



Memory, processing of emotional stimuli, and volume of limbic structures in pediatric-onset multiple sclerosis

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ABSTRACT

Objective: The limbic system is involved in memory and in processing of emotional stimuli. We measured volume of the hippocampus, amygdala, and thalamus, and assessed their relative contribution to episodic memory and emotion identification in POMS.

Method: Sixty-five POMS participants ($M_{age} = 18.3 \pm 3.9$ years; 48 female (73.8%)), average disease duration = 3.8 ± 3.8 years) and 76 age- and sex-matched controls ($M_{age} = 18.1 \pm 4.6$ years; 49 female (64.5%)) completed the Penn Computerized Neurocognitive Battery (PCNB); 59 of 65 POMS participants and 69 out of 76 controls underwent 3 T MRI scanning. We derived age-adjusted Z-scores on accuracy and response time (RT) measures of episodic memory and emotion identification of the PCNB. Magnetic resonance imaging (MRI) volumetrics were normalized using the scaling factor computed by SIENAX. On PCNB tests that differed between groups, we used multiple linear regression to assess relationships between regional brain volumes and either episodic memory or emotion identification outcomes controlling for age, sex, accuracy/RT, and parental education.

Results: POMS participants were slower and less accurate than controls on the episodic memory domain but did not differ from controls on emotion outcomes. At the subtest level, POMS participants showed reduced accuracy on Word Memory ($p = .002$) and slower performance on Face Memory ($p = .04$) subtests. POMS participants had smaller total and regional brain volumes of the hippocampus, amygdala, and thalamus (p values ≤ 0.01). Collapsing across groups, both hippocampal and thalamic volume were significant predictors of Word Memory accuracy; hippocampal volume ($B = 0.24$, $SE = 0.10$, $p = .02$) was more strongly associated with Word Memory accuracy than thalamic volume ($B = 0.16$, $SE = 0.05$, $p = .003$), though the estimate with was less precise.

Conclusions: POMS participants showed reduced episodic memory performance compared to controls. Aspects of episodic memory performance were associated with hippocampal and thalamic volume. Emotion identification was intact, despite volume loss in the amygdala.

1. Introduction

Children and adolescents with multiple sclerosis (MS) are particularly vulnerable to cognitive and psychosocial impairment given that the neuropathological processes involved in MS disrupt primary central nervous system myelination (Hacohen et al., 2017) and compromise cortical, white matter, and subcortical structural integrity (Ghezzi et al.,

2017). The thalamus is particularly vulnerable to the effects of MS (Aubert-Broche et al., 2014; Fadda et al., 2019; Kerbrat et al., 2012; Mesaros et al., 2008; Rocca et al., 2018) and has been identified as one of the most robust neuroimaging predictors of cognitive impairment in children and adults with MS (Cifelli et al., 2002; De Meo et al., 2017; Govindarajan et al., 2021; Houtchens et al., 2007; Omisade et al., 2012; Till et al., 2011). Due to the extensive connectivity between the

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thalamus and the hippocampal formation, episodic memory may become impaired with progressive loss of thalamic volume in persons with MS. In addition, the pathway from the amygdala to the mediodorsal thalamic nucleus is involved in emotion identification and reasoning (Timbie & Barbás, 2015).

The hippocampus is a structure associated with both spatial navigation and episodic memory (Burgess et al., 2002; Wixted et al., 2018), shows reduced volume in some (Rocca et al., 2016), but not all studies of pediatric-onset multiple sclerosis (POMS) (Fuentes et al., 2012). Analysis of hippocampal subregions reveals associations between the subiculum and dentate gyrus with cognition and has been shown to differentiate cognitively intact from impaired POMS participants (Rocca et al., 2016). In adults with MS, reduced volume of the amygdala or increased lesion load within the amygdala are among the strongest predictors of impairment in social cognition (Batista et al., 2017; Pitteri et al., 2019). To date, no studies have linked amygdala volume with the ability to identify emotional expressions in POMS, though reduced amygdala volume has been associated with greater risk of poor social and communication skills as reported by parents (Green et al., 2018). Emotion processing may be impacted in MS, although findings in the adult literature are mixed (Cotter et al., 2016; Henry et al., 2017; Pinto et al., 2012). Only higher order emotion processing such as Theory of Mind tasks, versus emotion recognition has been investigated in POMS (Charvet et al., 2014).

We conducted a cross-sectional analysis to investigate whether POMS participants differed from age- and sex-matched healthy controls (HCs) on (a) accuracy and response time (RT) PCNB measures of episodic memory and emotion identification, and (b) regional brain volumes of the hippocampus, amygdala, and thalamus. Finally, on outcomes that differed between groups, we assessed the relative contribution of hippocampal and thalamic volume to episodic memory outcomes, and amygdala volume to emotion identification outcomes.

