

Memory and Identification of Emotional Expression in Pediatric-Onset Multiple Sclerosis

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Abstract

This study investigated whether 72 patients with pediatric-onset multiple sclerosis (MS) differed from 94 healthy controls on accuracy and response time on tests of episodic memory and identification of emotional expression using the Penn Computerized Neurocognitive Battery. We then tested the potential association between performance on episodic memory and emotion identification tests collapsing across the patient and control groups. Finally, we aimed to elucidate how neuropathology of the hippocampus, amygdala, and thalamus (using structural MRI), may impact episodic memory and emotion identification abilities. Results suggest that patients with pediatric-onset MS have difficulty with aspects of both episodic memory and emotion identification. Response time on all episodic memory tasks was positively associated with response time on the emotion tasks. Although patients demonstrated significantly smaller total and regional brain volumes, only thalamic volume appeared to relate to cognitive performance (i.e., response time on the Emotion Recognition test). Implications of emotion identification difficulties are discussed.

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List of Abbreviations

ANOVA: Analysis of Variance

ANCOVA: Analysis of Covariance

CHOP: Children's Hospital of Philadelphia

CNS: Central Nervous System

CPDDS: Canadian Pediatric Demyelinating Disease Study

CSF: Cerebral Spinal Fluid

DMT: Disease Modifying Therapy

EDSS: Expanded Disability Status Scale

HADS: Hospital Anxiety and Depression Scale

HC: Healthy Control

PCNB: Penn Computerized Neurocognitive Battery

PI-ED: Paediatric Index of Emotional Distress

MS: Multiple Sclerosis

ms: milliseconds

MRI: Magnetic Resonance Imaging

RRMS: Relapsing Remitting Multiple Sclerosis

1.0 Introduction and Background

1.1 Overview of Multiple Sclerosis

1.1.1 Diagnosis and Causes

Multiple Sclerosis (MS) is a chronic, inflammatory demyelinating disease of the central nervous system (CNS) in which the immune system attacks myelin, the protective covering of nerve cells. This results in impaired neuronal transmission. MS is thought to be the result of an interaction between genetic and environmental factors although the cause is still not clear (Love, 2006). Some studies suggest that viruses, such as Epstein-Barr, may also play a role in the development of the disease (Wagner, Munger & Ascherio, 2004).

Patients experience different patterns of diffuse and focal lesions in both grey and white matter. Disease presentation is very heterogeneous as clinical symptoms may manifest depending on the location of neural damage (Love, 2006). Symptoms can include: sensory and physical impairment (e.g., visual and muscular disturbances including weakness, balance and pain), emotional changes (e.g., low mood), fatigue, and cognitive decline across several domains including memory (Compston & Coles, 2008; Amato, et al., 2016; Ekmekci, 2017; Parrish & Fields, 2019).

Across all countries, Canada reports one of the highest rates of MS, with approximately one in 385 individuals living with the disease (Multiple Sclerosis Society of Canada, 2017). MS also disproportionately affects females with a female to male ratio of approximately 3:1 (Ghezzi et al., 2017). There are marked differences in how the disease presents in males and females. Females typically have a slightly earlier disease onset, lower prevalence of primary progressive disease course, and slower progression of disability, in relation to males (Harbo, Gold & Tintoré, 2013). The most common course of MS presents as relapsing-remitting (RRMS) (i.e.,

neurological attack is followed by a relapse) versus primary progressive (i.e., consistent deterioration of neurologic function with no defined relapses) and secondary progressive (i.e., initially presenting as acute relapses and remissions, followed by a progressive course) (Multiple Sclerosis Society of Canada, 2017). The RRMS course is particularly prevalent in the pediatric-onset type, accounting for approximately 93 to 100 percent of diagnoses (Yeh et al., 2009; Boiko et al., 2002; Ghezzi et al., 2002; Parrish & Fields, 2019; Waldman et al., 2014).

1.2 Pediatric-Onset Multiple Sclerosis

Although MS is typically diagnosed in adulthood between the ages of 20 to 40 years, it can also occur in childhood and adolescence. Patients with pediatric-onset MS represent three to 10 percent of all MS cases (Boiko et al., 2002; Yeh et al., 2009; Banwell et al., 2007; Waldman et al., 2014; Ghezzi et al., 2017). Although there are similarities in how the disease presents in adulthood and adolescence, in young children with MS, disease onset is typically marked by a higher frequency of symptoms indicative of cerebellar or brainstem involvement (Ghezzi et al., 2017). Additionally, children and adolescents with MS have more pronounced inflammation and experience a greater number of relapses, particularly near disease onset, relative to adults with MS. It also takes longer to develop disability in this population compared to adults with MS despite more disease activity (i.e., high relapse rate) in pediatric patients (Suppiej & Cainelli, 2014; Ghezzi et al., 2017).

1.2.1 Multiple Sclerosis and the Developing Brain

The impact on brain development and consequences for brain function must be considered with earlier disease onset. Disease pathology (i.e., neuronal and axonal loss) develops during CNS myelinogenesis in pediatric-onset MS (Banwell & Anderson, 2005; Amato et al., 2016). Disease pathology may also interrupt the development of cortical and subcortical

structures resulting in a failure to achieve age-expected brain volume (Aubert-Broche, et al., 2014). The combination of having the disease before complete formation of white matter pathways and significant brain pathology including regional grey matter atrophy, may explain the unique cognitive and psychosocial difficulties patients with pediatric-onset MS experience (Ghezzi et al., 2017; Till et al., 2011).

1.3 Cognitive Impairment in Pediatric-Onset Multiple Sclerosis

Cognitive impairment is identified in approximately 30 percent of pediatric-onset MS diagnoses and is typically observed before pronounced physical disability (Amato et al., 2008; Amato et al., 2010; Julian et al., 2013; Banwell & Anderson, 2005; Ghezzi et al., 2017). Working memory, attention, executive functions and information-processing speed are often compromised, and deficits may appear early in the disease course (Till et al., 2011). These processes are largely governed by the frontal lobes. The frontal lobes are the final brain region to undergo myelination which may explain deficits in these cognitive domains in patients with early disease onset (MacAllister et al., 2013; Till et al., 2011). Studies have demonstrated that younger age at disease onset and declining global and regional brain volume appear to impact the severity of cognitive deficits (Till et al., 2011; Banwell & Anderson, 2005; Amato et al., 2008; MacAllister et al., 2005; Amato, et al., 2016; Ekmekci, 2017; Parrish & Fields, 2019). Additionally, greater impairment over time is often noted when cognitive performance is studied longitudinally in patients with pediatric-onset MS (Amato et al., 2010).

1.3.1 Memory

An American study of 37 pediatric-onset MS patients (MacAllister et al., 2005) reported impairment (defined as performance <1.5 standard deviations (SD) below normative data) in immediate and delayed recall of visual information among 8.1% and 11% of patients,

respectively. Impairment in delayed recall (but not immediate recall) of verbal information was slightly more common, affecting about 19% of the sample. Expanded Disability Status Scale (EDSS; Kurtzke, 1983) score, a measure of physical disability, was the strongest predictor of memory impairment in this study, despite the sample not being especially physically impaired overall (EDSS ranging from zero to four) (MacAllister et al., 2007).

Similar findings were reported by researchers of an Italian multicentre study which included 63 pediatric MS patients and 57 matched healthy controls (Amato et al., 2008). Again, greater verbal versus visual long-term memory deficits were found for pediatric-onset MS patients. Specifically, long-term recall was impaired among 39% of the sample for verbal information relative to 18% of the sample for visuospatial information. Immediate recall was impaired among 56% of the sample for verbal information. Similarly, immediate recall was impaired among 53% of the sample for visual information. In a later longitudinal study (Amato et al., 2010), declines in verbal memory were also found at two-year follow-up.

Conversely, in a Canadian study of 32 pediatric MS patients and 26 age- and sex-matched controls (Fuentes et al., 2012), groups performed similarly on verbal and nonverbal memory tasks when intellectual ability was held constant, though memory impairment was identified in approximately 20 percent of patients (similar to the rates reported in the American study). Memory was evaluated in this study using the Word Selective Reminding, Memory for Stories, Abstract Verbal Memory, and Face Memory tests from the Test of Memory and Learning, Second Edition (TOMAL-2; Reynolds & Voress, 2007). This study also investigated the association between regional brain volume and memory deficits in pediatric MS patients. Patients with MS showed reduced volume in the total brain, amygdala, and thalamus, but not the hippocampus, relative to controls. Total brain volume as well as regional brain volume of the

hippocampus, amygdala, and thalamus, correlated with memory performance in patients, but not controls. This brain-behaviour association has been observed in some (e.g., Benedict et al., 2009), but not all studies in adults with MS (e.g., Rocca et al., 2016).

A longitudinal Canadian study of 28 pediatric MS patients and 26 age-matched controls (Till et al., 2013) examined change in cognitive functioning within a 13- to 16-month interval. Again, the aforementioned subtests from the TOMAL-2 (Reynolds & Voress, 2007) were used to assess memory at both time points. A decline in visual memory performance was noted for three of 28 patients using the Reliable Change Index, although significant decline at the group level was not found on any measure for either group. Notably, patients did not show the same trajectory of memory development as controls over time, suggesting that the development of memory may be negatively impacted in patients with pediatric-onset MS.

In summary, the majority of studies within pediatric-onset MS document memory impairment occurring in approximately one-fifth or fewer of pediatric MS patients, with the exception of one study (Amato et al., 2008) where memory impairment was found in roughly half of the sample for both visual and verbal information.

1.3.2 Social Cognition

A recent focus in neuropsychological research within MS is social cognition. Social cognition is an umbrella term including theory of mind (ToM) and emotion recognition. Researchers have shown that infants are able to respond to happiness (e.g., the infant smiles in response to the presentation of a happy face) and sadness (e.g., the infant cries at the presentation of an angry face) at just a few months of age (Nelson, 1987). By the age of six, most typically developing children are able to discriminate several facial emotional expressions with a relatively high degree of accuracy (Lawrence, Campbell & Skuse, 2015; Herba & Phillips,

2004). Through development, happiness is generally recognized most accurately first, followed by negatively valenced emotions (e.g., sad, angry). Accuracy in identifying surprise and fear generally follow (Herba & Phillips, 2004). For the majority of children, emotions such as embarrassment, guilt, and pride are well recognized around age seven (Vetter et al., 2013). Sex differences also exist, whereby during childhood and adolescence females are significantly more accurate at recognizing facial emotional expressions overall, relative to males. There is a dearth of knowledge regarding the development of social cognitive abilities in adolescence. It has been suggested that emotion recognition and more complex aspects of social cognition show protracted development that extends into adulthood (Vetter et al., 2013). This may be due to ongoing development of brain networks that are responsible for these functions which continue to develop across adolescence and into early adulthood (Kilford et al., 2016). Social cognition may be impacted in MS, although findings are mixed (as described below).

A study by Pinto and colleagues (2012) examined the performance of adult patients with MS and healthy controls using the Emotion Recognition Test. In this task, after three seconds of examining a face on the computer, participants are given unlimited time to label faces as depicting either: anger, disgust, fear, happiness, sadness, surprise, or no expression. Performance of patients did not differ significantly from controls on the number of correct responses. However, deficits may not have been detected as these patients were in the early stages of MS (the mean time since clinical diagnosis was nine years). Worsening of cognitive abilities including challenges with recognizing facial expressions is expected with longer disease duration.

A recent meta-analysis by Cotter and colleagues (2016) included 13 studies of facial emotion recognition with adult MS patients and healthy controls matched for age, sex, years of

education, and IQ. In each study, participants were asked to label or discriminate between images of faces depicting different emotions (i.e., anger, disgust, fear, happiness, surprise, and sadness). Patients demonstrated poorer accuracy for all emotions tested relative to controls. However, statistically significant findings were only apparent for anger, sadness and fear; groups did not differ on happiness, surprise, or disgust (Cotter et al., 2016; Henry et al., 2017). Further, older patients with MS, irrespective of disease duration, were most impaired in identifying all emotions (Cotter et al., 2016).

ToM is another facet of social cognition that has been reported to be disturbed in pediatric-onset MS (Charvet et al., 2014). ToM is defined as the ability to infer one's own mental states as well as the mental states of others (Henry et al., 2017). In a 2014 study by Charvet and colleagues, 28 pediatric MS patients and 32 healthy controls were administered the Reading the Mind in the Eyes Test (Baron-Cohen et al., 2001), Faux-Pas Test (Brüne & Brüne-Cohrs, 2006), and First- and Second-Order False Beliefs (Perner & Wimmer, 1985) as measures of ToM. Overall, patients performed more poorly on all three tasks relative to controls. Taken together, there is a need for more studies to examine social cognitive outcomes in pediatric-onset MS.

1.4 Grey Matter Neuropathology in Pediatric-Onset MS

Studies have started to look beyond white matter in pediatric-onset MS based on findings in the adult MS literature. Researchers have discovered that the neuropathology in children with the disease also involves grey matter. Furthermore, the thalamus has been identified as a structure that is particularly vulnerable to pediatric-onset MS (Mesaros, 2008; Till et al., 2011; Kerbrat et al., 2012; Aubert-Broche et al., 2014). The consequences of thalamic damage include cognitive challenges, namely impairment in information processing, attention, memory, and auditory and visual integration (Till et al., 2011). The thalamus is also a highly connected

structure with projections to the hippocampus, making it a useful region of comparison when evaluating the pathology to other deep grey matter structures and consequences of this pathology for cognition.

1.4.1 The Limbic System

The limbic system consists of several subcortical structures including the hippocampus and amygdala. Together, these structures form a complex network that is responsible for controlling and processing memory and emotions (Phelps, 2004; Rajmohan & Mohandas, 2007). Brain regions that comprise the limbic system may be compromised by MS, although findings are mixed as described below.

