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Brain activation patterns and cognitive processing speed in patients with pediatric-onset multiple sclerosis

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ABSTRACT
Objective: This study aimed to determine the extent and pattern of brain activation elicited by a functional magnetic resonance imaging version of the Symbol Digit Modalities Test (fMRI–SDMT), a task of information processing speed, in pediatric-onset multiple sclerosis (MS) patients as compared to sex- and age-matched non-MS self-reported healthy individuals. Method: Participants included 20 right-handed individuals aged 13–24 years with pediatric-onset MS (mean age = 19 years, 15 female) and 16 non-MS self-reported healthy individuals. All participants underwent a 3.0-tesla MRI scan with structural (T1; T2; proton density, PD; fluid-attenuated inversion recovery, FLAIR) and fMRI–SDMT acquisition. Participants were instructed to indicate with a button press whether a single pairing of a symbol to a number matched any of those shown in a key that displays nine possible pairings. Results: Response time (p = .909) and accuracy (p = .832) on the fMRI–SDMT did not differ between groups. However, the MS group demonstrated lower overall activation than the non-MS group in the right middle frontal gyrus (p = .003). Within the MS group, faster response time was associated with greater activation of the right inferior occipital, anterior cingulate, right superior parietal, thalamus, and left superior occipital cortices (all p < .05). A significant interaction effect was demonstrated, indicating that faster response time was associated with greater activation of the left superior occipital region in the pediatric MS group than in the non-MS group (p = .002). Conclusions: Attenuated activation of frontal regions was observed in this cohort of pediatric-onset MS patients when performing the fMRI–SDMT, even in the absence of behaviorally detectable deficits. Within the MS group only, faster response time elicited greater activation, suggesting this to be an adaptive mechanism that may contribute to limiting the impact of disease-related structural pathology.

Cognitive dysfunction in youth with pediatric multiple sclerosis (MS) is associated with deficits in the domains of information processing speed, memory, attention, and executive function (Banwell & Anderson, 2005; MacAllister, Christodoulo, Milazzo, & Krupp, 2007; Portaccio et al., 2009; Till et al., 2011). The Symbol Digit Modalities Test (SDMT) primarily measures information processing speed and is sensitive to cognitive impairment in both pediatric and adult MS patients (Bethune et al., 2011; Parmenter, Weinstock-Guttman, Garg, Munschauer, & Benedict, 2007). Performance on this task correlates strongly with the white matter integrity of the corpus callosum (Bethune et al., 2011), as well as brain grey matter volume and specific subcortical structures, such as the thalamus (Till et al., 2011).

A computerized functional magnetic resonance imaging (MRI) version of the SDMT (fMRI–SDMT; Rypma et al., 2006) can be used in an...
MRI scanner to investigate brain functioning elicited during SDMT performance. As expected from the results of the traditional paper version of the SDMT, adults with MS tested using the fMRI–SDMT demonstrate slower processing speed than healthy individuals (Genova, Hillary, Wylie, Rypma, & DeLuca, 2009; Leavitt, Wylie, Genova, Chiaravalloti, & DeLuca, 2012). Functional MRI blood-oxygen-level-dependent (BOLD) pattern analyses of these adult MS patients performing the fMRI–SDMT show abnormalities in the pattern of regional activation (Genova et al., 2009) and an increased number of functional connections (Leavitt et al., 2012) relative to healthy individuals. Adult MS patients performing less accurately on the fMRI–SDMT also demonstrated greater frontal connectivity, suggesting inefficient functioning and requirement of a greater use of cognitive resources (Leavitt et al., 2012).

To our knowledge, there have been no published studies investigating the neural correlates of information processing in pediatric MS patients using a task-based fMRI paradigm. We therefore evaluated the pattern of brain activation associated with performance on the fMRI version of the SDMT in patients with pediatric-onset MS as compared with non-MS self-reported healthy individuals. We further explored whether differences in brain activation patterns in pediatric MS patients corresponded with performance on the fMRI–SDMT and measures of structural pathology.