2. Materials and methods

2.1. Participants

We used neurocognitive and neuroimaging data collected as part of the longitudinal Canadian Pediatric Demyelinating Study (CPDDS; Verhey et al., 2011; Fadda et al., 2018). The CPDDS includes 23 sites across Canada and the Children's Hospital of Philadelphia. This is an incident cohort of pediatric participants with acquired demyelinating syndromes. Participants were <16 years of age and within 90 days of disease onset at time of enrollment (between September 2004 and August 2015). Inclusion criteria were modified in August 2015 such that only youth aged <18 years, who consented within 180 days of disease onset, and met diagnostic criteria for POMS per the 2017 McDonald Diagnostic Criteria (Thompson et al., 2018) were enrolled. Only participants with a confirmed diagnosis of POMS, as determined by the 2017 McDonald criteria either at onset or based on clinical and MRI findings over time were included in the current analysis (Thompson et al., 2018).

HCs were enrolled between December 2015 and June 2019 using flyers and web-based advertising. Research ethics approval was obtained by all participating institutions. Written informed consent was obtained from participants or a parent/legal guardian.

All English-speaking participants enrolled in the CPDDS (80 POMS participants and 139 HCs) were offered neurocognitive testing between 2015 and 2020. Neurocognitive data was obtained for 67 (81.3%) POMS participants and 95 (68.3%) HCs. Participants were subsequently excluded from the analytic dataset if they were deemed to have: (a) insufficient visual/motor ability to perform cognitive testing ($n = 2$), or (b) prior exposure to the assessment battery ($n = 1$). To enhance age-matching between the groups, 18 HCs 13 years and younger were excluded, yielding a final sample of 65 POMS participants and 76 HCs with useable neurocognitive data.

MRI data were analyzed for 59 of the 65 (90.8%) POMS participants and 69 of the 76 (90.8%) HCs; one scan from a POMS participant was excluded as COMBAT cannot account for scanner-related variability when there are limited entries at a given site (i.e., less than three scans), research scans were not obtained for four POMS participants, and one POMS participant could not be scanned as there was no 3 T scanner at the testing site. Most participants were scanned on the same day as the neurocognitive assessment (99 of 128 participants; 77.3%); 28 participants (21.9%) returned for scanning within five months; one healthy control (0.8%) was scanned within approximately 10 months of the neurocognitive assessment.

There is minimal overlap between the samples in this study and our related prior work (Fuentes et al., 2012). Only six (9.2%) POMS participants and one (1.3%) HC included in the present study also participated in the 2012 study by Fuentes and colleagues.

2.2. Measures

Demographics, developmental milestones, education and occupation, and relevant medical histories (including date of MS onset, disease duration from first attack at time of cognitive testing, as well as the type of treatment with disease-modifying therapies) were recorded using standardized study case report forms. Study site neurologists documented neurological findings leading to determination of an approximated Expanded Disability Status Scale score (EDSS; Kurtzke, 1983; O'Mahony et al., 2015). 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). Scores on both the PI-ED and HADS range from 0 to 42, with a score greater than 20 indicating clinically significant emotional distress (O'Connor et al., 2016). Self- and proxy-reported fatigue were measured using the PedsQL Multidimensional Fatigue Scale; scores range from 0 to 100, with higher scores reflecting fewer problems (Varni et al., 2002). Socioeconomic status was measured by the Barratt Simplified Measure of Social Status, which yields a total education and occupation score for both parents/guardians (Barratt, 2006). Participants also reported the number of years of education completed by themselves and each of their parents; these parental education values were averaged.

2.2.1. Cognitive evaluation

Participants completed the Penn Computerized Neurocognitive Battery (PCNB) (see Roalf et al., 2014 for detailed test descriptions). For the purpose of this analysis, we examined accuracy and RT on episodic memory and emotion identification subtests as well as the composite domain score. The three subtests in the episodic memory domain include: *Word Memory* (immediate recognition of words), *Object Memory* (immediate recognition of objects), and *Face Memory* (immediate recognition of faces). The three subtests in the emotion identification domain (referred to as "Social Cognition" on the PCNB) include: *Age Differentiation* (i.e., "Which of two faces is older?"), *Emotion Identification* (i.e., "Which emotion is shown: happy, sad, angry, scared, or no feeling?"), and *Emotion Differentiation* (i.e., "Which of two faces is happier?"). For the purpose of the current study, the Age Differentiation subtest served as a control condition to help interpret performance on the subtests that involve identification of emotional expression. Thus, if reduced accuracy (or slower RT) was observed for the emotion-related subtests, but not the age-related subtest (face processing), we would have greater confidence that the effect was specific to processing emotional stimuli.

The battery was administered by a trained assessor in a single session, taking approximately one hour, with breaks offered at three standard intervals. Data underwent quality control procedures to exclude invalid participant data prior to analysis. This included identification of multiple key presses, removal of RT outliers, and a third-party review of

assessor administration comments regarding behavioral and environmental observations pertinent to testing (e.g., difficulty seeing the stimuli, presence of distractions, motivation, or misunderstanding of instructions).