1.4.2 The Hippocampus

The hippocampus is intricately involved in both spatial navigation and episodic memory (Wixted et al., 2018; Burgess et al., 2002). This structure undergoes progressive neuronal enlargement throughout childhood into adulthood. In typically developing individuals, myelination in the hippocampus increases in childhood until adolescence (Arnold & Trojanowski, 1996).

1.4.3 The Amygdala

The amygdala is a central component of the limbic system that facilitates threat response and regulates memory and identification of facial emotional expressions (Krause, 2009). The response of the amygdala to emotions appears to be lateralized such that surprise and negative emotions like anger and sadness activate the right amygdala whereas fear activates the amygdala bilaterally. This laterality has also been demonstrated in research with individuals with MS (Henry et al., 2017; Cristinzio, Sander & Vuilleumier, 2007). Further, specific impairment in recognizing fear has been noted with amygdala lesions (Henry et al., 2017; Adolphs, 2002).

Structurally, the amygdala is said to reach adult volume in females by four years of age with development continuing until approximately age six in males (Tottenham & Sheridan, 2009; Giedd et al., 1996; Gilmore et al., 2012). Some studies also suggest that the left amygdala develops more rapidly relative to the right amygdala.

1.4.4 The Hippocampus and Amygdala in Pediatric-Onset MS

One study in pediatric-onset MS which included structural MRI and analysis of limbic structures found that normalized amygdala volume, but not hippocampal volume, differed significantly between patients and controls (Fuentes et al., 2012). In contrast, a study by Rocca and colleagues (2016) assessing hippocampal volume (but not amygdala) documented global and regional hippocampal volume loss in pediatric-onset MS patients. Amygdala pathology has been suggested to have deleterious effects on retention of learned visual and verbal information in pediatric-onset MS (Batista et al., 2017; Fuentes et al., 2012). It is also considered the strongest predictor of impairment in decoding the mental states of others (Batista et al., 2017). However, the impact of hippocampal and amygdala volume loss on identification of emotional expression in pediatric-onset MS has not been examined to our knowledge.

2.0 Rationale

To date, no studies to our knowledge have examined the relationship between memory impairment and facial emotion identification in pediatric-onset MS. The association is important to clarify as navigating day-to-day interactions demand processing social cues in real-time while simultaneously relying on memories for past experiences that help to guide behaviour (Barnier et al., 2008; Spreng & Mar, 2012). As such, difficulties with memory and identifying others' emotional expressions, may have functional consequences in the real world which can influence quality of life among MS patients. This can be particularly concerning in childhood and

adolescence, as these are developmental periods when peer relationships are salient and professional and romantic connections may be evolving (Scherf et al., 2013).

Evidence from neuroimaging studies in MS suggest that abnormalities in brain structure and function may underlie cognitive and social processes. Further, several studies call for future research to examine the association between cognitive impairment, factors that contribute to social cognitive dysfunction, and neurologic changes that may predict difficulties in these areas (Cotter et al., 2016).

Another gap in the pediatric-onset MS literature is the role of reduced processing speed, which is another common symptom of the disease, in contributing to impairments in memory function and social cognition. For example, if patients show reduced memory performance, it is important to probe whether the reduced performance is simply a manifestation of a general slowing of cognitive processing or whether performance is less accurate independent of speed. The methodology employed in the current research study has the potential to elucidate the role of information processing speed in specific cognitive deficits (i.e., episodic memory and identification of emotional expression) observed in pediatric-onset MS.

3.0 Research Questions and Hypotheses

The overall objective of this study was to investigate the interrelationship between episodic memory, identification of emotional expression, and brain structures affiliated with these functions, in patients with pediatric-onset MS and healthy controls. The following specific aims were examined:

Aim 1: To assess whether there is an association between episodic memory and identification of emotional expression.

Hypothesis 1: Episodic memory will be positively associated with the ability to identify

emotional expressions collapsing across the patient and healthy control groups.

Aim 2: To examine whether patients with pediatric-onset MS differ from healthy controls on episodic memory and identification of emotional expression tasks.

Hypothesis 2: Patients will demonstrate poorer performance on measures of episodic memory and identification of emotional expression relative to healthy controls.

Aim 3a: To assess whether patients with pediatric-onset MS have smaller hippocampal, amygdala, and thalamic volume relative to healthy controls.

Hypothesis 3a: Regional brain volumes (hippocampal, amygdala, and thalamic volume) will be smaller among patients relative to healthy controls, with the thalamus showing the greatest difference between groups.

Aim 3b: To determine whether total hippocampal, amygdala, and thalamic volume are independently associated with memory performance and identification of emotional expression.

Hypothesis 3b: Given the role of the hippocampus and amygdala in processing emotion and regulating memory as well as the well-documented vulnerability of the thalamus to MS pathology (and its interconnections with limbic structures and the frontal lobe), smaller total hippocampal, amygdala, and thalamic volume will be independently associated with worse memory scores and poorer identification of emotional expression.

4.0 Method

4.1 Participants

Baseline neurocognitive and neuroimaging data from the ongoing longitudinal Canadian Pediatric Demyelinating Study (CPDDS) collected between December 2015 and June 2019 were used. The CPDDS is a multi-site, longitudinal initiative across Canada as well as the Children's

Hospital of Philadelphia (CHOP). Nine of the 15 participating sites had neurocognitive data available (Table 1). All participants had to be able to complete the test in English.

Ninety-three patients with pediatric-onset MS were enrolled by the sites offering neurocognitive testing and neurocognitive data were obtained for 73 of these patients. Patients with established MS were recruited from previous phases of the national project via a letter of invitation which was either provided at their routine visit or by mail. Patients with incident MS were recruited consecutively from MS clinics at the Hospital for Sick Children (SickKids) and CHOP, as well as the University of Western Ontario using advertising (i.e., flyers, letters to residents and staff physicians, and web advertisement). Patients were between the ages of eight and 27 at the time of the assessment. Pediatric-onset MS patients were all confirmed to have their first attack before age 19 and have met the revised McDonald 2010 diagnostic criteria for relapsing-remitting MS (Polman et al., 2011).

In addition, two sites enrolled 139 healthy controls (HCs; individuals in approximately the same age range as the patient group without MS). Recruitment of HCs took place at SickKids and CHOP using the same methods of advertisement used to recruit patients. HCs with a history of demyelinating syndrome were ineligible for the study. Forty-four HCs declined participation in the cognitive component of the study for unknown reasons. Of the HCs who completed the PCNB, one was excluded for expressing familiarity with the assessment battery. The final sample included 72 patients and 94 HCs (Figure 1).

A subset of MRIs was analyzed as data collection was still ongoing at the time of the data pull. Regarding the MRI data that were available for processing, three of 51 patients were excluded from analyses despite adherence to the standardized scanning protocol and scans that passed quality control. This is because COMBAT (a method for estimating and controlling for

differences between scanners), cannot account for scanner-related variability at a given site when there are limited entries (i.e., less than two or three scans). Consequently, COMBAT rejects the scans from processing. One HC and one patient were excluded because accurate segmentations could not be obtained. Two HCs were excluded due to the presence of abnormalities on MRI. Two patients declined a research MRI due to claustrophobia or another unspecified reason. Finally, one patient could not be scanned as there was no scanner on-site (Supplemental Table 2). Fifty-one patients (from a total of 72) and 61 HCs (of 94) had useable MRI data. Due to the scaling factor that was applied to the scans, participants were only included in MRI analyses if they were over 15 years of age at the time of their scan. This resulted in a final sample of 46 MS patients and 42 HCs with useable MRI data for the present study.

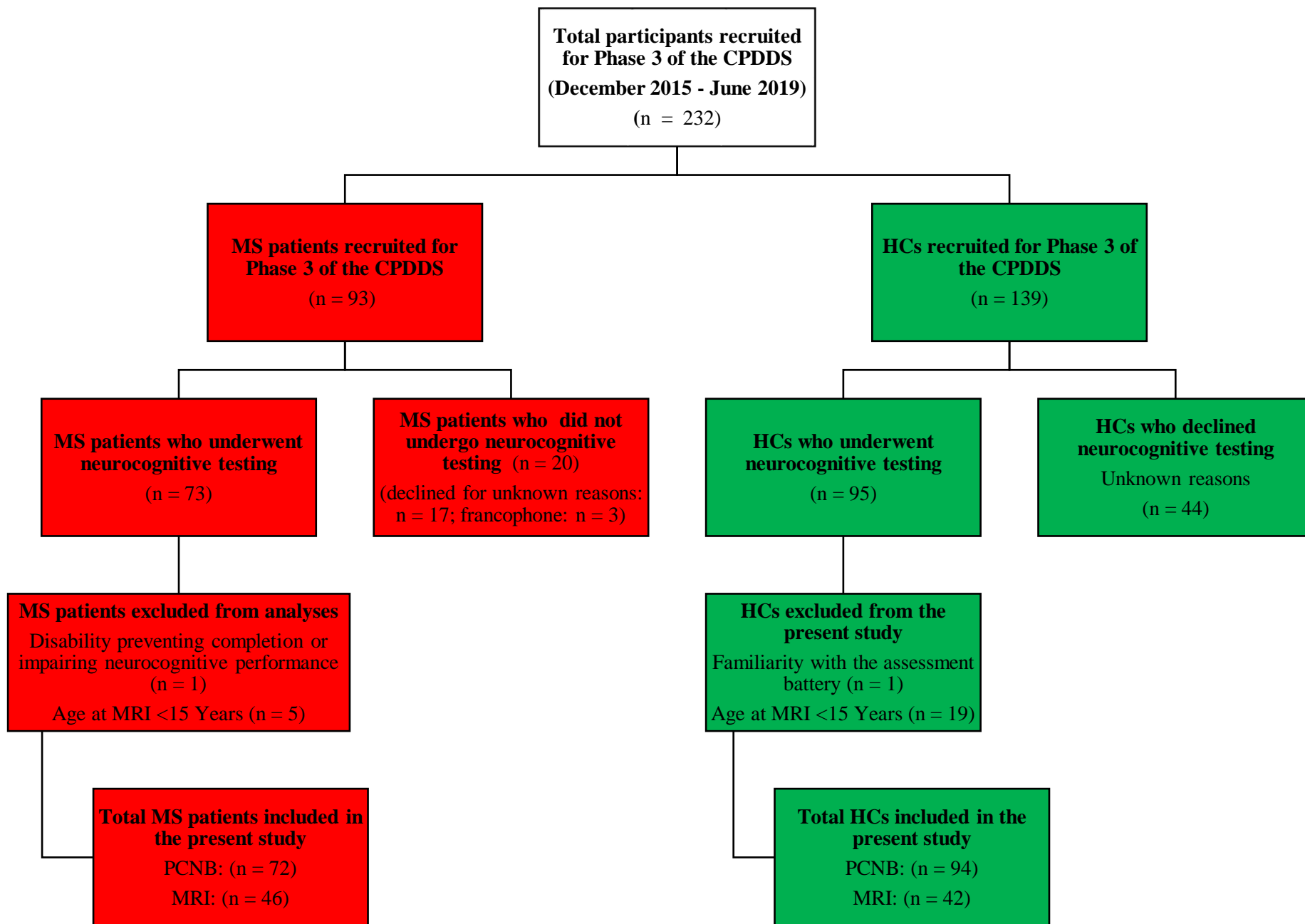
Figure 1. *Study Enrollment*

Table 1
Sites with Available Neurocognitive Assessment Data

Site	MS Patients Assessed	HCs Assessed
	N	N
Alberta Children's Hospital	1	-
Children's Hospital at London Health Sciences Centre	4	-
Children's Hospital of Philadelphia	19	28
Hospital for Sick Children	39	67
Janeway Children's Health and Rehabilitation Centre	1	-
Montreal Children's Hospital	5	-
The Children's Hospital of Manitoba	2	-
Trillium Health Partners	1	-
McMaster Children's Hospital	1	-
Total	73	95

Note. One HC from the Hospital for Sick Children as well as the patient from McMaster Children's Hospital were excluded from analyses.

4.2 Ethical Considerations

This research received ethics review and approval by the Human Participants Review Committee at York University as well as the Research Ethics Board (REB) at SickKids and all participating institutions involved in the CPDDS. Further, the research conforms to the standards of the Tri-Council Research Ethics guidelines. Research participants were fully informed about the research protocol and were asked to give their consent to participate. Participants age 16 years and older provided written informed consent. Participants under 16 years of age provided assent and their parents/legal guardians provided written informed consent. Participants were

guaranteed that all identifying information would remain confidential and would only be used for the intended research purpose. Participant numbers were assigned, and confidentiality was maintained through the study.

4.3 Measures

4.3.1 Clinical-Demographic Information

Core demographics, developmental milestones, education and occupation, and relevant personal and familial medical histories were recorded using standardized case report forms. Study site neurologists documented neurological findings, leading to determination of an approximated Expanded Disability Status Scale (EDSS) score.

Symptoms of depression and anxiety in participants under 16 years of age were measured using the Paediatric Index of Emotional Distress (PI-ED; O'Connor et al., 2016). Participants age 16 and over completed the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). Both are 14-item questionnaires that generate an emotional distress score, based on a combined depression and anxiety score. A score greater than 20 on both measures is indicative of clinically significant emotional distress (O'Connor et al., 2016). Fatigue was measured using the PedsQL Multidimensional Fatigue Scale (Varni et al., 2002), with higher scores reflecting fewer problems.

4.3.2 Cognitive Evaluation

Participants completed the children's version of the Penn Computerized Neurocognitive Battery (PCNB) which takes approximately one hour to complete. The PCNB consists of 14 tests (Table 2) which assess: executive function (i.e., abstraction and flexibility, working memory, and attention), episodic memory (i.e., face, object, and word memory), complex cognition (i.e., language, nonverbal, and spatial reasoning), social cognition (i.e., emotion recognition and

emotion and age differentiation), and sensorimotor function. The order of presentation of these tests is consistent between participants to maintain engagement and prevent fatigue (Gur et al., 2012) (Supplemental Table 1). Breaks are offered approximately every 15 minutes. All assessors completed a standard training protocol for administration of the PCNB.

