
<tr>
<td>Fatigue</td>
<td>• 20−75% prevalence rates • Children report less fatigue compared to their caregivers</td>
<td>• 65−95% prevalence rates • Comorbid with physical symptoms of MS and mood disturbances</td>
</tr>
<tr>
<td>Quality of life</td>
<td>• Impaired mental, physical, emotional, and school/academic functioning • Similar social functioning compared to controls</td>
<td>• Impaired work/occupational functioning and social functioning</td>
</tr>
</tbody>
</table>
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.37

With onset of MS in adulthood, language skills are thought to remain relatively intact apart from those emphasizing rapid retrieval, which is highly dependent on processing speed.31 Aphasia and alexia are rare, but can sometimes occur in the setting of an acute attack and quickly resolve at least to some degree.40 Of the deficits that do occur in this domain, verbal fluency is noted to be the most detrimentally affected,41–43 with one meta-analysis (including 57 studies with a total of 3891 participants) reporting an effect size of −0.689.31 Confrontation naming was also impaired in several studies, but it appears to be better preserved than verbal fluency.31,38

**Visual-spatial functions.** The initial symptoms of pediatric MS present as problems with vision in about 20% of patients.6 However, it remains unclear whether visual-spatial functions are affected in this population independent of primary visual impairment. One study reported a large degree of impairment on a measure of visual-motor integration and planning.23 However, on a visual-spatial measure that is independent of fine motor functioning (WASI Matrix Reasoning subtest), performances were relatively unimpaired.23 This suggests that the deficits on tasks of visual-spatial functioning may be in part due to fine motor impairment.

Many aspects of visual perception have been shown to be affected in adult MS, including visual form perception,44 facial perception,45 and visual-spatial perception.46 As noted above, many other functions can also affect visual-spatial abilities, including motor and executive abilities, which are also commonly impaired in MS.47 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.** 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.23 The authors attributed this finding to the effect of MS on both motor and cognitive functioning. A longitudinal study suggested that children with MS lack developmentally appropriate gains in fine motor coordination over time, rather than a loss of function.28

Similarly, in adult MS, motor symptoms are extremely common, with 80–90% of patients reporting limb weakness, spasticity, or coordination problems.48 Consequently, adult 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.31,49,50 Therefore, the measurement of other domains (e.g., processing speed using a written coding task) is often confounded by these motor deficits.

**Learning and memory.** Memory impairment is commonly reported in pediatric MS.29,30 Children with MS perform worse than controls on both immediate and delayed story memory, but not on any other memory subtests.51 This indicates difficulty with both learning and memory, specifically in the context of stories. A study using the Wide Range Assessment of Memory and Learning, Verbal Learning and Visual Learning subtests found that immediate verbal memory remained intact but delayed recall was impaired in children with MS.30,39

The effect of pediatric MS on nonverbal learning and memory is unclear due to limited studies. In one study, children with MS performed worse than age-matched controls on the Brief Visuospatial Memory Test-Revised.27 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. Similarly, in another study, 8.1% of pediatric MS patients had impaired immediate recall of visual information, and 11% had impaired delayed recall.30

Although global memory deficits are reported in adult MS, there is inconsistency across studies, perhaps related to the heterogeneity of MS and disease duration. Impaired learning strategies for verbal memory have been found in adult MS,52,53 resulting in lower scores on list learning tasks.54,55 By contrast, these patients tend to perform better on story memory tasks, which give context to the verbal information.56 A meta-analysis of cognitive impairments in adult relapsing-remitting MS found this population’s greatest memory deficits to be in verbal delayed recall.31 In a review of studies assessing memory functioning in adult MS, large effect sizes were also found for nonverbal memory deficits, including free recall (.546), cued recall (.753), and recognition (.636).55