Raw scores for each PCNB outcome were standardized into age-normed Z-scores using the means and standard deviations (SD) of our HC group; Z-scores were calculated from four age bands (i.e., 8–10; 11–13; 14–17; ≥ 18 years) (see Barlow-Kreling et al., in press). Age bands were determined based on sample size and consideration of the developmental curves for each test as outlined by Gur and colleagues (2012). Response time scores were transformed (i.e., multiplied by -1), such that higher Z-scores reflect better performance (i.e., shorter RTs). Domain scores were created by averaging Z-scores for accuracy and RT independently.

2.2.2. Neuroimaging

Structural MRI scans were performed on 3 T scanners at multiple sites according to a standardized research protocol conforming to rigorous standard operating procedures. Only 3D T1-weighted MPRAGE and FLAIR images were analyzed for the purpose of this analysis. T1 and FLAIR sequence acquisition parameters are available in Supplement 1.

Images underwent quality control examinations to assess for motion artifacts or signal dropouts. Lesions were identified on FLAIR images using Lesion Segmentation Toolbox (Schmidt et al., 2019), manually edited (if required) and in-painted on the MPRAGE images to look like the surrounding normally appearing voxels.

2.2.3. Neuroimaging segmentation pipeline

The FreeSurfer (v6) toolkit (<http://surfer.nmr.mgh.harvard.edu/>) was used to process the MPRAGE images. Briefly, the pre-processing includes spatial inhomogeneity correction, non-linear noise-reduction, skull-stripping, and intensity normalization. Volumes of the hippocampus and amygdala for each hemisphere were calculated using special modules available in FreeSurfer (Iglesias et al., 2015; Saygin et al., 2017). Automatic segmentation of the thalamus was obtained on the T1-weighted images using published methods (Datta et al., 2020).

2.2.4. Neuroimaging normalization procedures

As participants were scanned at multiple imaging sites on different MRI scanners, the effect of inter-scanner variability on the extracted volumes of the different regions of interest were controlled for using COMBAT (Fortin et al., 2018). To normalize the volumes for head size, SIENAX was run on all MPRAGE images for brain and skull extraction (Smith et al., 2001; Smith et al., 2002; Smith, 2002b; Smith et al., 2004). A volumetric scaling factor was obtained by affine-registering the brain image to the MNI152 space, using the skull image to determine the registration scaling (Jenkinson & Smith, 2001; Jenkinson et al., 2002). The hippocampal, amygdala, thalamic and brain volumes were normalized for subject head size by multiplying by the volumetric scaling factor.

2.3. Data analysis

All cognitive outcome variables were first plotted to assess normality and identify any outliers; extreme scores (which pertained to 0.95% of total number of scores examined) were Winsorized to 3 SD from the mean (Field, 2016). Between-group differences for PCNB outcomes (domain and subtest scores), clinical and demographic variables, and regional brain volumes were examined using one-way analysis of variance (ANOVA) or chi-squared (X^2) tests. Response times for each PCNB subtest (or domain) were included as covariates for analyses involving accuracy outcomes, and vice versa. Analyses of the cognitive outcomes were also adjusted for covariates that differed between groups at $p < .10$ (i.e., parental education). Effect sizes for the between-group comparisons on the cognitive outcomes were determined using Cohen's d . Given the intercorrelations between subtests in each domain for cognitive

data, p values of ≤ 0.05 at the subtest level were considered statistically significant only if the domain score reached this threshold. Spearman correlations collapsing across groups were used to examine associations between performance on subtests within the two domains of interest. Spearman correlations were also used to assess the relationship between left and right structural brain volumes. Finally, we used multiple linear regression to examine brain-behaviour relationships for PCNB domains and subtests demonstrating significant between-group differences. We entered MRI volumes (i.e., hippocampal, thalamic, and amygdala volume) into separate regressions for the combined sample; supplementary regression analyses were also conducted stratified by group. Covariates included task- or domain-specific accuracy/RT, age, sex, parental education; supplemental analyses were also run controlling for sensorimotor ability (assessed by the PCNB) to rule out the possibility that response time differences observed on the memory or emotion identification were simply due to reduced motor speed. We did not control for anxiety and depression in our analysis given that groups did not differ on our measures assessing mood; however, a sensitivity analysis was run removing three controls who endorsed clinically significant emotional distress. Finally, to confirm that the volumetric findings were not influenced by the interval between neurocognitive testing and when the MRI data were acquired, we ran a sensitivity analysis excluding the five participants who were scanned 3 or more months from their participation in the neurocognitive component of the study. Data were analyzed using IBM SPSS Statistics version 27.

Table 1
Demographic and clinical characteristics of POMS and healthy control participants.