Table 2
Penn Neurocognitive Battery Subtests by Domain

Domain	Subtests	Neurobehavioural function	Brief Description
Complex Cognition	Penn Verbal Reasoning Test for Children	verbal reasoning	select from a list the word that best completes the verbal analogy
	Penn Matrix Analysis Test	nonverbal reasoning	choose the geometric piece that best completes the pattern
	Variable Penn Line Orientation Test	spatial ability, visual discrimination	rotate a line until it is parallel to a fixed line of a different length and orientation, using as few clicks as possible
Executive Function	Letter N-Back	working memory, shifting	one letter shown on screen at a time; press according to three rules, across three different conditions: (1) press for X, (2) press when the current letter is the same as the previous letter, (3) press when the current letter is the same as the letter that came before the previous letter respond when the appropriate letter is displayed amongst a series of letters
	Penn Continuous Performance Test	sustained attention	press for a letter/number; do not press for distractor items
	Penn Conditional Exclusion Test	cognitive flexibility, rule learning, working memory	identify which object of four does not belong based on one of three sorting principles; sorting principles switch after 10 consecutive objects selected correctly
	Go-No-Go Task	inhibitory control, sustained attention	press for target letter in upper half of screen; do not press for nontarget letter or for letters in lower half of screen
Sensorimotor	Motor Praxis Test	motor planning and coordination	quickly manipulate a computer mouse to click on a target that moves and changes size
	Penn Computerized Finger-Tapping Test	fine motor speed	tap the spacebar using only the index finger as many times as possible within 10 000ms
Social Cognition	Age Differentiation Task	age differentiation, visual discrimination	identify which of two faces is older. Control condition task for current study.
	Penn Emotion Recognition Test for Children	emotion identification	identify the emotion shown on a given face from a list of emotions
	Measured Emotion Differentiation Task	emotion differentiation	identify which of two faces is showing an emotion to a greater degree
Episodic Memory	Penn Face Memory Test	face recognition memory	identify which faces have been seen previously
	Penn Word Memory Test for Children	verbal recognition memory	identify which words have been seen previously
	Visual Object Learning Test	spatial recognition memory	identify which figures have been seen previously

Note. Subtests in bold are the primary outcomes used in the current study.

Each test on the PCNB provides a measure of both accuracy (i.e., number of correct responses) and response time (or efficiency of responding), with the exception of sensorimotor tests specifically designed for measuring motor speed. The PCNB has high sensitivity for detecting cognitive impairment in youth with different neuropsychiatric and medical conditions (Gur et al., 2014; Merikangas et al., 2017; Thomas et al., 2013; Ibrahim et al., 2016) and has been used to probe well-established brain systems with functional neuroimaging (Roalf et al., 2014). Pediatric and adult versions have been developed with acceptable construct validity and psychometric properties (Gur et al., 2001; Roalf et al., 2014; Gur et al., 2010).

The episodic memory and social cognition domains are the focus of the present study. Raw scores for each measure of accuracy and response time were standardized into *Z*-scores based on the means and standard deviations of the HC group. This approach was adopted in lieu of using the available PCNB norms as our cohort was not well matched with the established PCNB normative group in terms of demographics (namely parental education, a proxy for socioeconomic status). Consequently, using the available PCNB norms would have limited our ability to derive clinically meaningful *Z*-scores. *Z*-scores were calculated from three age bands (i.e., 8-13; 14-17; >18 years). Age bands were determined based on the developmental curves for the PCNB tasks (Gur et al., 2012) and with consideration of the number of participants in each group. Scores were transformed (i.e., multiplied by -1), where necessary (i.e., response time), such that higher *Z*-scores reflect better performance (i.e., more accurate, shorter response times). Composite scores were obtained by averaging *Z*-scores across the cognitive domains. Test performance was considered to be impaired if the *Z*-score fell 1.5 SD below the mean.

Penn Age Differentiation Test. This test serves as a control condition to compare against the emotion-related tasks. More specifically, the Age Differentiation Test is used in the present research to ensure participants have intact performance on a face processing task that is not contingent on emotion processing. Intact performance on this test would allow us to rule out difficulty in face processing that could potentially generalize to difficulties in facial emotional recognition. Across 36 trials with equal representation of male and female stimuli, this test measures the ability to perceive small visual differences. Pairs of faces are presented from the same target face that has been morphed to appear older or younger (Figure 2). Participants are asked to click the button labeled “This Face” below the face that is older or the central button, labeled “Both faces are the same age”, if both faces appear to be the same age (as is the case for four trials). Trials are presented in random order, and the test is a forced-choice task with no time limit per trial. Participants are given three practice trials before the test begins.



Figure 2. Test Screenshot of the Age Differentiation Test from the PCNB. Copyright ©2006,

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Penn Emotion Identification Test. Participants are presented with 40 faces one at a time and asked to determine what emotion the face is showing (Figure 3). There are five answer choices: Happy, Sad, Angry, Scared, and No Feeling. Participants respond to each trial by clicking with the mouse on the word describing the emotion each face depicts. There are four female faces for each emotion for a total of 20 female faces and four male faces for each emotion for a total of 20 male faces. The stimuli (coloured faces) are balanced for equality and intensity or emotion, age, gender and ethnicity (Kohler, Turner, Gur & Gur, 2004). The test is a forced-choice task with no time limit per trial. Participants are given a practice trial before the test begins.

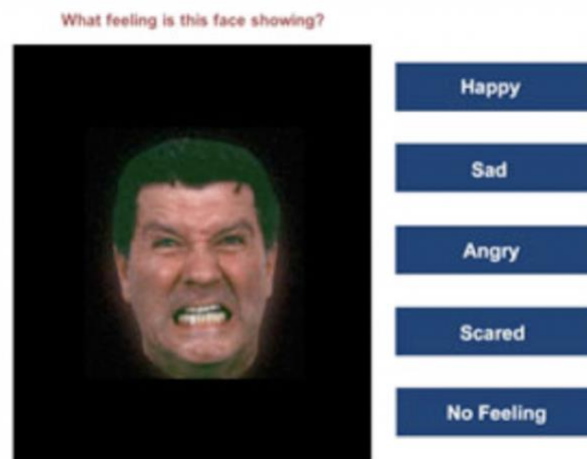


Figure 3. Test Screenshot of the Penn Emotion Identification Test from the PCNB.

Penn Emotion Differentiation Test. Across 36 trials with equal representation of male and female stimuli, this test measures the ability to detect emotional intensity (Figure 4). Pairs of emotional expressions from the same target face expressing the same emotion to varying degrees are presented. Participants are asked to click the button labeled “This Face” below the face that is

showing more emotion, or the central button, labeled “Equal”, if both faces are showing equal emotion (as is the case for 4 trials). Trials are presented in random order, and the test is a forced-choice task with no time limit. Participants are given three practice trials before the test begins.

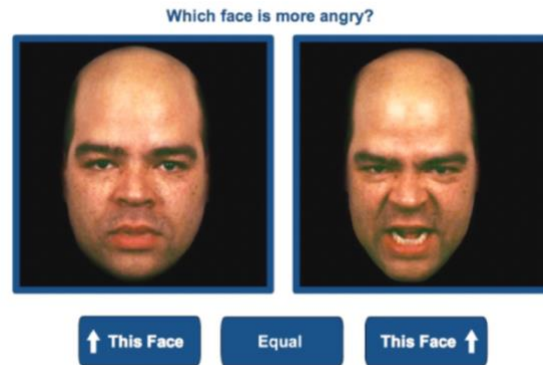


Figure 4. Test Screenshot of the Measured Emotion Differentiation Test from the PCNB.

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Penn Face Memory Test. Participants are presented with 20 black and white photographs of cropped faces (balanced for gender and age) one at a time for an encoding period of 5000 milliseconds (ms) each and are asked to remember each face (Figure 5). Immediately upon completion of the presentation, participants are asked to identify, one at a time, which of 40 faces (20 test faces and 20 novel faces) they have seen before. Responses are made by using the computer mouse to select one option on a four-point scale: “definitely yes”, “probably yes”, “probably no” and “definitely no”. There are no practice trials for this test.

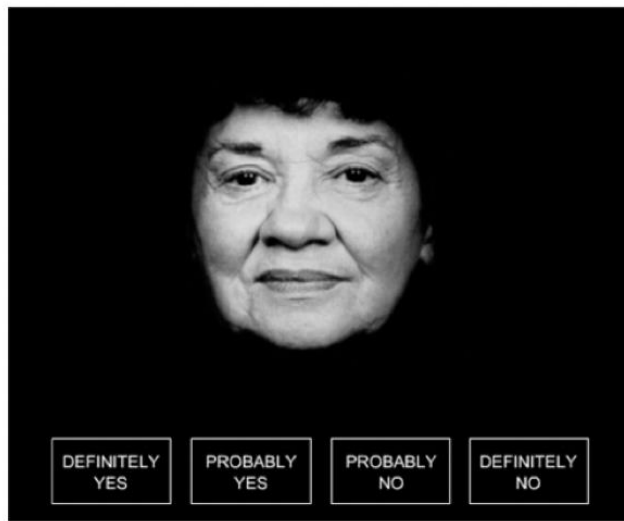


Figure 5. Test Screenshot of the Penn Face Memory Test from the PCNB.

Penn Word Memory Test for Children. Participants are shown 20 words one at a time for an encoding period of 5000 ms each that they are asked to remember and later recognize (Figure 6). Immediately upon completion of the presentation, participants are asked to identify, one at a time, which of 40 words (20 test words and 20 novel words) they have seen before by using the computer mouse to select one option on a four-point scale: “definitely yes”, “probably yes”, “probably no” and “definitely no”. All novel stimuli are matched for frequency, length, concreteness and imageability using Pavio’s norms (Pavio, Yuille & Madigan, 1968). There are no practice trials for this test.

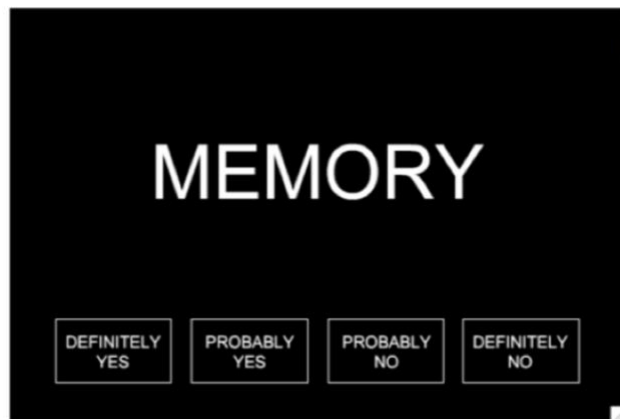


Figure 6. Test Screenshot of the Penn Word Memory Test from the PCNB.

Visual Object Learning Test. In this measure of visual object learning and memory, participants are shown 10 three-dimensional shapes one at a time for an encoding period of 5000 ms each that they are asked to remember and later recognize (Figure 7). All stimuli have a geometric blue two-dimension shape within a three-dimensional figure which together comprise the 'whole figure' they are to remember. Immediately upon completion of the presentation, participants are asked to identify, one at a time which of 20 shapes (10 test shapes and 20 novel shapes) they have seen before by using the computer mouse to select one option on a four-point scale: “definitely yes”, “probably yes”, “probably no” and “definitely no”. There are no practice trials for this test.



Figure 7. Test Screenshot of the Visual Object Learning Test from the PCNB.

4.3.3 MRI Protocol: Image Acquisition

A structural MRI scan was performed on a 3T scanner (different model at each site; Supplemental Table 2) according to a standardized research protocol. Four-fifths (80.36%) of participants were scanned on the same day as the neurocognitive assessment; the remaining one-fifth (19.64%) of participants returned for scanning within an interval of one day to five months, eight days. The following list of sequences is outlined in the MRI Standard Operating Procedures from the Montreal Neurological Institute and were used to set up the scanners at each site.

Notably, the parameters may vary slightly at each location depending on the manufacturer and model of the scanner: T1-weighted MPRAGE (TR 1810 ms, TE 3.51 ms, TI 1100 ms, flip angle 9°, 160 slices, voxel size 0.9 x 0.9 x 1 mm³); 3D FLASH without and with a magnetization transfer pulse to compute magnetization transfer ratio (MTR) (TR 33 ms, TE 3.86 ms, flip angle 10°, 192 slices, voxel size 1 x 1 x 1 mm³, GRAPPA factor 2; dual-angle B1 mapping pair (EPI-SE, TR 4000 ms, TE 18 ms, voxel size 2 x 2 x 5 mm³, flip angles 60° and 120°); 2D TSE proton density (PD)-weighted (TR 2200 ms, TE 10 ms, 60 slices, ETL 4, voxel size 1 x 1 x 3 mm³); 2D

TSE T2-weighted (TR 4500 ms, TE 84 ms, 60 slices, ETL 11, voxel size 1 x 1 x 3 mm³); 3D FLAIR (TR 5000 ms, TE 388 ms, TI 1800 ms, ETL 155, 208 slices, voxel size 1 x 1 x 1 mm³), DTI (TR 10300 ms, TE 94 ms, 30 diffusion-encoding directions, 50 slices, voxel size 2 x 2 x 2 mm³, GRAPPA factor 2); T1-weighted pre/post gadolinium (3D FLASH TR 30 ms, TE 6.15 ms, flip angle 27°, 60 slices, voxel size 1 x 1 x 3 mm³). Only T1-weighted images were analyzed for the purpose of the present study. Differences between scanners were controlled for using COMBAT (a computer algorithm that estimates scanner-related variability in the data).