**Executive functions.** 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.57 Studies using the Trail Making Test Part B in pediatric patients have...
reported impairment in rapidly shifting attention between competing stimuli.\textsuperscript{28,30,39} Regarding other executive function capacities, a study using the Wisconsin Card Sorting Test and the Rey-Osterreith Complex Figure Copy found that half of their sample achieved copy scores in the poor (2\textsuperscript{nd} to 5\textsuperscript{th} percentile) or very poor (<1\textsuperscript{st} percentile) range, suggesting impairment in self-generated organizational strategies.\textsuperscript{26} Although these patients performed in the normal range on the Wisconsin Card Sorting Test, a larger study (\(N = 63\)) reported 12–40\% of their sample to be impaired on a similar task (Modified Card Sorting Test).\textsuperscript{29}

Adults with MS have been noted to have difficulty with tasks requiring planning and sequencing, although differences between the patient and control groups sometimes only emerge with the most difficult levels of tasks.\textsuperscript{33,53} In addition, problem-solving,\textsuperscript{28} cognitive estimation and inhibition,\textsuperscript{33} monitoring of internal and external stimuli,\textsuperscript{59} and self-regulation\textsuperscript{60} have also been shown to be disrupted.

**Social cognition.** Although there has been some variability in the findings, several studies now support that adult MS patients demonstrate theory of mind impairments independent of neuropsychological functioning.\textsuperscript{61,62} One study recently replicated these findings in the pediatric population, 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.\textsuperscript{64} This difference remained significant even after accounting for deficits in processing speed. Impairments in social cognition may contribute to difficulties in interpersonal relationships and decreased social support for MS patients, but further research is needed to clarify these relationships.

**Summary of cognitive functioning.** The existing research suggests that the cognitive 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 complex attention, visual-motor integration, aspects of memory, executive functioning, verbal fluency, and confrontation naming. Furthermore, children with MS may show additional deficits in linguistic abilities that are more apparent compared to adults, including receptive language problems. 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.

Although a thorough discussion of longitudinal data is not within the scope of this review, it is important to note that while studies have been variable, the course of cognitive functioning in MS does appear to differ depending on age of onset. Longitudinal studies in adults have found that cognitive impairment remains relatively stable over a one- to two-year period.\textsuperscript{65–68} While some earlier longitudinal studies of pediatric MS demonstrated decline in certain cognitive functions over time,\textsuperscript{39,63} others have shown a lack of age-related gains relative to healthy controls.\textsuperscript{69,70} 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.\textsuperscript{71} Declines in cognitive functioning were linked to younger age at testing and age of MS onset. Recent work has also suggested 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.\textsuperscript{72}

**Psychosocial functioning**

Depression, anxiety, adjustment disorders, and attention deficit hyperactivity disorder are thought to be the most prevalent psychiatric disorders in childhood MS, with 30–60\% of children with MS meeting criteria for one or more of these disorders.\textsuperscript{29,30,73,74} Concordant with adult MS, depression is thought to be the most common psychiatric disorder affecting children with MS.\textsuperscript{29,30,75}

**Depression.** Estimates for the prevalence of depression in childhood MS range from 6–50\%.\textsuperscript{29,30,74,75} This large range is likely due to different assessment strategies and disease duration at the time of evaluation. Parents of youths with MS reported that their children exhibited more symptoms of depression and somatization than parents of controls.\textsuperscript{77} Almost 30\% of children with MS were rated by their parents as experiencing moderate to severe symptoms of depression.\textsuperscript{77} Similarly, adolescents with MS also endorsed symptoms of depression more often than controls. Two larger studies (\(N = 57; N = 56\)) investigated depression in children and adolescents with MS using the Children’s Depression Inventory, finding that 17–21\% of patients endorsed depressive symptoms.\textsuperscript{74,75} No study has yet examined depressive symptoms in pediatric MS as compared to other children with depression.
Major depressive disorder is also common in adult MS, with a prevalence rate between 27% and 54%. In psychiatric interviews, 34–54% of MS patients reported a clinical history consistent with the symptoms of major depression. 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 adults with MS aged 18 to 45, as compared with 8% of the general population. Suicide rates are also higher in this population, and depressive symptoms tend to increase as MS progresses.