**Method**

**Participants**

Twenty-three pediatric-onset MS patients (younger than age 18 years at time of first MS attack, all meeting current MS diagnostic criteria; Polman et al., 2011) and 19 age- and sex-matched non-MS self-reported healthy individuals were recruited. Three MS patients and three non-MS individuals were excluded due to scanner artifact or excessive motion (movement greater than 1.5 mm), resulting in a final sample of 20 MS and 16 non-MS participants (see Table 1 for sample characteristics). MS patients were recruited from the MS programs at two hospitals in Toronto. Non-MS individuals were recruited through advertisement. The research protocol was reviewed and approved by the Research Ethics Boards at both hospitals, as well as the site of MRI scanning (York University). Written informed consent was obtained from all participants and/or a parent or legal guardian. All participants were carefully screened using structured interview at the time of recruitment. Participants were excluded if they endorsed any of the following: born preterm (<37 weeks), history of head trauma, current or past alcohol abuse, illicit drug use, diagnosis of major medical illness potentially affecting neurological and/or cognitive function (e.g. epilepsy, cancer, stroke), and any current or past history of attention disorder, anxiety, autism spectrum disorder, psychiatric disorder, learning disability, or language disorder. Non-MS individuals were carefully screened for the presence of clinically diagnosed depression, and no participant endorsed exposure to antidepressant medication at the time of enrolment or in the past. Participants were required to be proficient in English and free of any visual or motor difficulties that would preclude testing. MS participants were evaluated at least four weeks from clinical relapse or corticosteroid treatment. For each participant, the study took place in one 4-hour session consisting of questionnaires, neuropsychological assessment, and the MRI scan.

**Measures**

Demographic and disease-related information were obtained from clinical records. The Expanded Disability Status Scale (EDSS; Kurtzke, 1983) score reported within the last six months, relapse history, disease duration, and medications were recorded. All participants completed a 45-min neuropsychological assessment in order to define cognitive function. Cognitive impairment was defined as performance falling below the 5th percentile ($z \leq 1.64$ SDs below the normative mean) on two or more of the nine subtests on at least two separate measures. These measures included Matrix Reasoning and Vocabulary from the Wechsler Abbreviated Scales of Intelligence (Wechsler, 1999), SDMT Oral version (A. Smith, 1982), Decision Speed and Auditory Working Memory from the Woodcock–Johnson III (WJ–III) Test of Cognitive Abilities (Woodcock, McGrew, & Mather, 2001), Trail Making Test (TMT) Parts A and B (Reitan, 1958), and the Rey Auditory Verbal Learning Test (RAVLT; total learned and
Table 1. Demographic, disease-related, and fMRI–SDMT behavioral data for all participants.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pediatric-onset MS (n = 20)</th>
<th>Non-MS individuals (n = 16)</th>
<th>Between-groups comparison (t or χ²)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at evaluation [mean (range)]</td>
<td>18.6 (13–24)</td>
<td>19.1 (14–24)</td>
<td>0.587</td>
<td>.561</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>15/5</td>
<td>11/5</td>
<td>0.173</td>
<td>.677</td>
</tr>
<tr>
<td>Disease duration [in months; mean (SD)]</td>
<td>64.5 (39.1)</td>
<td>13.1 (2.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at MS onset [in years; mean (SD)]</td>
<td>4.15 (1.13)</td>
<td>1.5 (0–4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of relapses since MS onset [median (range)]</td>
<td>4 (1–13)</td>
<td>15/5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receiving disease-modifying medication [Y/N]</td>
<td>15/5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Socioeconomic status: BSMSS score [mean (SD)]</td>
<td>43.7 (14.0)</td>
<td>38.3 (16.0)</td>
<td>−1.06</td>
<td>.299</td>
</tr>
<tr>
<td>Depression: CES-DC score [mean (SD)]</td>
<td>16.2 (13.8)</td>
<td>10.9 (7.68)</td>
<td>−1.36</td>
<td>.182</td>
</tr>
<tr>
<td>Fatigue: PedsQL multidimensional fatigue score [mean (SD)]</td>
<td>30.4 (13.3)</td>
<td>22.6 (9.01)</td>
<td>−2.01</td>
<td>.052</td>
</tr>
<tr>
<td>Handedness [right/left]</td>
<td>18/2</td>
<td>15/1</td>
<td>1.03</td>
<td>.599</td>
</tr>
</tbody>
</table>

fMRI–SDMT behavioral measures

| Response time [in s] | 1.61 (0.275) | 1.60 (0.267) | −0.115 | .909 |
| Mean coefficient of variation | 0.208 (0.033) | 0.210 (0.033) | 0.137 | .892 |
| Percentage accuracy [mean (SD)] | 98.9 (1.26) | 98.8 (1.41) | 138 | .851 |