5.0 Analyses

5.1 Processing Cognitive Data

During neurocognitive testing, the assessor noted behavioral and/or environmental observations pertinent to testing (e.g., presence of distractions, motivation towards the task, misunderstanding of instructions, and technical problems). Upon completion of the battery, data were sent to the CNB team at the University of Pennsylvania where quality control procedures were applied to each participant's dataset. The data were plotted on a scatterplot to examine outliers (accuracy plotted on the Y axis and speed on the X axis). The data were then transferred via a data transfer agreement to SickKids and later to York University where the data underwent further quality control procedures (i.e., examination of assessor comments and removal of invalid participant data, checking for outliers, and Winsorizing). Secondary data analysis was then performed.

5.2 MRI Processing

Briefly, all images underwent quality control examination by neuroimaging experts at CHOP via the following preprocessing steps: evaluation for adequate signal-to-noise ratio,

ensuring freedom from significant motion or other artifact, and ensuring consistency of the sequence parameters.

Total and lateralized brain volume of the hippocampus, amygdala, and thalamus for each hemisphere were calculated at CHOP by customizing existing routines (Iglesias et al., 2015; Saygin et al., 2017) available in FreeSurfer. Specifically, N4 was used for inhomogeneity correction as opposed to the default N3 and multi atlas skull stripping was used as a substitute for the default watershed algorithm. Lesions were in-painted using Lesion Segmentation Toolbox, to look like the normally appearing tissue around it. This step is important for ensuring that the segmentations are accurate.

Brain tissue volume was then normalized for subject head size with the SIENAx tool in FSL (Smith et al., 2001; Smith et al., 2002; Smith et al., 2004). SIENAx extracts brain and skull images from the T1 MPRAGE data (Smith, 2002b). To normalize for head size, a volumetric scaling factor is obtained by affine-registering the brain image to MNI152 space (Jenkinson & Smith, 2001; Jenkinson et al., 2002). The skull image is used to determine the registration scaling. Specific tissue-type segmentation with partial volume estimation is then carried out (Zhang et al., 2001) and total volume of brain tissue is calculated (including separate volumes of grey matter, white matter, and ventricular cerebral spinal fluid (CSF). This process confirms that any differences in regional brain volume are not just due to differences in overall head size.

Finally, the data were adjusted for scanner type using COMBAT. Data for participants at sites where there were only one or two entries, were excluded from MRI analyses as data could not be run through COMBAT.

5.3 Statistical Analyses

Data were analyzed using IBM SPSS Statistics version 24. To reduce the likelihood of a Type 1 error due to the multiple comparisons conducted, we adjusted the p -value to .01. Trends were also considered for group differences that did not meet this threshold for statistical significance. First, variables were plotted (histograms and boxplots) to assess normality and identify any outliers, across all outcomes. Outliers were Winsorized to three SD from the mean. The Shapiro-Wilk and Levene's tests were used to identify possible violations of normality and homogeneity of variance within the data set.

Descriptive statistics were examined for the clinical characteristics of the MS sample (i.e., fatigue, age at disease onset, disease duration, EDSS score, and use of disease-modifying therapies (DMT)). One-way analysis of variance (ANOVA) was used to compare the MS and HC groups on demographic variables (i.e., age, sex, level of education, and years of parental education).

Two-tailed partial Pearson correlations (adjusted for accuracy or response time and/or sex where indicated) were used to examine relationships between each memory and emotional identification task, for MS patients, HCs, and collapsing across groups (Aim 1). Fisher's Z-Transformations were used to compare the strength of the differences in the correlation coefficients between the MS and HC groups.

One-way analysis of covariance (ANCOVA) was used to compare groups on each of the episodic memory and social cognition tasks from the PCNB (Aim 2). Task-specific response time was included as a covariate for analyses of accuracy, and vice versa. Sex was included as a covariate when sex effects were present, as determined by comparison of male and female HC groups using independent samples t -tests. Effect sizes were determined using partial eta-squared

(η^2). Rates of impairment were compared between MS patients and HCs using a chi-squared (X^2) test. One-way ANCOVAs were then used to probe whether there were differences between groups on the processing of specific emotions (e.g., anger, scared, sadness, happy, etc.) that were part of the Emotion Recognition and Emotion Differentiation tasks. Again, task-specific response time was included as a covariate for analyses of accuracy, and vice versa.

In a sensitivity analysis, we excluded participants who failed the control task (as indicated by accuracy falling 1.5 SD below the mean on the Age Differentiation Test) and re-ran the analyses involving the emotion identification tasks. This approach allowed us to probe whether participants who struggled with face processing may have influenced the emotion identification findings. For the response time analyses, we also re-ran the between-group analyses controlling for sensorimotor speed. This approach allowed us to determine whether the differences in response time on the cognitive tasks were observed over-and-above expected differences on simple motor tasks.

One-way ANOVAs using regional brain volumes scaled with SIENAx were used to test whether patients with pediatric-onset MS have smaller total and lateralized hippocampal and amygdala volume relative to controls (Aim 3a). Thalamic volume was used to validate findings (i.e., to ensure that thalamic volume differed significantly between patients and HCs as demonstrated consistently in the literature).

We ran two-tailed partial Pearson correlations (adjusted for accuracy or response time and/or sex where indicated) to examine the association between hippocampal, amygdala, thalamic, and total brain volume with cognitive outcomes for which MS patients differed significantly from HCs in terms of Z-score accuracy and Z-score response time (Aim 3b). Finally, multiple linear regressions predicting cognitive outcome were only conducted when near

significant associations were observed between a given task and regional brain volume to elucidate the variance in performance accounted for by a given brain structure. Statistical significance was established for regression analyses using a p -value of $<.05$ to capture the smaller effect sizes.

6.0 Results

6.1 Neurocognitive Outcomes

6.1.1 Sample Characteristics

In total, cognitive data were analyzed for 72 MS patients and 94 healthy controls. Demographic and disease-related characteristics of the sample are reported in Table 3. MS patients were, on average, older than controls at the time of the neurocognitive assessment (18.1 versus 16.7 years) ($p = .05$); groups did not differ significantly with respect to sex, level of education, years of parental education, or emotional distress. However, they did differ significantly (all values $\leq .01$) with respect to both parent and participant rated levels of fatigue. MS patients were tested at variable intervals from disease onset, ranging from less than one month to 11 years ($M = 4.0$ years, $SD = 3.9$ years); 25 of 72 (34.72%) patients had a disease duration greater than five years. Age at MS onset ranged from 5.9 to 18.8 years ($M = 14.5$, $SD = 2.8$), and 11 of 72 (15.3%) had their first attack prior to age 12 years. MS patients had a median EDSS score of 1.5 ranging from 0-6.5 and 56 of 72 (77.8%) patients were receiving disease-modifying treatment at the time of the assessment.

Table 3
Demographic and Clinical Characteristics of the PCNB MS and HC Groups

Characteristic	MS (n = 72)	HC (n = 94)	p
	M(SD) / N(%)	M(SD) / N(%)	
Age at testing (years, range)	18.1 (8-27)	16.7 (8-29)	.05
Sex (male/female, %)	18/54 (75%)	35/59 (62.8%)	1.00
Participant education (years)	11.5 (3.3)	10.8 (4.3)	.23
Parental education			
Father's education (years)	12.5 (4.9)	13.2 (5.5)	.39
Mother's education (years)	13.8 (3.7)	13.8 (5.1)	1.00
Emotional Distress (normal/high, %)†	67/7 (9.7)	76/3 (3.2)	.13
Fatigue			
Parent†			
General Fatigue	67.5 (85.6)	85.6 (15.6)	<.001
Sleep Rest Fatigue	67.2 (24.3)	83.6 (17.2)	<.001
Cognitive Fatigue	70.7 (25.7)	85.6 (16.5)	<.001
Total	68.4 (22.2)	84.9 (14.6)	<.001
Participant†			
General Fatigue	66.9 (23.0)	79.3 (15.1)	<.001
Sleep Rest Fatigue	60.3 (21.6)	68.4 (17.4)	.01
Cognitive Fatigue	66.6 (25.5)	78.4 (17.0)	.001
Total	64.5 (20.6)	75.4 (13.9)	<.001
EDSS (median, range)	1.5 (0-6.5)	-	-
Age at disease onset (years)†	14.5 (2.8)	-	-
DMT (N/Y, %)	16/56 (77.8)	-	-
Disease Duration (months)	48.1 (46.9)	-	-

Abbreviations: MS = multiple sclerosis; HC = healthy control; EDSS = Expanded Disability Status Scale; DMT = Disease Modifying Therapy

†Emotional Distress data not available for two patients and 17 HCs.

†Parent rated fatigue data not available for 11 patients and 25 HCs.

†Participant rated fatigue data not available for 2 patients and 8 HCs.

†Age at disease onset data not available for one patient.

6.1.2 Associations between Episodic Memory and Identification of Emotional Expression (Accuracy)

Table 4 shows the correlations between the subtests in the social cognition and episodic memory domains. Overall, accuracy of performance on Face Memory (controlling for reaction time) correlated moderately with Emotion Recognition ($r = .28, p = .001$) and Emotion Differentiation ($r = .32, p < .001$), collapsing across groups.

Collapsing across groups, accuracy on Object Memory (controlling for reaction time) did not reach significance with accuracy on the Emotion Recognition ($r = -.03, p = .73$) but approached significance with the Emotion Differentiation subtest ($r = .16, p = .04$). Object Memory was significantly positively associated with Emotion Differentiation for patients ($r = .31, p = .01$) but not controls.

Finally, accuracy on the Word Memory subtest (controlling for reaction time) demonstrated a significant positive association with accuracy on the Emotion Differentiation subtest collapsing across groups ($r = .25, p = .001$) but not Emotion Recognition.

Correlations between Face and Object Memory with the social cognition tasks were slightly stronger among the MS group relative to controls, although the differences were not statistically significant when compared using Fisher's Z-transformation.

Table 4

Correlations (two-tailed) Between Z-score Accuracy on Episodic Memory and Social Cognition Subtests in Patients with MS and HCs

<u>Social Cognition Subtests</u>	<u>Episodic Memory Subtests</u>						
	N	Face Memory ^a	N	Object Memory ^{a,b}	N	Word Memory ^a	N
Emotion Recognition ^{a,b}	164	$r = .28, p = .001^{***}$	163	$r = -.03, p = .73$	163	$r = -.01, p = .90$	165
	71	$r = .38, p = .001^{***}$	72	$r = .07, p = .59$	70	$r = -.05, p = .68$	72
	93	$r = .26, p = .01^*$	91	$r = -.05, p = .67$	93	$r = .05, p = .62$	93
Emotion Differentiation ^a	166	$r = .32, p < .001^{***}$	163	$r = .16, p = .04^*$	163	$r = .25, p = .001^{***}$	165
	72	$r = .35, p = .003^{***}$	72	$r = .31, p = .01^*$	70	$r = .21, p = .08$	72
	94	$r = .27, p = .009^{**}$	91	$r = .04, p = .72$	93	$r = .25, p = .02^*$	93

All participants (166), MS patients (n = 72), Healthy Controls (n = 94)

^a Partial correlations controlling for response time

^b Partial correlations controlling for sex

Note. Sample size differs across tests because data were missing or deemed invalid for some patients.

* $p < .05$; ** $p < .01$; *** $p < .005$

6.1.3 Associations between Episodic Memory and Identification of Emotional Expression (Response Time)

Response time across all episodic memory and social cognition tasks (controlling for accuracy) were moderately to highly correlated collapsing across groups (r values ranging from .25 to .49; all p values $\leq .001$). As with the associations using the accuracy data, correlations were slightly stronger (though not statistically different) among the MS group relative to controls for all relationships except for two comparisons: Object Memory and Emotion Recognition (for which the strength of the correlation was similar between groups) and Word Memory and Emotion Differentiation (Table 5).

Table 5

Correlations (two-tailed) Between Z-score Response Time on Episodic Memory and Social Cognition Subtests in Patients with MS and HCs

<u>Social Cognition Subtests</u>	<u>Episodic Memory Subtests</u>						
	N	Face Memory ^a	N	Object Memory ^a	N	Word Memory ^a	N
Emotion Recognition ^a	164	$r = .43, p < .001^{***}$	163	$r = .41, p < .001^{***}$	163	$r = .49, p < .001^{***}$	165
	71	$r = .48, p < .001^{***}$	72	$r = .41, p < .001^{***}$	70	$r = .59, p < .001^{***}$	72
	93	$r = .31, p = .003^{***}$	91	$r = .42, p < .001^{***}$	93	$r = .28, p = .007^{**}$	93
Emotion Differentiation ^a	166	$r = .36, p < .001^{***}$	163	$r = .35, p < .001^{***}$	163	$r = .25, p = .001^{***}$	165
	72	$r = .40, p = .001^{***}$	72	$r = .36, p = .003^{***}$	70	$r = .20, p = .10$	72
	94	$r = .31, p = .003^{***}$	91	$r = .33, p = .001^{***}$	93	$r = .28, p = .006^{**}$	93

All participants (n = 166), MS patients (n = 72), Healthy Controls (n = 94)

^aPartial correlations controlling for accuracy

Note. Sample size differs across tests because data were missing or deemed invalid for some patients.

* $p < .05$; ** $p < .01$; *** $p < .005$

6.1.4 Between Group Comparisons on the Social Cognition and Episodic Memory Outcomes on the PCNB

Overall, the mean scores across all subtests examined and across both groups fell solidly within the average range. Accuracy and response time were compared separately for each group on each test (Tables 6 and 7). Overall, these two metrics were weakly correlated across all subtests (r values ranging from -.03 to .28 collapsing across groups, -.27 to .20 in the patient group, and -.07 to .26 among HCs) (Table 8).