	POMS (n = 65)	HC (n = 76)	p	Cohen's d
Age at testing (years)	18.3 \pm 3.9 (8–27)	18.1 \pm 4.6 (8–29)	0.87	0.05
Sex (#female, %female)	48 (73.8)	49 (64.5)	0.28	
Participant education (years)	11.7 \pm 3.1 (2–19)	12.1 \pm 3.6 (3–20)	0.53	0.12
Parental education (years)	14.3 \pm 1.9 (10–19)	15.0 \pm 2.3 (10–20)	0.06	0.33
Socioeconomic status	39.6 \pm 14.5 (10–66)	43.1 \pm 14.4 (8.5–66)	0.10	0.29
Nationality (#Canadian, % Canadian)	48 (73.8)	58 (76.3)	0.85	
Emotional Distress (#high, %clinically significant)	6 (10.0)	3 (5.0)	0.49	
Participant Fatigue				
Parent-rated	69.9 \pm 20.8 (33.3–100)	83.9 \pm 14.8 (45.8–100)	<0.001	0.78
Participant-rated	64.5 \pm 20.9 (26.4–98.6)	74.3 \pm 14.3 (43.1–100)	0.002	0.55
Age at disease onset (years)	14.9 \pm 2.3 (6.3–17.9)	–	–	–
Disease Duration (years)	3.5 \pm 3.7 (0–11)	–	–	–
EDSS (median, range)	1.5 (0–3.5)	–	–	–
DMT (#yes, %yes)	53 (81.5)	–	–	–
Interval between PCNB and MRI (months; median, range)	0.00 (0–5.3)	0.00 (0–10.8)	0.22	0.64

Note. Values represent $M \pm SD$ unless otherwise stated. Participant education was not available for 1 patient; Parental education data was not available for 4 MS and 2 HCs. Socioeconomic status data was not available for 4 MS participants and 7 HCs. Emotional distress data was not available for 5 MS participants and 16 HCs. Parent-rated fatigue data was not available for 11 POMS participants and 24 HCs. Participant-rated fatigue data was not available for 3 POMS participants and 7 HCs.

3. Results

Table 1 presents the clinical and demographic characteristics of the patient and control groups. There were no differences between groups with respect to age, sex, participant level of education, socioeconomic status or emotional distress. POMS participants reported higher self- and parent-reported fatigue relative to HCs (p values < 0.01). There was a trend towards lower parental education ($p = .06$) in the POMS group relative to HCs.

3.1. Between-group comparisons on the neurocognitive outcomes

3.1.1. Episodic memory outcomes (Table 2)

POMS participants were both less accurate ($p < .01$) and slower ($p = .05$) than HCs on the episodic memory domain, after controlling for covariates. At the subtest level, the POMS group performed less accurately than HCs on the Word Memory test (Mean Z-score = -0.63 vs. -0.03 , Cohen's $d = 0.57$, $p = .002$) and were slower than HCs on the Face Memory test (Mean Z-score = -0.41 vs. 0.00 , Cohen's $d = 0.36$, $p = .04$).

3.1.2. Emotion identification outcomes (Table 2)

POMS participants were more accurate than HCs on the Emotion Identification subtest (Mean Z-score = 0.32 vs. 0.02 , Cohen's $d = 0.35$, $p = .05$), although this difference did not meet our domain threshold for significance. No other significant differences were found.

3.1.3. Sensitivity analyses

Exclusion of three controls with an emotional distress score greater than or equal to 20 did not alter the results in any meaningful way (data not shown) but did attenuate the difference between POMS and HCs on the Face Memory subtest for response time. The exclusion of these three control participants reduced the mean value from $Z = 0.00$ ($SE = 0.13$) to -0.04 ($SE = 0.14$), indicating that the participants who reported lower mood had higher performance on the Face Memory test. These participants were therefore retained in all subsequent analyses because they were not deemed to bias the group towards having worse performance on the subtests included in this study.

Supplemental analyses were also run controlling for sensorimotor ability (assessed by the PCNB) to rule out the possibility that response time differences observed on the memory or emotion identification were simply due to reduced motor speed. Results remained consistent (data

not shown).

3.2. Associations between performance on the episodic memory and emotion identification subtests

Collapsing across groups, accuracy on the episodic memory subtests was weakly correlated with accuracy on emotion identification subtests (all Spearman r values ≤ 0.26), with the exception of Face Memory and Emotion Differentiation (Spearman $r = 0.38$, $p < .001$). In contrast, response times on episodic memory subtests were moderately correlated with response times on the Age Differentiation and Emotion Identification subtests (Spearman r values ≥ 0.36) and weakly correlated with the Emotion Differentiation subtest (see Supplement 2).

3.3. Neuroimaging outcomes

POMS participants had lower total and lateralized normalized volumes of the hippocampus, amygdala, and thalamus compared to HCs (all p values ≤ 0.01 , Table 3). Normalized total brain volume ($p = .001$) and grey matter volume ($p = .01$) were also smaller in POMS participants versus HCs. Although normalized white matter ($p = .08$) did not differ between groups, the means are in the anticipated direction with the MS group having slightly smaller volumes. Collapsing across groups (and within-groups, data not presented), lateralized (left and right) hippocampal ($r = 0.89$, $p < .001$), amygdala ($r = 0.85$, $p < .001$), or thalamic volumes ($r = 0.92$, $p < .001$) were highly correlated. Thus, total (bilateral) volumes rather than the lateralized volumes were used in the regression analyses.