Adults with MS who have depression exhibit less apathy and social withdrawal than other depressed patients, instead showing increased irritability, worry, and discouragement. Furthermore, other features of MS such as fatigue and concentration difficulties may resemble depressive symptoms, making differential diagnosis more challenging.

**Anxiety.** The MS literature pertaining to anxiety in pediatric MS is more modest. Among 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 (not otherwise specified − NOS). An evaluation of cognitive functioning in 37 children with MS found that 30% had a diagnosis of an anxiety disorder, including generalized anxiety disorder, panic disorder, and anxiety disorder NOS. In a study of 61 children with MS, 31% reported elevated anxiety symptoms, but these symptoms were not significantly different from controls.

Anxiety is also common and often comorbid with depression in adult MS, with prevalence estimates ranging from 25–41% on self-report measures. Generalized anxiety disorder is reported to be the most common anxiety diagnosis in this population, with 18.6% of patients meeting criteria. This is followed by 10% of patients meeting criteria for panic disorder and 8.6% meeting criteria for obsessive-compulsive disorder.

**Fatigue.** Fatigue is reported in 20–75% of children with MS, suggesting that it may be as common in children as in adults. 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. 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.

As one of the most common symptoms in MS, fatigue is reported in 65–95% of the adult MS population. In adults with MS, fatigue is fairly independent of physical disability, disease duration, and disease course. MS-associated fatigue has also been linked to reduced quality of life.

**Quality of life.** There are very few formal studies of quality of life in patients with MS. In children, quality of life has been typically measured using the PedsQL, which examines mental functioning, physical functioning, social functioning, and school functioning. A study of 51 children with MS reported greater physical and academic problems compared to controls, but no significant difference in social and emotional functioning. 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. Another study of 50 children with MS reported worse overall health-related quality of life than controls.

Adult MS frequently limits patients’ independence within the community and at home. In a recent large prospective study of 201 MS outpatients, predictors of overall quality of life included social support, depression, religiosity, living area, and years of education. Unemployment correlated with poor quality of life, while absence of fatigue correlated with good quality of life.

**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 neuropsychological respects and possibly life consequences. While physical disability progression is slower to accrue in pediatric patients, significant cognitive issues may occur that can impact life trajectories to a greater degree than in adults. These issues have been underestimated until recently as most MS clinic-based outcome measures do not evaluate cognitive function.

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. Research
suggests that many facets of cognitive functioning are affected in MS across the lifespan, with the most outstanding difference being impairment of linguistic functions in pediatric MS. The roles of psychosocial factors such as depression, anxiety, fatigue, and quality of life in pediatric MS remain less clear. Although fatigue and depression appear to play an important role in children with MS, large, case-controlled studies have not yet been conducted.

One notable limitation of this review is the interrelationship between age and disease duration. Although these two factors cannot be easily teased apart, elucidating the impact of pediatric MS on neurobiological and cognitive development is vital to understanding the effects of MS throughout the lifespan. In addition, understanding how MS manifests across the lifespan has important clinical implications. Careful consideration of the ways in which pediatric- and adult-onset MS differ should inform assessment and treatment approaches that are tailored to evaluate and optimize cognitive and psychosocial functioning across the lifespan. Given the potential for childhood onset MS to have a greater impact on life trajectories, there is a significant need for improved early detection of cognitive impairments in children. Detection of these impairments 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.

Conflicts of interest
Ms Nunan-Saah, Ms Paulraj, and Dr Gomez report no disclosures.

Dr Waubant has received an honorarium from Genentech for an educational lecture and has received an educational grant from Biogen Idec. She has received funding from the National Institutes of Health, Race to Erase MS, and the National Multiple Sclerosis Society.

Dr Krupp has received either funding for research, honoraria, consulting fees, or royalties from Biogen Idec, Bristol-Myers Squibb, EMD Serono, Genzyme, Johnson & Johnson, Novartis, and Teva Neuroscience.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References