6.1.5. Between Group Comparisons on the Social Cognition and Episodic Memory Outcomes on the PCNB (Accuracy)

Accuracy on the episodic memory and social cognition subtests is presented in Table 6 and depicted visually in Figure 8. After controlling for response time and sex where indicated, MS patients demonstrated significantly poorer performance on the Word Memory subtest ($p = .002$, $\eta^2_p = .06$) and the episodic memory domain score ($p < .001$, $\eta^2_p = .07$) relative to HCs. Overall, patients were less accurate than HCs on five of six subtests (though statistical significance was only reached for Word Memory) and were more accurate on one subtest (i.e., Emotion Recognition). The proportion of participants showing impairment on the social cognition and episodic memory subtests did not differ significantly between groups.

Accuracy on the Age Differentiation subtest was used as a control condition to ensure intact face processing. Results showed that six of 72 (8.3%) of MS patients and 7 of 94 (7.4%) of HCs were impaired on this subtest. In a sensitivity analysis, analyses for the emotion identification tasks were re-run after excluding all participants who were identified as impaired on accuracy for the Age Differentiation Test. Excluding these participants did not influence the results (Supplemental Table 3). Therefore, it was decided to retain these data points in

subsequent analyses as exclusion of these participants did not impact performance at the group level on the emotion tasks that were of primary interest.

As demonstrated in previous research within MS, the amygdala has a differential ability to recognize (i.e., accuracy) and respond to (i.e., reaction time; efficiency of responding) specific emotions such as surprise and negative emotions (e.g., anger and sadness). Therefore, as an exploratory analysis, we then probed whether the patients with MS would show a disproportionate deficit in their ability to recognize and respond to faces depicting fear, anger, and sadness relative to faces with happy and neutral expressions. Notably, Z-scores for the happy expression were not computed due to lack of variation caused by a ceiling effect. Contrary to previous research within MS, the patient group did not show a disproportionate deficit in their ability to recognize faces depicting various emotions, relative to controls (Table 9). Consistent with the literature, MS patients appear to respond significantly slower than HCs to faces depicting anger and sadness relative to faces with fearful and neutral expressions (Table 10).

Table 6

Comparison Between Patients with MS and HCs on Accuracy Z-scores and With Respect to the Proportion Showing Impairment on Episodic Memory and Social Cognition Subtests

Domain	Task	MS group		HC group		Group difference			Proportional analysis	
		<i>M</i> (<i>SE</i>)	<i>Impaired %</i> (<i>n/N</i>)	<i>M</i> (<i>SE</i>)	<i>Impaired %</i> (<i>n/N</i>)	<i>F</i>	<i>p</i>	<i>partial</i> η^2	<i>X</i> ²	<i>p</i>
Social Cognition ^{a,b}		-0.01 (0.08)		0.01 (0.07)		.01	.91	<.001		
	Age Differentiation ^a	-0.06 (0.11)	8.3 (6/72)	-0.01 (0.10)	7.4 (7/94)	.09	.77	.001	0.04	1.00
	Emotion Recognition ^{a,b}	0.28 (0.12)	0 (0/71)	-0.06 (0.09)	8.6 (8/93)	5.19	.02	.03	6.42	.01
	Emotion Differentiation ^a	-0.25 (0.11)	5.6 (4/72)	0.02 (0.10)	5.3 (5/94)	3.17	.08	.02	0.004	1.00
Episodic Memory ^a		-0.44 (0.09)		-0.02 (0.08)		12.64	<.001	.07		
	Face Memory ^a	-0.29 (0.12)	18.1 (13/72)	-0.02 (0.11)	8.8 (8/91)	2.92	.10	.02	3.07	.10
	Object Memory ^{a,b}	-0.23 (0.15)	18.6 (13/70)	0.04 (0.12)	8.6 (8/93)	1.94	.17	.01	3.54	.10
	Word Memory ^a	-0.60 (0.13)	22.2 (16/72)	-0.06 (0.12)	11.8 (11/93)	9.61	.002	.06	3.20	.09

Abbreviations: MS = multiple sclerosis; HC = healthy control

Note. *p*-values (ANCOVA) represent group differences after controlling for response time^a and sex^b (where indicated); Classification of impairment was based on a score falling 1.5 standard deviations below the mean; Sample size differs across tests because data were missing or deemed invalid for some patients.

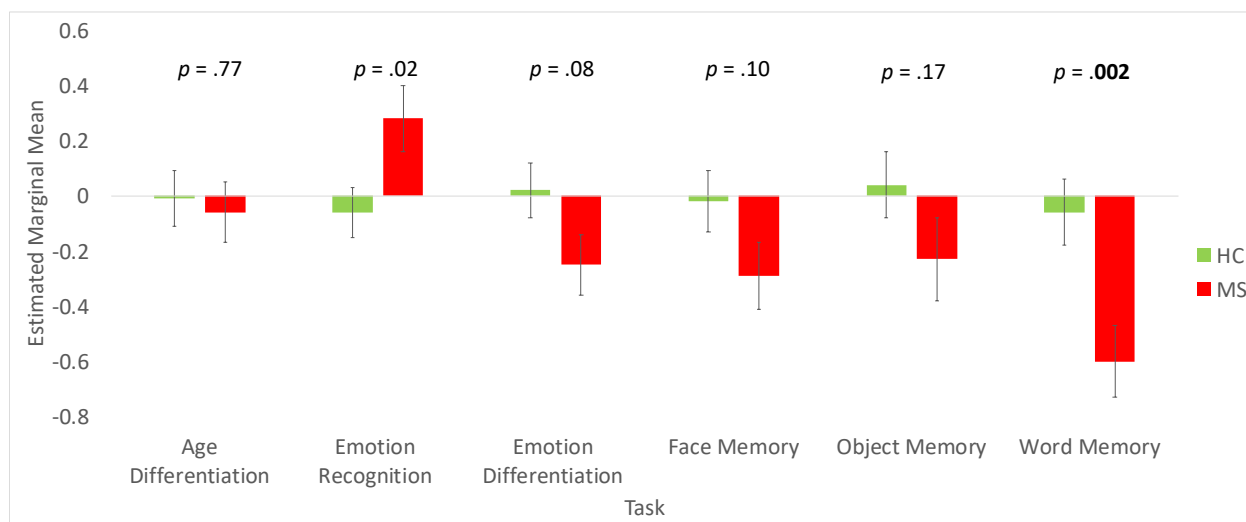


Figure 8. Accuracy Z-score for MS and HC Groups on Episodic Memory and Social Cognition Subtests.

Note. Error bars reflect ± 1 standard error.

6.1.6 Between Group Comparisons on the Social Cognition and Episodic Memory Outcomes on the PCNB (Response Time)

First, group differences on sensorimotor tasks (i.e., Motor Praxis (mouse control) and Finger Tapping (finger speed using the spacebar)) were examined as potential confounds. The sensorimotor tasks included in the PCNB are described briefly above (Table 2). Significant between group differences were observed on Finger Tapping ($p = .009$, $\eta^2_p = .04$), but not Motor Praxis.

Response time Z-scores on the episodic memory and social cognition subtests are presented in Table 7a and depicted visually in Figure 9. After controlling for accuracy, on average the MS group was slower to respond on all tasks, although significant group differences were only apparent on Emotion Recognition ($p = .009$, $\eta^2_p = .04$). The proportion of patients meeting criteria for impairment was higher on all social cognition and episodic memory subtests among the MS patients, although none reached statistical significance. Of note, 12 of 72 (16.7%)

of MS patients were impaired on the Word Memory subtest as compared with only five of 93 in the HC group ($X^2 = 5.60, p = .02$). Post-hoc analyses examining between group differences on response time were examined holding response time on the motor tasks (i.e., sensorimotor domain score) constant. The pattern of results remained the same (Table 7b) confirming that the deficits in response time on Emotion Recognition exist above and beyond motor slowness. Additionally, response time on the Word Memory test reached significance controlling for motor speed.

Table 7a
Response Time Z-scores and Impairment on Episodic Memory, Social Cognition, and Sensorimotor Subtests

Domain	Task	MS group		HC group		Group difference			Proportional analysis	
		<i>M(SE)</i>	<i>Impaired % (n/N)</i>	<i>M(SE)</i>	<i>Impaired % (n/N)</i>	<i>F</i>	<i>p</i>	<i>partial η²</i>	<i>X²</i>	<i>p</i>
Social Cognition ^a		-0.35 (0.11)		-0.001 (0.10)		5.86	.02	.04		
	Age Differentiation ^a	-0.37 (0.13)	16.7 (12/72)	-0.01 (0.11)	8.5 (8/94)	4.54	.04	.03	2.56	.15
	Emotion Recognition ^a	-0.49 (0.14)	15.5 (11/71)	0.00 (0.12)	6.5 (6/93)	6.90	.009	.04	3.54	.07
	Emotion Differentiation ^a	-0.20 (0.13)	12.5 (9/72)	0.02 (0.11)	7.4 (7/94)	1.63	.20	.01	1.20	.30
Sensorimotor		-0.13 (0.07)		0.00 (0.06)		1.89	.17	.01		
	Motor Praxis	0.29 (1.15)	0 (0/72)	0.00 (0.99)	2.1 (2/94)	3.10	.08	.02	1.55	.51
	Finger Tapping ^b	-0.39 (0.14)	15.7 (11/70)	0.06 (0.10)	8.5 (8/94)	6.96	.009	.04	2.03	.22
Episodic Memory ^a		-0.41 (0.11)		-0.07 (0.10)		4.97	.03	.03		
	Face Memory ^a	-0.38 (0.13)	16.7 (12/72)	-0.02 (0.12)	7.7 (7/91)	4.27	.04	.03	3.14	.09
	Object Memory ^a	-0.27 (0.13)	14.3 (10/70)	-0.11 (0.11)	6.5 (6/93)	0.76	.38	.01	2.77	.12
	Word Memory ^a	-0.46 (0.13)	16.7 (12/72)	-0.05 (0.11)	5.4 (5/93)	5.47	.02	.03	5.60	.02

Abbreviations: MS = multiple sclerosis; HC = healthy control

Note. *p*-values (ANCOVA) represent group differences after controlling for accuracy^a and sex^b (where indicated); Classification of impairment was based on a score falling 1.5 standard deviations below the mean; Sample size differs across tests because data were missing or deemed invalid for some patients.

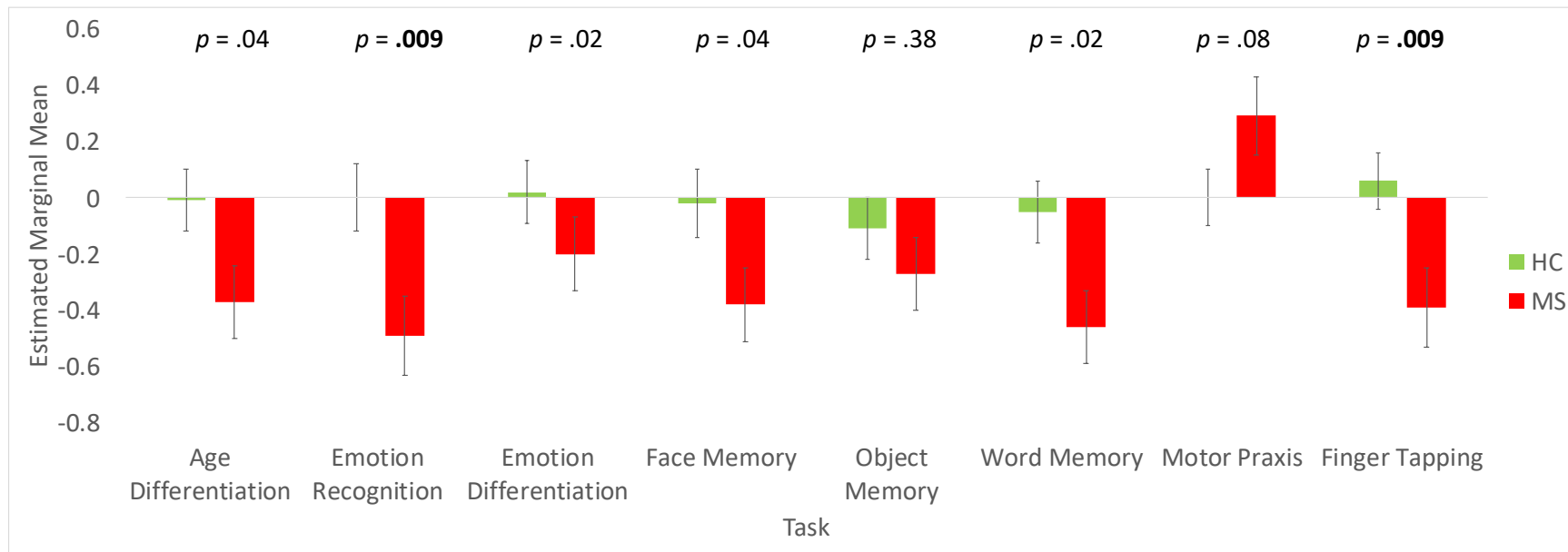


Figure 9. Response Time Z-score for MS and HC Groups on Episodic Memory, Social Cognition, and Sensorimotor Subtests.
Note. Error bars reflect ± 1 standard error.

Table 7b
Response Time Z-scores and Impairment on Episodic Memory and Social Cognition Subtests controlling for Motor Speed

Domain	Task	Group difference		
		<i>F</i>	<i>p</i>	<i>partial η²</i>
Social Cognition ^{a,b}		7.03	.009	.04
	Age Differentiation ^{a,b}	4.89	.03	.03
	Emotion Recognition ^{a,b}	8.52	.004	.05
	Emotion Differentiation ^{a,b}	1.89	.17	.01
Episodic Memory ^{a,b}		5.66	.02	.03
	Face Memory ^{a,b}	4.34	.04	.03
	Object Memory ^{a,b}	0.94	.33	.01
	Word Memory ^{a,b}	6.20	.01	.04

Note. *p*-values (ANCOVA) represent group differences after controlling for accuracy^a and motor speed (i.e., sensorimotor domain score)^b; Sample size differs across tests because data were missing or deemed invalid for some patients.