3.4. Brain-behaviour relationships

We ran multivariate regression models for the episodic memory domain score (both accuracy and RT), and two subtests: Word Memory (accuracy only) and Face Memory (RT only) (Table 4). Collapsing across groups, accuracy on the Word Memory subtest was associated with volume of the hippocampus ($F(5, 116) = 5.2$, $p < .001$, adjusted R^2 of 0.15) and volume of the thalamus ($F(5, 116) = 6.0$, $p < .001$, adjusted R^2 of 0.17), controlling for covariates. Accuracy on the Word Memory subtest was more strongly associated with hippocampal volume ($B = 0.24$, $SE = 0.10$, $p = .02$) than thalamic volume ($B = 0.16$, $SE = 0.05$, $p = .003$), though the estimate was less precise. No significant relationships were found between the volumetric structures and Word Memory

Table 2

Accuracy and response time outcomes on the episodic memory and emotion identification domains on the Penn Computerized Neurocognitive Battery. Scores shown as Z-scores for POMS and HC participants.

Domain	Test	POMS	HC	Group difference		
		<i>M</i> (<i>SE</i>)	<i>M</i> (<i>SE</i>)	<i>F</i>	<i>p</i>	Cohen's <i>d</i>
EPISODIC MEMORY						
Accuracy		-0.45 (0.10)	-0.00 (0.09)	11.1	0.001	0.57
	Face Memory	-0.30 (0.13)	-0.01 (0.12)	2.6	0.11	0.28
	Object Memory	-0.33 (0.15)	-0.02 (0.13)	2.5	0.12	0.18
	Word Memory	-0.63 (0.14)	-0.03 (0.12)	10.5	0.002	0.57
Response Time		-0.34 (0.12)	-0.01 (0.11)	4.1	0.05	0.35
	Face Memory	-0.41 (0.15)	0.00 (0.13)	4.1	0.04	0.36
	Object Memory	-0.12 (0.13)	-0.01 (0.11)	0.4	0.53	0.11
	Word Memory	-0.43 (0.14)	-0.08 (0.13)	3.1	0.08	0.32
EMOTION IDENTIFICATION						
Accuracy		0.01 (0.09)	-0.02 (0.08)	0.0	0.87	0.03
	Age Differentiation	-0.05 (0.12)	-0.04 (0.11)	0.0	0.98	0.00
	Emotion Identification	0.32 (0.11)	0.02 (0.10)	3.8	0.05	0.35
	Emotion Differentiation	-0.26 (0.12)	-0.01 (0.11)	2.1	0.15	0.26
Response Time		-0.23 (0.11)	0.0 (0.10)	2.2	0.14	0.27
	Age Differentiation	-0.24 (0.14)	-0.01 (0.13)	1.6	0.21	0.21
	Emotion Identification	-0.41 (0.15)	-0.01 (0.14)	3.7	0.06	0.34
	Emotion Differentiation	-0.06 (0.13)	0.05 (0.12)	0.4	0.54	0.11

Note. P values represent group differences after controlling for accuracy/RT and parental education using ANCOVA. Cohen's d 's of 0.2, 0.5, and 0.8 reflect small, medium, and large effect sizes. Sample size differs across tests due to exclusion of invalid data.

Table 3
Combattted, SIENAx-scaled structural MRI metrics (mm³) for POMS and HCs.

Normalized MRI metric	POMS (n = 59)	HC (n = 69)	F	p	Cohen's d
	<i>M(SE)</i>	<i>M(SE)</i>			
Hippocampal volume					
Total	8997.76 (132.44)	9660.90 (116.77)	15.3	<0.001	0.67
Left	4409.60 (65.51)	4738.70 (57.76)	15.4	<0.001	0.70
Right	4588.16 (70.86)	4922.20 (62.48)	13.6	<0.001	0.63
Amygdala volume					
Total	4530.09 (64.27)	4774.75 (56.67)	8.9	0.004	0.51
Left	2232.25 (32.05)	2342.60 (28.26)	7.2	0.01	0.46
Right	2297.84 (34.23)	2432.15 (30.18)	9.4	0.003	0.52
Thalamic volume					
Total	14104.99 (244.46)	16191.85 (215.55)	44.5	<0.001	1.14
Left	7032.22 (124.93)	8084.24 (110.15)	43.3	<0.001	1.22
Right	7072.77 (125.50)	8107.61 (110.65)	41.5	<0.001	1.10
Grey Matter volume	859672.49 (7065.27)	884439.48 (6228.67)	7.5	0.01	0.47
White Matter volume	720039.18 (5437.02)	732508.80 (4793.90)	3.2	0.08	0.31
Total Brain volume	1578933.80 (8810.26)	1616963.70 (7768.13)	11.4	0.001	0.58

Note. *P* values represent group differences after controlling for age and sex using ANCOVA. Cohen's *d*'s of 0.2, 0.5, and 0.8 reflect small, medium, and large effect sizes. We excluded five participants (3 patients and 2 controls) whose scans were acquired more than three months from their participation in the neurocognitive component of the study. This sensitivity analysis confirmed that the pattern of findings was unchanged (data not shown).