Cognitive z scores [mean (SD)]

| RAVLT: total immediate recall | −0.101 (1.17) | −0.400 (1.44) | −0.687 | .497 |
| RAVLT: delayed recall | −0.302 (1.09) | −0.140 (1.21) | 0.424 | .674 |
| WASI Vocabulary | 0.422 (0.744) | 0.522 (0.714) | 0.407 | .686 |
| WASI Matrix Reasoning | 0.277 (0.773) | 0.416 (0.554) | 0.561 | .579 |
| SDMT | 0.704 (1.26) | 0.225 (1.23) | −1.141 | .262 |
| TMT-A | 0.137 (1.23) | 0.555 (0.793) | 1.179 | .247 |
| TMT-B | −0.686 (2.37) | 0.035 (1.29) | 1.091 | .283 |
| WJ–III decision speed | −0.157 (0.859) | 0.062 (1.34) | 0.594 | .557 |
| WJ–III auditory working memory | 0.343 (0.638) | 0.352 (0.616) | 0.044 | .965 |

Structural MRI metrics [mean (SD)]

| T1 lesion volume (log cm³) | 0.744 (0.525) |
| T1 lesion volume (log cm³) | 0.581 (0.490) | 1303 (126.8) |
| Brain volume (cm³) | 1308 (113.9) | 12.71 (1.00) | −0.131 | .897 |
| Thalamic volume (cm³) | 11.55 (1.22) | 0.0978 | 3.07 | .004** |
| Normalized thalamic volume | .00887 (.00095) | .0035 | 3.64 | .001** |

Note. fMRI–SDMT = functional magnetic resonance imaging version of the Symbol Digit Modalities Test; EDSS = Expanded Disability Status Scale Score; BSMSS = Barratt Simplified Measure of Social Status; CES-DC = Centre for Epidemiological Studies Depression Scale for Children; PedsQL = Pediatric Quality of Life Inventory Multidimensional Fatigue Scale; RAVLT = Rey Auditory Verbal Learning Test; WASI = Wechsler Abbreviated Scales of Intelligence; SDMT = Symbol Digit Modalities Test; TMT-A and TMT-B = Trail Making Test Parts A and B; WJ–III = Woodcock-Johnson Test of Cognitive Abilities–3rd edition; F = female; M = male; MS = multiple sclerosis; Y = yes; N = no.

*Months since first attack. **Age at first attack. †Based on Dutch Handedness Questionnaire. ‡Only correct trials. §Normalized thalamic volume = thalamic volume/brain volume. *p < .01.

delayed recall; Schmidt, 1996). Participants also completed the following questionnaires: (a) Dutch Handedness Questionnaire (Van Strien, 2002); (b) Centre for Epidemiological Studies Depression Scale for Children (CES-DC; Faulstich, Carey, Ruggiero, Enyart, & Gresham, 1986); (c) Pediatric Quality of Life Inventory Multidimensional Fatigue Scale (PedsQL; Varni, Burwinkle, Katz, Meeske, & Dickinson, 2002); and (d) Barratt Simplified Measure of Social Status (BSMSS; Barratt, 2006).

Functional MRI version of the SDMT

Participants completed an fMRI-adapted SDMT (Figure 1), which differs from the traditional oral version of the SDMT in that it measures response time to stimulus presentation and involves a yes/no response. Using a keypad led by the dominant index and middle fingers, participants indicated “yes” or “no” whether or not a probe symbol-digit pairing matched any of

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![Figure 1. Example of fMRI–SDMT (functional magnetic resonance imaging version of the Symbol Digit Modalities Test) stimuli. Reprinted from Rypma et al. (2006) with permission from Elsevier.](image)
those shown in an array above. Response time and accuracy were measured. This is an event-related design whereby stimuli are presented for 4 s followed by a variable interstimulus interval of 0, 4, 8, or 12 s. There are a total of 52 trials for an entire duration of 5 min. E-prime software (Psychology Software Tools, Inc.) was used to present the stimuli and record responses. The tasks and instructions were presented on a back projection screen and were viewed through a mirror mounted onto the 32-channel head coil. Prior to completion of the task in the scanner, practice was given to ensure task familiarity and capacity (i.e., to ensure that MS patients did not have significant visual or motor impairment to preclude performance).