Table 8

Correlations (two-tailed) Between Z-score Accuracy and Response Time on Episodic Memory and Social Cognition Subtests in Patients with MS and HCs

<u>Accuracy</u>	N	<u>Response Time</u>				
		Emotion Recognition^c	Emotion Differentiation^c	Face Memory^c	Object Memory^c	Word Memory^c
Emotion Recognition ^{a,b}	164	r = -.04, p = .61	-	-	-	-
	71	r = -.19, p = .11	-	-	-	-
	93	r = .13, p = .21	-	-	-	-
Emotion Differentiation ^a	166	-	r = -.15, p = .05	-	-	-
	72	-	r = -.27, p = .02*	-	-	-
	94	-	r = -.07, p = .51	-	-	-
Face Memory ^a	163	-	-	r = .14, p = .09	-	-
	72	-	-	r = .17, p = .33	-	-
	91	-	-	r = .11, p = .32	-	-
Object Memory ^{a,b}	163	-	-	-	r = -.03, p = .70	-
	70	-	-	-	r = -.05, p = .71	-
	93	-	-	-	r = -.04, p = .73	-
Word Memory ^a	165	-	-	-	-	r = .28, p < .001***
	72	-	-	-	-	r = .20, p = .10
	93	-	-	-	-	r = .26, p = .01*

All participants (n = 166), MS patients (n = 72), Healthy Controls (n = 94)

^a Partial correlations controlling for response time

^b Partial correlations controlling for sex

^c Partial correlations controlling for accuracy

Note: Sample size differs across tests because data were missing or deemed invalid for some patients.

* p < .05; ** p < .01; *** p < .005

Table 9
Estimated Marginal Means (Standard Error) for Comparison of MS and HCs on Z-scores of Accuracy by Emotion

Subtest	Emotion	MS	HC	<i>F</i>	<i>p</i>	partial η^2
		<i>M (SE)</i>	<i>M (SE)</i>			
Emotion Recognition						
	Angry ^a	0.08 (0.11)	-0.03 (0.09)	0.58	.45	.004
	Scared ^{a,b}	0.15 (0.13)	-0.05 (0.10)	1.50	.22	.01
	Sad ^a	0.22 (0.10)	-0.02 (0.09)	2.88	.09	.02
	Happy [†]	N/A	N/A	-	-	-
	No Expression ^a	0.23 (0.10)	0.02 (0.08)	2.73	.10	.02
Emotion Differentiation						
	Angry ^a	-0.10 (0.12)	0.01 (0.10)	0.45	.50	.003
	Scared ^a	-0.28 (0.11)	0.01 (0.10)	3.86	.05	.02
	Sad ^a	-0.24 (0.12)	0.01 (0.10)	2.62	.11	.02
	Happy ^{a,b}	-0.13 (0.12)	-0.04 (0.10)	0.33	.56	.002

Abbreviations: MS = multiple sclerosis; HC = healthy control

Note. *p*-values (ANCOVA) represent group differences after controlling for response time^a and sex^b (where indicated); Sample size differs across tests because data were missing or deemed invalid for some patients.

[†]Norms for Emotion Recognition Happy could not be computed due to ceiling effect (i.e., lack of variation)

Table 10
Estimated Marginal Means (Standard Error) for Comparison of MS and HCs on Z-scores of Response Time by Emotion

Subtest	Emotion	MS	HC	<i>F</i>	<i>p</i>	partial η^2
		<i>M (SE)</i>	<i>M (SE)</i>			
Emotion Recognition						
	Angry ^a	-0.50 (0.13)	0.00 (0.11)	8.61	.004	.05
	Scared ^a	-0.27 (0.13)	0.01 (0.12)	3.05	.12	.02
	Sad ^a	-0.38 (0.12)	0.04 (0.10)	7.52	.007	.05
	Happy [†]	N/A	N/A	-	-	-
	No Expression ^a	-0.09 (0.12)	0.03 (0.10)	0.56	.46	.003
Emotion Differentiation						
	Angry ^a	-0.15 (0.12)	0.01 (0.11)	0.95	.33	.01
	Scared ^a	-0.26 (0.14)	0.01 (0.12)	3.31	.13	.01
	Sad ^a	-0.11 (0.11)	0.04 (0.10)	0.95	.33	.01
	Happy ^a	-0.04 (0.11)	0.01 (0.10)	0.11	.74	.001

Abbreviations: MS = multiple sclerosis; HC = healthy control

Note. *p*-values (ANCOVA) represent group differences after controlling for accuracy^a (where indicated); Sample size differs across tests because data were missing or deemed invalid for some patients.

[†]Norms for Emotion Recognition Happy could not be computed due to ceiling effect (i.e., lack of variation)

6.1.7 Clinical Predictors of Cognitive Outcomes

There were no significant associations between clinical characteristics of the MS group and performance on tasks that was identified as being poorer in the MS group relative to HCs (i.e., Word Memory accuracy and Emotion Recognition response time).

6.2 Magnetic Resonance Imaging (MRI) Results

6.2.1 Sample Characteristics

In total, MRI data were analyzed for 46 of the 72 (63.9%) MS patients and 42 of the 94 (44.7%) healthy controls (data for some participants were not yet available at the writing of this thesis). Participants were only included in MRI analyses if they were at least 15 years of age at the time of scan (this decision was made due to concerns about the brain normalization procedure (SIENAx) possibly being affected by smaller head size, which in turn could impact the brain volumetric outcomes in the current analyses). Demographic and disease-related characteristics of the sample are reported in Table 11. Patients included in the MRI subsample did not differ significantly from HCs in the subsample with respect to age, sex, level of education, years of parental education or emotional distress. MS patients were scanned at variable intervals from disease onset (mean = 4 years; SD = 4), with 18 of 46 (39.1%) having a disease duration greater than five years. Age at MS onset ranged from 5.9 to 17.9 years ($M = 14.99$, $SD = 2.39$), and 6 of 46 (13.0%) had their first attack prior to age 12 years. MS patients had a median EDSS score of 1.5 (range = 0-6.5) and 35 of 46 (76.1%) patients were receiving disease-modifying treatment at the time of the assessment.

Table 11
Demographic and Clinical Characteristics of MS and HCs ≥ 15 Years at Scan

Characteristic	MS (n = 46)	HC (n = 42)	<i>p</i>
	M(SD) / N(%)	M(SD) / N(%)	
Age at scan (years, range)	19.0 (15-27)	19.8 (15-28)	.32
Sex (female, %)	33 (71.7)	31 (73.8)	.83
Participant education (years)	12.1 (3.0)	13.9 (3.0)	.01
Parental education			
Father's education (years)	12.5 (5.0)	14.3 (4.6)	.10
Mother's education (years)	13.8 (3.0)	14.5 (4.2)	.39
Emotional Distress [†]	10.1 (7.1)	9.15	.52
EDSS (median, range)	1.50 (0-6.5)	-	-
Age at disease onset (years)	15.0 (2.4)	-	-
DMT (N/Y, %)	11/35 (76.1)	-	-
Disease Duration (months)	51.7 (47.1)	-	-

Abbreviations: MS = multiple sclerosis; HC = healthy control; EDSS = Expanded Disability Status Scale; DMT = Disease Modifying Therapy

[†]Emotional Distress data not available for 1 patient and 8 HCs.

6.2.2 MRI Outcomes

MRI analysis, in line with our hypotheses, revealed that total regional brain volumes of the hippocampus, amygdala, and thalamus (all corrected for skull size using SIENAx) differed significantly between the two groups, with the MS group displaying reduced volumes compared to the HC group (Table 12; Figure 10). Normalized total brain volume was also significantly smaller among patients versus HCs. Normalized grey matter volume was significant at trend levels ($p = .03$) with the MS group having lower grey matter volumes than HCs. Additionally,

although normalized white matter volume did not differ significantly between groups, the means are in the anticipated direction with the MS group having slightly smaller volume. Brain regions in the left and right hippocampus ($r = .85, p < .001$), amygdala ($r = .86, p < .001$), and thalamus ($r = .80, p < .01$), were all highly correlated (collapsing across groups). Thus, total bilateral volumes were used in all analyses.

Table 12
Structural MRI metrics (mm³) for MS and HCs ≥ 15 Years at Scan

MRI metric	MS (n = 46)	HC (n = 42)			
	M(SD)	M(SD)	<i>F</i>	<i>p</i>	<i>partial η^2</i>
Hippocampal volume					
Total	9003.22 (838.05)	9617.74 (741.51)	13.17	<.001	.13
Left	4423.97 (445.85)	4720.23 (352.65)	11.80	.001	.12
Right	4579.25 (424.43)	4897.51 (415.02)	12.61	.001	.13
Amygdala volume					
Total	4510.33 (423.40)	4728.22 (334.45)	7.15	.009	.08
Left	2216.62 (224.27)	2317.29 (167.07)	5.39	.02	.06
Right	2291.72 (214.30)	2411.94 (181.41)	7.99	.006	.09
Thalamic volume					
Total	19524.84 (2256.68)	21934.03 (1923.20)	28.78	<.001	.25
Left	9961.09 (1157.29)	11142.85 (1020.01)	25.62	<.001	.23
Right	9563.76 (1224.08)	10791.18 (984.71)	26.54	<.001	.24
Normalized Grey Matter volume	844335.9 (52322.46)	867553.5 (47863.01)	4.68	.03	.05
Normalized White Matter volume	714744.31 (44557.13)	730302.4 (40989.52)	2.89	.09	.03
Normalized Total Brain volume	1559337 (61201.72)	1596860 (68728.77)	7.34	.008	.08

Note. Brain volumes normalized with SIENAx scaling

†MRI data not available for 21 MS patients and 33 HCs.



Figure 10. Regional Structural MRI Metrics (mm^3) for MS and HC Groups. Note. Error bars reflect ± 1 standard deviation.

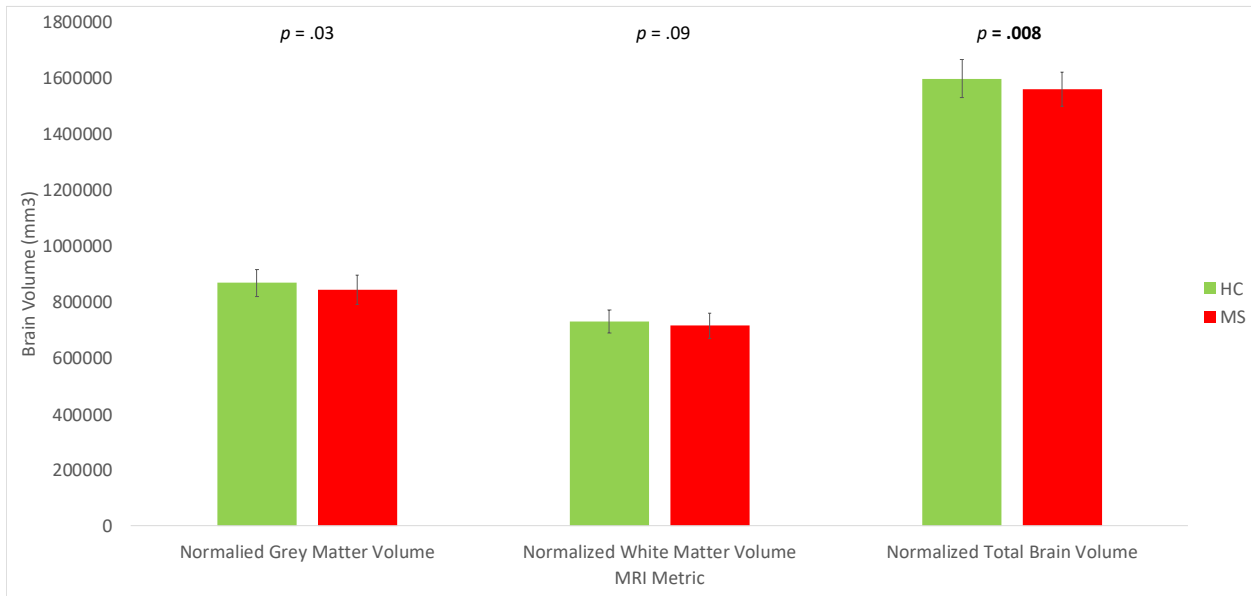


Figure 11. Normalized Grey Matter, White Matter, and Total Brain Volume MRI Metrics (mm^3) for MS and HC Groups. Note. Error bars reflect ± 1 standard deviation.

6.2.3 Clinical Predictors of Brain Volume

Within the MS group, EDSS score was correlated with both total amygdala ($r = .29, p < .05$) and right amygdala ($r = .31, p < .05$) volume. No correlations were observed between age at disease onset or disease duration with regional or total brain volume.

6.3 Structure-Function Relationships

6.3.1. Total and Lateralized Regional Brain Volumes and Cognitive Outcomes

Hippocampal, amygdala, and thalamic volumes were not significantly associated with accuracy on Word Memory collapsing across groups (Table 13), though trends were observed with the total ($r = .21, p = .05$) and left thalamus ($r = .23, p = .03$). In contrast, higher total ($r = .32, p = .003$) and left thalamic volume ($r = .34, p = .001$) was associated with faster response time on Emotion Recognition collapsing across groups. Trends were also noted between the right thalamus ($r = .27, p = .01$), total hippocampus ($r = .22, p = .05$), and the left hippocampus ($r = .23, p = .03$) with faster response time on Emotion Recognition collapsing across groups (Table 13). The relationship between total thalamus and Emotion Recognition are presented by group in Figures 12 and 13.