Table 4

Linear regression model results showing associations between hippocampal (Model 1) and thalamic volumes (Model 2) and memory outcomes on the PCNB that differed between participants with POMS and HCs.

Dependent	Adjusted R ²	F	p	Independent Variables	B (SE)	t	p	95% CI	
								Lower limit	Upper limit
Episodic Memory Domain (Accuracy) (Model 1)	0.07	2.7	.03	Parental Education	0.10 (0.03)	3.18	.002	0.04	0.17
				Age	-0.001 (0.02)	-0.04	.97	-0.04	0.03
				Sex	-0.19 (0.16)	-1.23	.22	-0.50	0.12
				Episodic Memory (RT)	0.04 (0.08)	0.49	.63	-0.12	0.19
				Hippocampal volume	0.07 (0.07)	0.99	.33	-0.07	0.21
Episodic Memory Domain (Accuracy) (Model 2)	0.09	3.3	.01	Parental Education	0.10 (0.03)	3.09	.003	0.04	0.16
				Age	0.003 (0.02)	0.15	.88	-0.03	0.04
				Sex	-0.17 (0.15)	-1.12	.27	-0.47	0.13
				Episodic Memory (RT)	0.03 (0.08)	0.40	.69	-0.12	0.18
				Thalamic volume	0.07 (0.04)	1.91	.06	-0.003	0.14
Word Memory Subtests (Accuracy) (Model 1)	0.15	5.2	<.001	Parental Education	0.13 (0.05)	2.89	.01	0.04	0.22
				Age	-0.01 (0.02)	-0.33	.74	-0.06	0.04
				Sex	-0.01 (0.21)	-0.06	.95	-0.44	0.41
				Word Memory (RT)	0.23 (0.09)	2.52	.01	0.05	0.40
				Hippocampal volume	0.24 (0.10)	2.40	.02	0.04	0.44
Word Memory Subtests (Accuracy) (Model 2)	0.17	6.0	<0.001	Parental Education	0.12 (0.05)	2.77	.01	.004	0.21
				Age	-0.002 (0.02)	-0.08	.94	-0.05	0.05
				Sex	0.05 (0.21)	0.25	.80	-0.36	0.47
				Word Memory (RT)	0.21 (0.09)	2.42	.02	0.04	0.39
				Thalamic volume	0.16 (0.05)	3.08	.003	0.06	0.26

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

accuracy when stratifying the results by group (regression data not shown, see Figs. 1 and 2). Additionally, no significant relationships were found between hippocampal or thalamic volumes on the episodic memory domain score nor the face memory subtest. We did not test associations with amygdala volume given that there were no significant between-group differences on the emotion identification outcomes.

4. Discussion

We found that patients with POMS demonstrated reduced accuracy on a test of verbal recognition (i.e., word list) and were slower to recognize faces that were recently presented. Consistent with previous imaging research in POMS (Fuentes et al., 2012; Green et al., 2018; Kerbrat et al., 2012; Mesaros et al., 2008; Till et al., 2011), we also found that patients with POMS showed smaller normalized thalamic volume compared to HCs and this effect was most robust relative to other brain regions examined in our study. Difficulty with verbal recognition is consistent with prior POMS studies that evaluated episodic memory using word list recall (Amato et al., 2008; Fuentes et al., 2012; MacAllister et al., 2005; MacAllister et al., 2007; Smerbeck et al., 2011; Till et al., 2013), suggesting a deficit at the encoding stage for verbal information. While participants with POMS did not show lower accuracy on visual memory tasks involving object and face recognition, they were slower to recognize faces. This finding differs from prior studies in POMS that have examined visual memory (recall) and have consistently reported deficits (e.g., Amato et al., 2008; MacAllister et al., 2005; Smerbeck et al., 2011), perhaps reflecting the decreased demands associated with recognition tasks relative to information recall (Haist et al., 1992; Janowsky et al., 1989). Moreover, preserved accuracy in face recognition in the POMS group appeared to occur at the expense of slower processing.