**MRI protocol**

Data were acquired on a Siemens MAGNETOM 3T Tim Trio MRI scanner at York University. Images were recorded using a gradient-echo T₂*-weighted echo-planar imaging sequence. Parameters included: echo time (TE) = 30 ms, voxel size = 3·0 × 3·0 × 40 mm³, field of view (FOV) = 256 × 191 × 136 mm, 34 axial slices, flip angle = 90°. This acquisition was proceeded by a sagittal high-resolution threedimensional (3D) magnetization prepared rapid gradient echo (MPRAGE) T₁-weighted image (time to repetition, TR = 2300 ms; TE = 2·96 ms; field of view = 256 × 240 × 192 mm; number of slices = 192; voxel size = 1·0 × 1·0 × 1·0 mm) that was used for anatomical definition. The duration of the fMRI–SDMT task was five minutes (150 volumes, 2000-ms repetition time) and was part of a fixed 90-min protocol. The scanning protocol included two other task-based fMRI paradigms, fMRI resting-state, diffusion tensor imaging (DTI), proton-density, T₂-weighted, and fluid-attenuated inversion recovery (FLAIR) sequences. The last three acquisitions were used to define total brain T₂ lesion volume according to previously published methods (Ghassemi et al., 2014). Global and regional brain volumes were obtained using the T1-weighted images also according to previously established methods (Aubert-Broche et al., 2013). Normalized thalamic volumes were calculated by dividing absolute thalamic volume by total brain volume. DTI images were processed using FMRIB Software Library (FSL) software library tools (www.fmrib.ox.ac.uk/fsl; S. M. Smith et al., 2004). After correction for eddy currents and head motion, as well as brain extraction, DTI images were entered into the program DTIFIT, which fits a diffusion tensor model at each voxel. Using DTIFIT, fractional anisotropy (FA) maps were created for each subject. Using tract-based spatial statistics (TBSS; S. M. Smith et al., 2007), a mean FA white matter skeleton was created that was applied to each subject’s FA image. The mean FA value across the entire white matter skeleton was computed for each subject.

**Functional MRI data analysis**

Functional MRI data analysis was carried out using FSL’s fMRI Expert Analysis Tool (FEAT) Version 5.3 (S. M. Smith et al., 2004). Preprocessing was done according to the following steps: (a) removal of the first 2 volumes; (b) high-pass temporal filtering (0.01 Hz); (c) motion correction by realigning via rigid transformation to the first volume (scans with a maximum displacement of more than 1.5 mm were discarded); (d) removal of skull and nonbrain tissue using FSL’s Brain Extraction Tool; (e) spatial smoothing at a Gaussian kernel of 5-mm full width at half maximum; and (f) spatial transformation to ICBM152 template space (Fonov et al., 2011). The transformation was done using a 12-parameter affine transformation (FLIRT) and incorporating the T₁-weighted image.

Functional MRI data were linearly modelled on a voxel-by-voxel basis using FILM (FMRIB’s improved linear model) with autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001). Each stimulus presentation (event) was modelled with a double gamma hemodynamic response function, which incorporates the late undershoot. The model took into account temporal shifts in the hemodynamic response function by including the temporal derivative as a regressor. Regressors corresponding to the six motion parameters were also included. Only correct trials were entered into this analysis. However, because most participants responded with >98% accuracy, the number of trials removed was negligible. The contrast of interest was BOLD activation during SDMT stimulus presentation compared to rest/interstimulus interval.

Higher level (between-subject) analyses were carried out using FLAME (FMRIB’s Local Analysis of Mixed Effects) as implemented using FSL (Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). An independent-sample t test was used to assess...
between-group differences in mean activation maps of the contrast of SDMT stimulus presentation compared to rest. For regions in which there were significant differences between groups, mean activation values were computed for each subject and then correlated with total $T_2$ lesion volume, thalamic volume (raw and normalized), brain volume, and mean FA of the white matter skeleton using Pearson correlation coefficients with SPSS software (Version 22.0). This was performed only in the pediatric MS group in order to determine whether differences in activation were related to the amount of MS-related structural pathology.