Finally, given the near significant association between the hippocampus and faster response time on Emotion Recognition ($p = .03$), we used multiple linear regression to examine whether total hippocampal volume accounts for additional variance in response time on Emotion Recognition after controlling for accuracy on this task, as well as total volume of the thalamus and brain (Table 14). This multiple linear regression predicting response time on the Emotion Recognition test revealed that hippocampal volume ($\beta = 0.06, 95\% \text{ CI } [-0.39, 0.50], p = .80$) did not account for any additional variance in the model after controlling for accuracy ($\beta = -0.21,$

95% CI [-0.53, 0.11], $p = .19$), volume of the total thalamus ($\beta = 0.19$, 95% CI [0.02, 0.35], $p = .03$), and total brain volume ($\beta = -0.002$, 95% CI [-0.01, 0.003], $p = .41$). These set of variables explained 12% of variance in response time on Emotion Recognition, $R^2 = 0.12$, $F(4,83) = 2.89$, $p = .03$.

Table 13
Correlations (two-tailed) Between MRI and Z-score Accuracy on Word Memory and Z-score Response time on Emotion Recognition for MS and HCs ≥ 15 Years at Scan

Outcome	N	MRI Metric	Pearson r Correlations		
			Total	Left	Right
Word Memory Accuracy ^a	87				
	46				
	42				
		Hippocampus	.11 .04 .04	.08 -.02 -.02	.14 .10 -.05
		Amygdala	.09 .11 -.16	.10 .12 -.14	.08 .09 -.16
		Thalamus	.21 .06 .13	.22 .07 .14	.19 .05 .10
		Total brain	.19 .20 .02	- - -	- - -
Emotion Recognition Response Time ^a	88				
	46				
	42				
		Hippocampus	.23* .18 .13	.23* .19 .11	.22 .16 .14
		Amygdala	.20 .15 .16	.20 .16 .15	.19 .12 .15
		Thalamus	.32*** .26 .09	.34*** .24 .21	.27* .25 -.05
		Total brain	.12 -.01 -.10	- - -	- - -

All participants (n = 88), MS patients (n = 46), Healthy Controls (n = 42)

^aPartial correlations controlling for response time

Note: Sample size differs across tests because data were missing or deemed invalid for some patients.

* $p < .05$; ** $p < .01$; *** $p < .005$

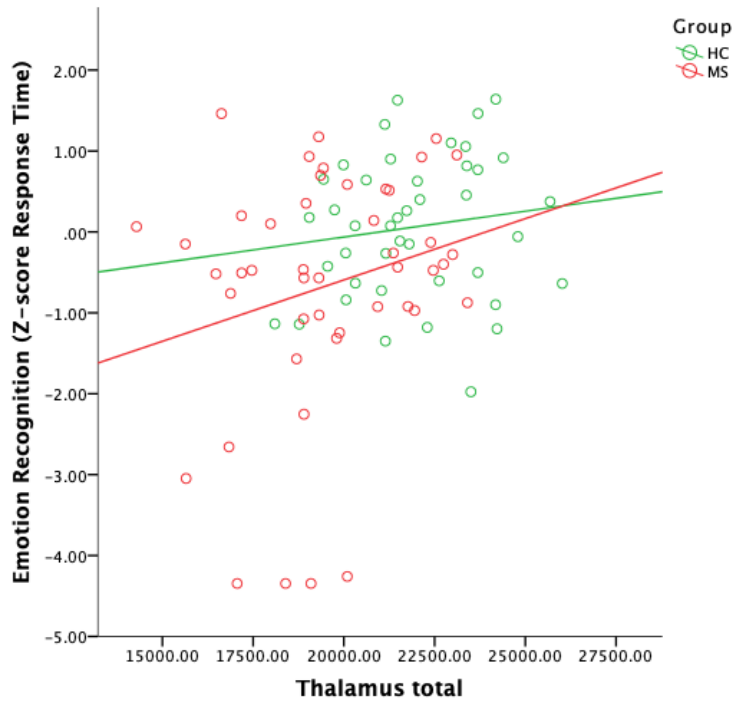


Figure 12. Scatterplot of Emotion Recognition Response Time Z-score with Total Thalamic Volume by Group.

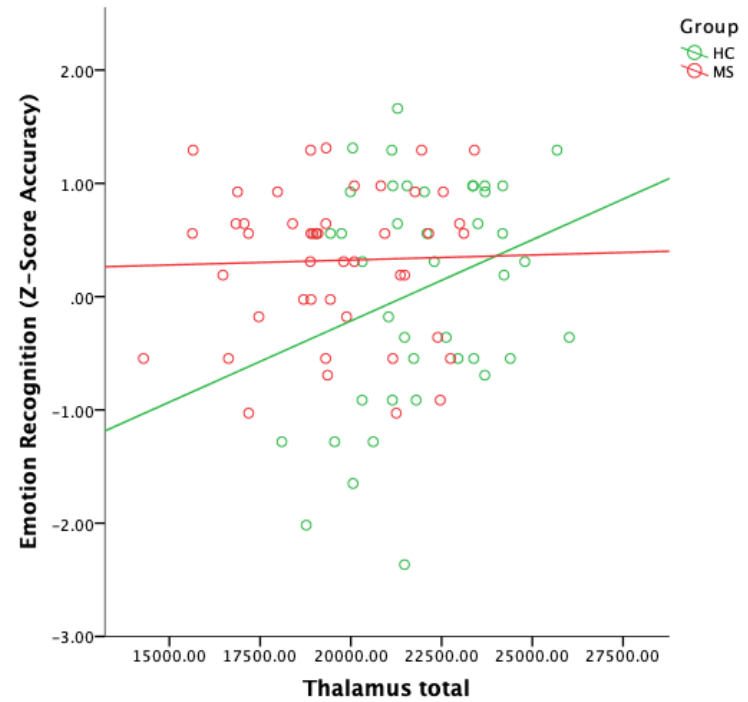


Figure 13. Scatterplot of Emotion Recognition Accuracy Z-score with Total Thalamic Volume by Group.

Table 14
 Multiple Linear Regression Predicting Response Time on the Emotion Recognition Test from Accuracy, and MRI Volumetrics of the Total Hippocampus, Thalamus, and Brain Volume

Model	B (cm ³)	SE	<i>p</i>	95% Confidence Interval for Mean		R ²
				Lower	Upper	
<i>Emotion Recognition</i>						
<i>(Response Time)</i>						
Intercept			.03			0.12
Accuracy	-0.21	0.16	.19	-0.53	0.11	
Total Hippocampus	0.06	0.22	.80	-0.39	0.50	
Total Thalamus	0.19	0.08	.03	0.02	0.35	
Total Brain Volume	-0.002	0.002	.41	-0.01	0.003	

Note: MRI values were rescaled to cm³ (from mm³) to yield interpretable unstandardized Beta coefficients.

7.0 Discussion

The purpose of this research was to clarify the association between episodic memory and social cognition (i.e., identification of emotional expression) using relevant subtests from the PCNB. We also investigated whether patients with pediatric-onset MS differed from healthy controls on 1) accuracy and response time on these tasks and 2) the volume of brain structures thought to be affiliated with these functions. Broadly, the results provide evidence of a relationship between memory and identification of emotional expression. The findings also suggest that patients have smaller total and regional brain volume (i.e., hippocampus, amygdala, and thalamus). Despite the reduction in total and regional brain volumes in the MS group, only the thalamus was associated with response time on the Emotion Recognition task. The following sections will consider patient characteristics, overall findings and interpretation of the findings in the context of the current literature, and limitations of the present study as well as future directions.

7.1 Findings from the Present Study

7.1.1 Sample Characteristics

Our patient group was similar to some previous pediatric-onset MS samples in terms of the female-to-male ratio, disease duration, presence of fatigue, and level of disability (Till et al. 2011; Fuentes et al. 2012; Green et al. 2018). Also comparable to these samples, our patients did not differ on a self-report questionnaire assessing symptoms of anxiety and depression. Additionally, patients and controls did not differ from each other with respect to sex, level of education, and socioeconomic status as measured by years of parental education. Hence, the conclusions of the current study are felt to be generalizable in the context of pediatric-onset MS.

7.1.2 Cognitive Outcomes

The first aim of this research was to assess whether there is an association between memory and identification of emotional expression. Accuracy on the Face Memory subtest was positively correlated with performance on the Emotion Recognition and Emotion Differentiation tasks collapsing across groups. It may be that accuracy on the Face Memory subtest demonstrated the strongest correlation with accuracy on the emotion tasks (versus Object and Word Memory with the emotion tasks) given the common face processing aspect. In addition to this finding and in line with our hypothesis, slower response time across all tasks was also positively associated with response time on the aforementioned social cognition tasks collapsing across groups. This is a novel finding given that no studies to our knowledge have directly examined the correlation between memory and facial emotion identification abilities in patients with pediatric-onset MS. Though a similar recent study by our lab (Green et al. 2018), from which we based the present research, showed independent relationships for patients (but not HCs) between Memory for Stories and Abstract Visual Memory on the TOMAL-2 (Reynolds & Voress, 2007) with Functional Communication on the Behaviour Assessment System for Children, 2nd Edition: Parent Rating Scale (BASC-2 PRS; Reynolds & Kamphaus, 2004). Green and colleagues (2018) also found significant associations between reduced amygdala volume with Abstract Visual Memory, Functional Communication, and Social Skills (also measured by the BASC-2). Again, these relationships were only evident for patients.

In our study, we also examined whether the performance of pediatric-onset MS patients differed from healthy controls on episodic memory and identification of emotional expression tasks. In line with previous research (MacAllister et al. 2005; Amato et al. 2008; Till et al. 2013), our study identified that patients with pediatric-onset MS experience greater challenges with

verbal memory versus visual memory. Specifically, our patient group performed significantly less accurately than controls on Word Memory after controlling for response time. No significant differences were observed between groups on the visual memory tasks (i.e., Face and Object Memory), although the mean scores of the patients were lower than the mean scores of the HCs on both visual memory subtests.

Prior studies have reported a deficit in remembering word lists in individuals with pediatric-onset MS, although researchers of these studies used immediate and delayed recall tasks (Amato et al. 2008; Till et al. 2013; MacAllister et al. 2005; Fuentes et al. 2012; MacAllister et al. 2007; Smerbeck et al. 2011). In contrast to the methodology employed in previous research, we used an immediate recognition word task and observed deficits which may suggest a deficit at the encoding stage for verbal information. However, deficiency with word recall cannot be ruled out as this was not assessed.

Interestingly, we also observed that patients with pediatric-onset MS were better able to recognize emotional states from facial expressions (on the Emotion Recognition subtest) than HCs after controlling for accuracy, however, they needed significantly more time to do so ($p = .009$). Patients did not differ from controls on accuracy or response time when asked to identify which of two faces was showing a particular emotion to a greater extreme (i.e., Emotion Differentiation). Social cognition has only been examined in a few studies of adults with MS (Pinto et al. 2012; see meta-analysis by Cotter et al. 2016; Henry et al. 2017) and one group of patients with pediatric-onset MS (Charvet et al. 2014). Charvet and colleagues used higher-level ToM tasks which require inferential and deductive reasoning. The Emotion Recognition task administered in our research is easier in comparison to that employed by the other researchers. Although the Emotion Recognition test we used has an open-ended response format that permits

participants to adjust their response speed for improved accuracy, this is the only subtest included in our analyses where the instructions state that participants should respond as quickly and as accurately as possible. As such, a speed-accuracy trade-off is hypothesized whereby HCs were less accurate on this task as they decreased their response latency and MS patients were more accurate and significantly slower. Alternately, the discrepancy between results when looking at accuracy and response time on the Emotion Recognition test may suggest that response time is more sensitive to MS pathology than accuracy.

Overall, the episodic memory and social cognitive performance of MS patients across all subtests examined on the PCNB fell within the average range. Relative to healthy controls, however, we observed lower mean scores among patients on all tests for both accuracy and response time (with the exception of accuracy on Emotion Recognition where patients outperformed controls). The groups differed significantly on Word Memory (accuracy) and Emotion Recognition (response time). Despite small effect sizes at the group level, our findings do have clinical relevance at the individual level. A higher proportion (although not statistically significant) of patients in the MS group (relative to HCs) showed impaired performance on most tasks (excluding accuracy on Emotion Recognition (again highlighting a compromise between speed and accuracy on this test) and the Motor Praxis test) for both accuracy and response time. Functional implications of our findings are discussed further below.

There were no significant associations between clinical characteristics of the MS group and performance on tasks that were identified as being significantly poorer in the MS group relative to HCs. Earlier identification and diagnosis of the disease in recent years, access to quality care at specialized clinics, and improvements in disease modifying therapies may explain, at least in part, why most patients are not impaired. Furthermore, the majority (73.6%) of our

sample was recruited from urban, Canadian pediatric health-care centres where several medical services are covered by provincial health care plans. At this time, there is insufficient evidence to suggest that the plasticity of the young brain can compensate for the impact of disease in this population (Till et al., 2011; Charvet et al., 2014; Ghezzi et al., 2017). There is some indication that plasticity may occur early in the disease for some individuals, but then reach a threshold where the compensatory networks cannot meet demands and impairment manifests. Thus, longitudinal research is needed to examine the trajectory of episodic memory and social cognitive performance as time from disease onset increases. On average, our patients were relatively early in their disease course ($M = 3.61$ years).

7.1.3 MRI Outcomes

A third goal of this research was to assess whether patients with pediatric-onset MS have smaller hippocampal, amygdala, and thalamic volume in comparison to healthy controls. We also examined normalized total brain, grey matter, and white matter volumes.

Consistent with previous imaging research in this population (Mesaros et al., 2008; Till et al., 2011; Kerbrat et al., 2012; Green et al., 2018; Fuentes et al., 2012), normalized total brain and thalamic volumes differed significantly between the two groups, with the MS group displaying smaller volumes compared to HCs. As previously mentioned, MRI studies in pediatric-onset MS have yielded mixed findings regarding volume of limbic structures. Our research is aligned with Rocca and colleagues (2016) in that we also found that patients have smaller hippocampal volumes and Fuentes and colleagues (2012) in that we also noted that patients had smaller amygdala volumes than HCs. Importantly, the effect size was disproportionately larger for the thalamus compared with the amygdala and hippocampus suggesting (and in line with previous studies) that the thalamus is particularly susceptible to the

disease with relative sparing of the other structures we examined. Longitudinal studies are needed to determine whether the reduction in brain volume for patients indicates atrophy or reflects lack of age-expected brain development.