Overall, the episodic memory and social cognitive performance of POMS participants across all subtests examined on the PCNB fell within the range of normative age-expected performance. Still, the group-level differences showed small-to-moderate effect sizes (Cohen's *d* ranging from 0 to 0.57). These findings lead us to question whether and how these differences may be experienced in day-to-day life such as in academic, occupational, and social spheres at the individual level and how

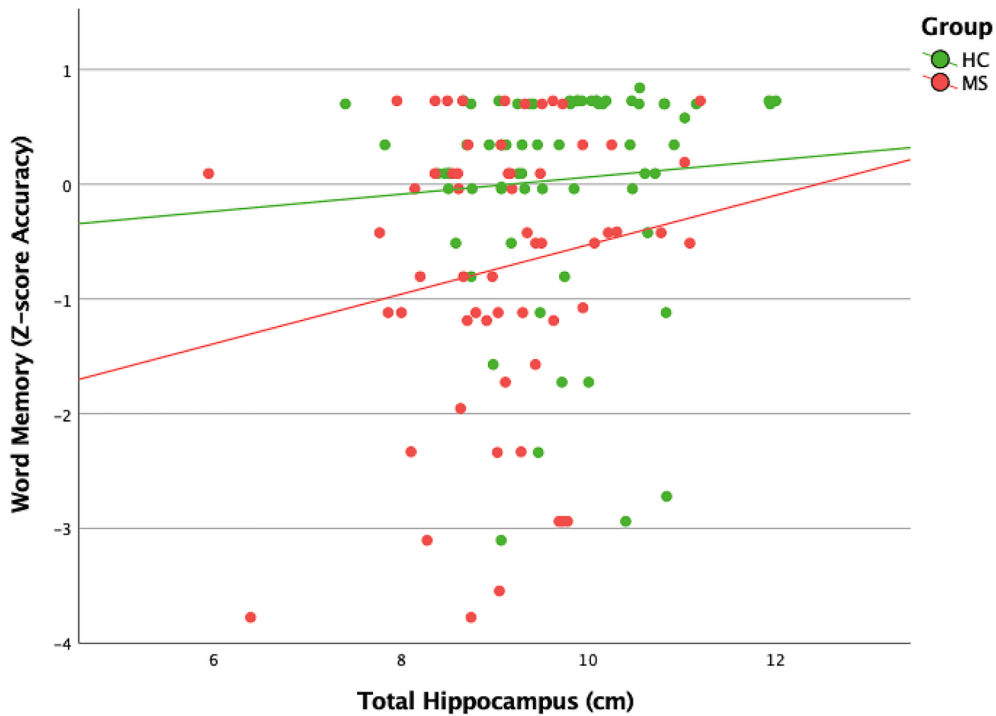


Fig. 1. Scatterplot of Word Memory accuracy Z-score with total hippocampal volume by group.

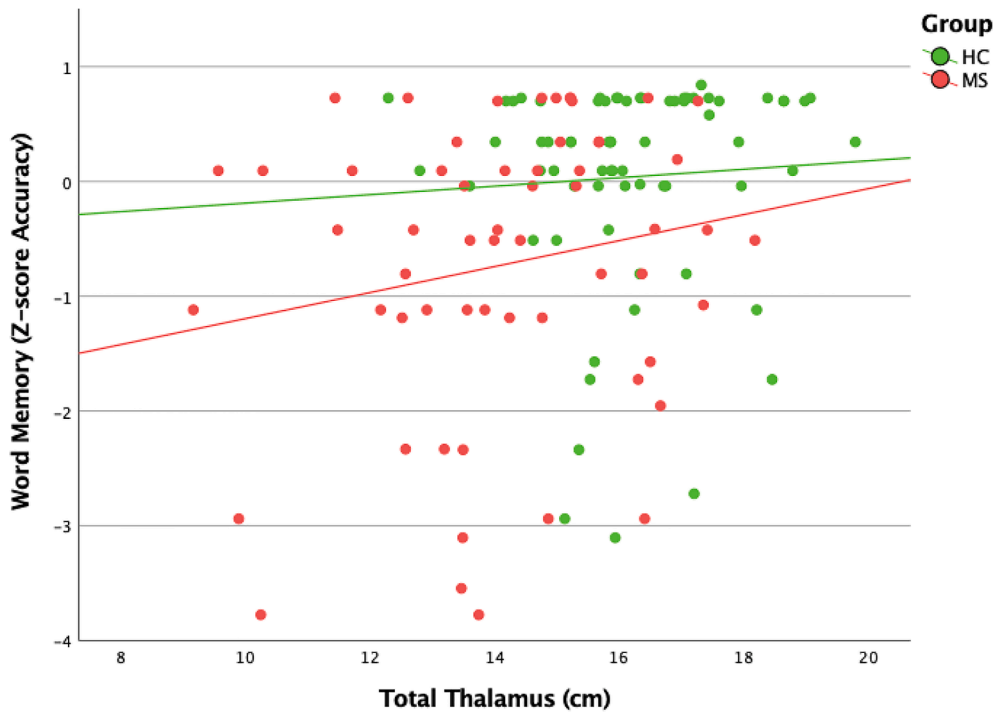


Fig. 2. Scatterplot of Word Memory accuracy Z-score with total thalamic volume by group.

to examine this in future work (e.g., Green et al., 2018; MacAllister et al., 2007; Till et al., 2012). Though depression and anxiety can influence cognitive performance in MS including memory and emotion identification (Leavitt et al., 2020; Ziccardi et al., 2021), our sample of POMS participants did not report greater emotional distress relative to HCs. This finding allows us to rule out mood as a factor influencing the observed lower memory performance among POMS participants relative to HCs.