Tests for the association between mean activation and mean fMRI–SDMT response time were also conducted using FSL’s FLAME. This was first done separately for each group, followed by test of the interaction effect in order to determine differences between groups in the association between activation and response time. For all fMRI analyses, $z$ (Gaussianized T/F) statistic images were estimated and thresholded at $z = 2.3$ (Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994; Worsley, Evans, Marrett, & Neelin, 1992). Clusters of contiguous suprathreshold voxels were identified. The corrected $p$-value for each cluster was determined on the basis of its size according to Gaussian random field theory. Using this approach, the corrected $p$-value is the probability that a cluster of that particular size or larger could occur simply by chance. Significant clusters were those with a corrected $p < .05$ (Friston et al., 1994; Worsley et al., 1992).

**Results**

Summaries of demographic and disease-related variables are given in Table 1. As shown in Table 1, the patient group did not differ from the non-MS group on any age-normed neuropsychological measures of attention and processing speed. Based on the assessment battery, only two (10%) of the 20 pediatric-onset MS patients demonstrated evidence of cognitive impairment versus one (6%) of the 16 non-MS individuals. Eight (40%) MS patients versus three (19%) non-MS individuals had clinically elevated scores on the depression scale (CES-DC score > 15). There was no difference between the two groups with respect to the proportion showing elevated depressive symptoms ($x^2 = 1.89, p = .17$). Nine MS patients (45%) versus two (13%) non-MS individuals endorsed moderate or greater levels of fatigue (PedsQL score ≥36). No differences were observed between groups in handedness (Dutch Handedness Questionnaire score) or socioeconomic status (BSMSS score).

**Behavioral performance on the fMRI–SDMT**

No differences were found between groups on behavioral performance of the fMRI–SDMT with respect to mean response time and coefficient of variation in response time computed using only correct trials. Percentage accuracy also did not differ between groups and was near ceiling (average of 99% for both groups). The median (range) number of events used in response modelling was 51 for both groups, with range of 46–52 for the non-MS group and 44–52 for the MS group. Age was not correlated with fMRI–SDMT mean response time in either the MS or the non-MS group ($r = −.121, p = .632$, and $r = −.100, p = .712$, respectively). Among MS patients, fMRI–SDMT mean response time was also not correlated with thalamic volume ($r = .050, p = .845$) or $T_2$ lesion volume ($r = −.105, p = .678$). Faster response time on the fMRI–SDMT was correlated with a greater number of correct responses on the paper-and-pencil version of the SDMT when calculated across the entire sample ($r = −.335, p = .05$), suggesting that this paradigm was successful in assessing processing speed.

**Between-group activational differences on the fMRI–SDMT**

Both groups demonstrated widespread bilateral activation of the occipital cortex, precentral gyrus, and thalamus (Figures 2a and 2b). The non-MS group showed greater BOLD activation of the right middle frontal gyrus than the pediatric-onset MS group (Figure 2c).

**Relationships between brain activation, behavioral performance, and measures of structural pathology**

Faster response time correlated with greater BOLD activation of the bilateral occipital, anterior cingulate, right superior parietal, and thalamus regions in the MS group (Figure 3, clusters of significant correlation reported in Table 2). However, no significant correlations between regional activation and response time were detected in the non-MS group. In testing for the interaction effect, areas in
Figure 2. Mean fMRI–SDMT (functional magnetic resonance imaging version of the Symbol Digit Modalities Test) activation maps of (a) pediatric-onset MS (multiple sclerosis) group, and (b) non-MS group. In the pediatric-onset MS group, the highest peaks of activation were located in the left occipital pole \( z = 6.82 \) at cluster peak, MNI (Montreal Neurological Institute) coordinates \((x, y, z)\) in mm = \(-26, -96, -14, p < .001\), left precentral gyrus \( z = 4.59 \) at cluster peak, MNI coordinates = 28, 2, 44, \( p < .001 \), and thalamus \( z = 3.39 \) at cluster peak, MNI coordinates = 20, 2, 8, \( p = .027 \). In the non-MS group, the highest peak area of activation was in the left occipital pole \( z = 6.51 \) at cluster peak, MNI coordinates = \(-20, -96, -12, p < .001\). (c) \( t \) test results indicating the voxels in which the pediatric-onset MS group demonstrated significantly lower activation than the non-MS group cluster thresholded at \( p = .05 \). This was the right middle frontal gyrus \( z = 3.21 \) at cluster peak, MNI coordinates = 42, 30, 28, \( p = .0026 \). Sagittal, axial, and coronal slice location are indicated by crosshairs. All images are displayed in radiological convention (subject’s right side shown on the left). To view a color version of this figure, please see the online issue of the Journal.