7.1.4 Structure-Function Relationships

Brain-behaviour relationships were only examined for tasks that demonstrated significant between group differences. Contrary to our hypothesis, the hippocampus and amygdala independently did not show any significant associations with accuracy on the Word Memory test or response time on the Emotion Recognition test. The thalamus was most robustly associated with response time on the Emotion Recognition task. A near-significant association ($p = .03$) was observed between the hippocampus and response time on the Emotion Recognition task. Based on correlations alone, it is hard to disentangle whether the hippocampus is actually related to performance on this task or if the thalamus (due to its diffuse connectivity with structures of the limbic system and entire cerebral cortex) is actually driving the relationship (Mesaros et al., 2008; Hwang, et al., 2017). Therefore, we examined whether total hippocampal volume accounts for any additional variance after controlling for accuracy on the Emotion Recognition task, total thalamic volume, and total brain volume. This multiple linear regression predicting response time on the Emotion Recognition task revealed that total thalamic volume ($\beta = 0.19, p = .03$) was a significant predictor, whereas volume of the total hippocampus ($\beta = 0.06, p = .80$) did not account for any additional variance in the model, $R^2 = 0.12, p = .03$.

7.2 Methodological Considerations

The present research acts as a starting point to describe aspects of cognition that have not been explored in-depth or at all (i.e., identification of emotional expression) in young people

with MS. Our study goes beyond commenting on significant relationships and describes the pattern of findings which suggest that overall, patients with MS demonstrate challenges with aspects of both episodic memory and social cognition, with the greatest difficulties observed in Word Memory and Emotion Recognition tasks.

Currently, the Symbol Digit Modalities Test (SDMT) is the gold standard screening measure for cognitive impairment in pediatric-onset MS due to its quick administration and high sensitivity (Charvet et al., 2014). However, it can be argued that the PCNB may be a tool with greater specificity. When deciding whether to use the SDMT or PCNB, one must consider clinical feasibility as the PCNB requires approximately one-hour to complete in the presence of a trained assessor, versus the 90-second SDMT which can be administered by a neurologist during a medical appointment. An advantage of the PCNB over the SDMT is the evaluation of multiple domains of functioning versus one domain which may or may not capture challenges that the patient is experiencing. The PCNB also has the capacity for separate measurement of speed and accuracy of performance, unlike the SDMT and many other commonly used neuropsychological assessment tools. Considering both when assessing patients with pediatric-onset MS is important, as our results suggest that patients have specific deficits in response time that exist independently of accuracy and vice-versa. For example, if a patient is found to perform within normal limits on the Affect Recognition subtest of A Developmental Neuropsychological Assessment, 2nd edition (NEPSY-II; Korkman, Kirk, & Kemp, 2007), based on our findings, we cannot conclude that they do not have challenges with identification of emotional expression. Creating tests for future versions of neuropsychological assessment tools that assess both accuracy and response time would be optimal, similar to the utility of a d-prime score for task performance which takes into account the hit rate (i.e., proportion of trials where a participant

responds to a stimulus) and false alarm rate (i.e., proportion of trials where a participant responds when the stimulus is not present). Assessment measures that provide a score that considers both accuracy and response time on a given task may be helpful in evaluating a speed-accuracy trade-off and results are likely to also be more generalizable to performance in the real-world.

Experimenters have long been interested in understanding the relationship between speed and accuracy. Although researchers have developed methods that consider these two important metrics simultaneously, many cognitive psychology studies still use either response time or accuracy (the latter is primarily used in memory research) as the primary outcome (Voss et al., 2013). Some researchers have used binning, whereby data is organized into “bins” by response time. Other researchers use the inverse efficiency score (IES; Townsend & Ashby, 1983) which is a proportion of response time to errors. The IES has been used in emotion recognition research (e.g., Rossignol et al., 2009) and according to the researchers, provided more meaningful data than response time alone. We suggest that an overall performance measure will be helpful in examining the influence of latency on accuracy in pediatric-onset MS, versus examining the independent outcomes for these constructs (Heitz, 2014; Hughes et al., 2014).

Despite its strengths, we are not advocating that the PCNB replace the use of traditional individualized neuropsychological assessment for patients reporting cognitive and/or academic challenges. This point cannot be minimized, particularly given the limitation of the memory tests that do not assess immediate or delayed recall of visual or verbal information which may be the most at-risk memory functions in MS (MacAllister et al., 2005; Amato et al., 2008; Amato et al., 2010). Rather, the PCNB likely has the most value as a screener to identify aspects of cognition that may be problematic at the individual-level, which can then be followed-up with traditional neuropsychological assessments for those particular domains. Despite the sensitivity of the

Motor Praxis test (i.e., ability of the test to successfully differentiate patients and HCs), we also suggest that the PCNB be supplemented by higher-level visuomotor integration tasks (e.g., Beery-Buktenica Developmental Test of Visual-Motor Integration 6th edition; Beery et al., 2010) and physical tasks of fine motor dexterity (e.g., 9-Hole Peg Test; Mathiowetz et al., 1985). Performance on these tasks have been shown to be impacted early on in pediatric-onset MS (Julian et al., 2013). Moreover, dual-tasks that simultaneously assess executive-control/motor planning and fine-motor function has utility in better understanding motor speed-accuracy trade-offs which in-turn may better reflect day-to-day functioning in this domain.

7.3 Relevance

At present, there is no cure for MS. It is therefore necessary to strive to continue to understand the cognitive and psychosocial sequelae of the disease. Reduced processing speed is a common consequence of pediatric-onset MS although the role of reduced processing speed in memory function and social cognition had not been explored until this study to our knowledge. Our results provide important big picture insights into challenges that may be faced by children and youth in relation to episodic memory and identification of emotional expression. We believe that this is the first study to examine the latter in young people with MS.

We identified that patients with pediatric-onset MS do experience challenges with aspects of episodic memory and identification of emotional expression that may have clinically relevant implications. In particular, slowed identification of emotional expression may be problematic in social interactions. Prompt and accurate emotion identification is vital for successful social interactions and relationships as faces provide us with information about what others may be thinking or feeling (Charvet et al., 2014). Studies that have demonstrated deficits in identification of emotional expression in adult MS note that it is associated with reduced psychosocial quality

of life (Phillips et al., 2011; Cotter et al., 2016; Bora, Özakbaş, Velakoulis & Walterfang, 2016). In children with MS, challenges which emotion recognition may also lead to restricted opportunities for socialization and diminished quality of life (Charvet et al., 2014; Cotter et al., 2016; Bora et al., 2016). This is particularly concerning in a pediatric population given the heightened importance of socialization in adolescence, the developmental transition between childhood and adulthood (Smetana et al., 2015).

In addition, social cognitive dysfunction may combine with other consequences of MS that were not examined in this particular study (e.g., fatigue and frequent medically-related absences from school) to further disrupt social interactions and/or willingness to engage in relationships (Green et al., 2018). This may exacerbate feelings of sadness and insecurity that have been endorsed by pediatric MS patients in previous work (Till et al., 2012). Understanding memory and social cognitive challenges in this population is important so that targeted interventions and recommendations can be developed to support patients with MS.

7.4 Limitations and Future Directions

Our research is limited by its cross-sectional, correlational design. Longitudinal studies have the capacity to examine trajectories of cognitive challenges and causality (i.e., does neuropathology caused by the disease lead to cognitive impairment). This could not be accomplished with our design. Future studies in pediatric-onset MS are needed to explore whether brain volumes continue to decrease over time and if this can account for the documented decline in cognitive capacity with longer disease duration (Amato et al., 2010; Till et al., 2013).

Additionally, there is a potential concern regarding scaling with SIENAx in a developing cohort given that the images are registered to an adult template. Despite concerns, this approach has been used in previously published cross-sectional work (Kerbrat et al., 2012; Fuentes et al.,

2012). Therefore, by using SIENAx we are able to place our findings obtained from volumetric analyses in the context of these prior results. We excluded participants less than 15 years of age from our MRI analyses to avoid as much as possible the confound of brain growth.

Another limitation of this study is that proper comparison to individuals of the same age was not feasible. Z-scores were created based on our sample of HCs and age effects were accounted for by the use of three sets of norms (i.e., 8-13 years, 14-17 years and >18 years). This method was deemed more appropriate than comparison to the American PCNB normative sample, given significant differences in parental education (a proxy for socioeconomic status) between our participants and the normative sample. A final limitation is in the uniform use of pediatric versions of the PCNB tasks despite our recruitment of participants over the age of 18. This may have led to ceiling effects (most evident for both patients and controls on Word Memory) for older individuals. An adult version of the PCNB is available and may be more appropriate for use in clinical settings.

Finally, while we considered the impact of total and lateralized volumes of the entire hippocampus and amygdala, this study did not assess the numerous and heterogeneous subfields and nuclei of these brain structures that have to been shown to have different functions for specific aspects of emotion processing and memory (e.g., the lateral nucleus of the amygdala participates in encoding and storage of affective memory) (Mueller et al., 2011; Erlich et al., 2012). As well, previous pathological studies in adult MS have seen differential impact of the disease on hippocampal subfields with relative sparing of CA4 and the subiculum (Papadopoulos, 2009). Future studies should segment the hippocampus and amygdala and also utilize functional imaging modalities (e.g., electroencephalography, functional magnetic resonance imaging) in order to visualize brain activity and see if there are differences in the

recruitment of networks between patients with pediatric-onset MS and HCs when completing subtests from the PCNB.

7.5 Conclusions

We explored the relationship between performance on tests of episodic memory and identification of emotional expression using the PCNB in a sample of patients with pediatric-onset MS and HCs. Qualitative brain volumetric measures were used to elucidate the relationship between neuropathology and cognitive performance. In summary, our findings revealed that accuracy on the Face Memory subtest was correlated with performance on all social cognition tasks collapsing across groups. Slower response time across all episodic memory tasks was associated with slower response time on all social cognition tasks collapsing across groups. Our sample of pediatric-onset MS patients demonstrated lower accuracy on the Word Memory task, slower response time on the Emotion Recognition task, and significantly reduced volume of the hippocampus, amygdala, and thalamus as well as total brain volume relative to HCs. Despite group differences in total and regional brain volume, only thalamic volume appeared to show a moderate positive association with response time on the Emotion Recognition test.

The PCNB has been used in previous studies to detect cognitive impairment in youth with psychotic symptoms, mood disorders, herpes simplex virus, type 1, and the hepatitis C virus (Gur et al., 2014; Merikangas et al., 2017; Thomas et al., 2013; Ibrahim et al., 2016). Our data validates that the PCNB is also sensitive to episodic memory and social cognitive impairment in pediatric-onset MS as it was able to successfully differentiate the performance of patients and HCs. Further understanding of the temporal progression for atrophy of the hippocampus, amygdala, and thalamus, as well as their consequences for memory and social cognitive dysfunction in pediatric-onset MS, necessitates longitudinal investigation.

8.0 References

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9.0 APPENDIX. Supplemental Tables

Supplemental Table 1
PCNB Subtests in Order of Appearance

Subtest	Domain
Motor Praxis Test	Sensorimotor
Measured Emotion Differentiation Test	Social Cognition
Penn Verbal Reasoning Test	Complex Cognition
Face Memory Test	Episodic Memory
Emotion Recognition Test	Social Cognition
Letter N-Back	Executive Function
Word Memory Test	Episodic Memory
Age Differentiation Test	Social Cognition
Variable Penn Line Orientation Test	Complex Cognition
Visual Object Learning Test	Episodic Memory
Penn Matrix Analysis Test	Complex Cognition
Penn Continuous Performance Test	Executive Function
Penn Conditional Exclusion Test	Executive Function/Complex Cognition
Go-No-Go Test	Executive Function
Computerized Finger-Tapping Task	Sensorimotor

Note. Subtests in bold are the primary outcomes used in the current study.

Supplemental Table 2
Scanner Utilized at Each Site in the CPDDS

Site	Scanner(s)
Alberta Children's Hospital	GE - 750W - 3.0T
Children's Hospital at London Health Sciences Centre	Siemens –PRISMA Fit – 3.0T
Children's Hospital of Philadelphia	Siemens – Verio – 3.0T
Hospital for Sick Children	Siemens – Tim Trio – 3.0T Siemens – PRISMA Fit – 3.0T
Janeway Children's Health and Rehabilitation Centre	N/A
Montreal Children's Hospital	Siemens – TimTrio– 3.0T Siemens – PRISMA Fit 3.0T
The Children's Hospital of Manitoba	Siemens – Verio – 3.0T
Trillium Health Partners	N/A

Note. Site in Newfoundland (Janeway Children's Health and Rehabilitation Centre) does not have a 3T scanner. No scans for the present study were acquired at Trillium Health Partners.

Supplemental Table 3
Sensitivity Analysis: Participants Impaired on Age Differentiation (Z-score Accuracy) Excluded

Domain	Task	MS Group	HC Group	<i>p</i>
		M(SE)	M(SE)	
Social Cognition ^{a,b}	Age Differentiation ^a	-	-	-
	Emotion Recognition ^{a,b}	0.33 (0.10)	0.07 (0.09)	.06
	Emotion Differentiation ^a	-0.12 (0.11)	0.11 (0.09)	.12

Abbreviations: MS = multiple sclerosis; HC = healthy control

Note. *p*-values (ANCOVA) represent group differences after controlling for response time^a and sex^b (where indicated); Classification of impairment was based on a score falling 1.5 standard deviations below the mean; Sample size differs across tests because data were missing or deemed invalid for some patients.