Regarding limbic structure volumes, our research is aligned with Rocca et al., (2016) as well as a previous study conducted by our group on an almost fully independent sample (Fuentes et al., 2012) in that we also found smaller hippocampal and amygdala volumes in participants with POMS relative to HCs. We also explored brain-behaviour relationships between the thalamus, limbic structures, and several cognitive outcomes and found that both reduced thalamic and hippocampal volume were associated with poorer accuracy on the Word

Memory substest. The effect was only observed when we collapsed across groups and not when we considered the POMS group on its own. Using 15 cm³ as the cut-off for normal thalamic volume in our sample (Fig. 2), we found that the majority of the “low” values are POMS participants whereas the majority of the “high” values (i.e., greater than 15 cm³) are HCs. We see similar findings for the hippocampus (Fig. 1). This minimal variation in brain volumes when groups are stratified may account for the lack of association between brain region and neurocognitive outcome.

Given the extensive connectivity of the thalamus with multiple cortical and subcortical structures, reduced thalamic volume may impact functioning of limbic structures, including the hippocampus via processes like Wallerian degeneration. The amygdala was not included in models for memory outcomes given that prior research in POMS has not demonstrated associations between the amygdala and memory (Fuentes et al., 2012; Green et al., 2018). As well, traditionally, the amygdala is thought to be involved in enhancing specific types of declarative memory such as affective memory (Phelps & Anderson, 1997) but its role in the type of episodic memory assessed by the PCNB is less recognized. Relationships between the thalamus and hippocampus with memory outcomes have been established in prior studies of adult MS and POMS (e.g., Benedict et al., 2009; Fuentes et al., 2012).

4.1. Limitations and future directions

A limitation of this research is that the PCNB only assessed recognition and not recall memory. Therefore, we could not speak to whether there are deficits in word retrieval and can only identify a deficit at the encoding stage for verbal information. Future research may wish to assess brain-behaviour relationships between the hippocampus and cognition using recall tests thought to be hippocampally-mediated, such as the Spatial Recall Test (SPART and SRT-Delayed) from Rao's Brief Repeatable Battery (BRB; Rao, 1995). The Rao battery has been administered in POMS with demonstrated sensitivity in detecting cognitive challenges in POMS (for example see Ekmecki, 2017). Moreover, we cannot conclude that emotional identification abilities are unaffected in POMS as our tests may be too simple. Future research should aim to use higher order emotion processing tasks that assess aspects of social cognition such as Theory of Mind (e.g., The Awareness of Social Inference Test (TASIT; McDonald et al., 2003), versus the more primitive emotion identification tasks used in this study. Basic emotion recognition tasks may lack the sensitivity to detect deficits in emotion processing. Finally, while our imaging was not optimized for maximal hippocampal visualization, future research should consider examining subfields and nuclei of the hippocampus and amygdala given their distinct roles in memory and processing of emotional stimuli (Erlich et al., 2012; Mueller et al., 2011). Previous studies in adult MS have seen differential impact of the disease on hippocampal subfields with CA1 and the subiculum as the regions with the greatest atrophy (Papadopoulos et al., 2009; Rocca et al., 2018). Atrophy of CA1 and the subiculum may explain poorer verbal memory performance among POMS participants, as shown in prior work (Longoni et al., 2015; Rocca et al., 2018; Sicotte et al., 2008).

4.2. Conclusions

In conclusion, the present study provides evidence showing that patients with POMS may experience deficits in episodic memory and in their ability to recognize faces quickly. Reduced volume of the thalamus and hippocampus may contribute to some observed deficits in episodic memory.

CRediT authorship contribution statement

Tracy L. Fabri: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing, Visualization, Funding

acquisition. **Ritobrato Datta:** Methodology, Formal analysis, Resources. **Julia O'Mahony:** Project administration, Data curation, Writing - review & editing. **Emily Barlow-Krelina:** Validation. **Elisea De Somma:** Writing - review & editing. **Giulia Longoni:** Writing - review & editing. **Raquel E. Gur:** Resources, Writing - review & editing. **Ruben C. Gur:** Resources, Writing - review & editing. **Micky Bacchus:** Project administration. **E. Ann Yeh:** Funding acquisition, Writing - review & editing. **Brenda L. Banwell:** Conceptualization, Funding acquisition, Writing - review & editing, Supervision. **Christine Till:** Conceptualization, Funding acquisition, Writing - original draft, Writing - review & editing, Supervision.

Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nicl.2021.102753>.

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