Figure 3. Regions in which BOLD (blood-oxygen-level-dependent) activation was significantly negatively correlated with fMRI–SDMT (functional magnetic resonance imaging version of the Symbol Digit Modalities Test) mean response time in the pediatric-onset MS (multiple sclerosis) group cluster thresholded at \( p = .05 \). Statistics are reported in Table 2. All images are displayed in radiological convention. To view a color version of this figure, please see the online issue of the Journal.
which the interaction was significant are shown in Figure 4 and include the left middle temporal gyrus, angular gyrus, and superior occipital regions. The correlations between mean activation of this cluster and mean fMRI–SDMT response time in each group are shown in Figure 5.

Table 2. Clusters in which BOLD activation was significantly negatively correlated with response time in the pediatric-onset MS group.

<table>
<thead>
<tr>
<th>Cluster size</th>
<th>Brain region (local maxima)</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>z (at peak)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1951</td>
<td>Right inferior occipital</td>
<td>38</td>
<td>-86</td>
<td>-14</td>
<td>-3.81</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>901</td>
<td>Anterior cingulate</td>
<td>-4</td>
<td>6</td>
<td>32</td>
<td>-3.69</td>
<td>.0003</td>
</tr>
<tr>
<td>862</td>
<td>Right superior parietal</td>
<td>12</td>
<td>-56</td>
<td>74</td>
<td>-3.54</td>
<td>.0005</td>
</tr>
<tr>
<td>487</td>
<td>Thalamus</td>
<td>16</td>
<td>16</td>
<td>8</td>
<td>-3.33</td>
<td>.0234</td>
</tr>
<tr>
<td>459</td>
<td>Left superior occipital</td>
<td>-10</td>
<td>-86</td>
<td>46</td>
<td>-4.09</td>
<td>.0321</td>
</tr>
</tbody>
</table>

Note. BOLD = blood-oxygen-level-dependent; MS = multiple sclerosis. Montreal Neurological Institute (MNI) co-ordinates (in mm) are reported for the peak of each cluster.

Figure 4. Areas in which the interaction effect was significant indicating difference between groups in the association between activation and fMRI–SDMT (functional magnetic resonance imaging version of the Symbol Digit Modalities Test) mean response time, cluster thresholded at $p = .05$. These areas included the left middle temporal gyrus, angular gyrus, and superior occipital regions ($z = 4.06$, $p = .002$; Montreal Neurological Institute, MNI, coordinates = $-48, -76, 24$ in mm at cluster peak, which is indicated by crosshair; cluster size = 778 voxels). To view a color version of this figure, please see the online issue of the Journal.

Figure 5. Interaction effect demonstrating differences between groups in the association between activation and fMRI–SDMT (functional magnetic resonance imaging version of the Symbol Digit Modalities Test) response time. Mean activation (y-axis) is that of cluster depicted in Figure 4. MS = multiple sclerosis.
indicating the presence of a negative correlation \( r = -0.71, p = 0.001 \) in the pediatric MS group compared to a positive correlation \( r = 0.674, p = 0.004 \) in the non-MS group.

Given that activation of the right middle frontal gyrus emerged as a region with reduced activation in the MS group, we specifically evaluated whether this finding related to total \( T_2 \) lesion volume, thalamic volume (raw and normalized), brain volume, and mean FA of the white matter skeleton within the MS group. Mean activation of the right middle frontal gyrus (only of those voxels that showed differences between groups in the \( t \) test analysis) was not correlated with any structural MRI metric in the pediatric MS group, with values reported as follows: (a) thalamic volume in cm\(^3\) \( r = -0.179, p = 0.477 \); (b) total brain volume in cm\(^3\) \( r = -0.261, p = 0.295 \); (c) normalized thalamic volume fraction \( r = 0.50, p = 0.845 \); (d) \( T_2 \) lesion volume in cm\(^3\) \( r = -0.133, p = 0.600 \); (e) \( T_1 \) lesion volume in cm\(^3\) \( r = -0.150, p = 0.551 \); and (f) DTI derived FA of the entire white matter skeleton \( r = -0.250, p = 0.316 \).

**Discussion**

We evaluated regional activation patterns in pediatric MS patients performing the fMRI–SDMT, a task that interrogates processing speed. Both pediatric MS patients and non-MS youth demonstrated the expected bilateral activation of the motor and visual cortices. Activation of the right middle frontal gyrus, however, was significantly lower in our pediatric-onset MS patients, despite equivalent overall fMRI–SDMT performance between groups. In pediatric MS patients relative to the non-MS individuals, faster performance was associated with greater activation of the left superior occipital region.

Our findings have some similarity to those reported by Genova et al. (2009) who also found lower activation of bilateral frontal and parietal regions, including the right middle frontal gyrus, during fMRI–SDMT performance in 16 adult MS patients than in healthy individuals, albeit their patient cohort was significantly slower relative to the group. Lower activation correlated with \( T_2 \) lesion load, a finding that we did not replicate in our pediatric MS patients. We hypothesize that while visible lesion load did not contribute to the lower activation seen in our pediatric MS patients, the onset of MS during active myelination may impair relevant white matter myelinating pathways even in the absence of visible \( T_2 \) lesions. Supporting this concept, studies conducted in typically developing adolescents show greater recruitment of fronto-temporal regions with increasing age (Rubia et al., 2000). Future studies utilizing more complex cognitive tasks may provide further support for this theory. More complex tasks are likely to require utilization of frontally mediated attentional networks, and we hypothesize that pediatric MS patients may show reduced capacity to marshal these networks as visualized by reduced BOLD activation and clinically by impaired speeded performance.

A second aim of the current study was to examine the relationship between brain activation patterns and behavioral performance on the fMRI–SDMT. In the pediatric MS group, faster performance was associated with greater activation of a number of regions including the bilateral occipital cortices, anterior cingulate, right superior parietal cortex, and thalamus. This is similar to what has been observed in non-MS adults completing a high-speed relative to low-speed attention task (Lazeron, Rombouts, de Sonneville, Barkhof, & Scheltens, 2003). Using the same fMRI–SDMT paradigm as the one that we used, Genova et al. (2009) observed that activation of the thalamus and anterior cingulate was correlated with faster reaction time on the fMRI–SDMT in adult MS, a relationship that we confirmed in our pediatric patients. These regions are also considered part of the salience network (Seeley et al., 2007), which is thought to subserve, among other activities, the ability to process cognitive error processing and attention. The salience network may thus be an important contributor to performance on the SDMT. Genova and colleagues (2009) also found a greater number of areas (including the anterior cingulate and thalamus) correlating with processing speed performance in non-MS individuals than in MS patients. On the contrary, we found no relationship between processing speed and regional activation in our group, although we may have been underpowered to evaluate this relationship. In our comparison of the two groups, however, faster fMRI–SDMT performance was associated with greater activation of the left superior occipital region in the pediatric MS group, whereas the opposite directional trend was observed in the non-MS group. All of these results suggest that the regions that may mediate processing speed, or at least performance on the SDMT, may differ in pediatric MS patients compared to non-MS individuals.

Our study included a fairly homogeneous group of high-functioning MS patients whose
performance on the SDMT did not differ from that of the age-matched non-MS individuals. While this afforded the opportunity to investigate activation patterns in pediatric MS in the context of preserved information processing ability, the results are not generalizable to the pediatric MS population as a whole. Further studies will be informed not only by inclusion of pediatric MS patients with a broader range of cognitive performance, but also by large, longitudinal study designs that will permit evaluation of age at MS onset, disease duration, and disease impact over time on cognitive performance and fMRI activation patterns. Such studies will require multisite collaboration given the rarity of pediatric MS and the inherent challenges of obtaining research quality fMRI studies in younger patients.

We also acknowledge the potential impact of depressive symptoms on our findings. The CES-DC questionnaire indicated elevated scores for depressive symptoms in three non-MS individuals, although none had been formally diagnosed with depression nor had any of these individuals ever received treatment with antidepressants. Studies have suggested that mood disorders often underrecognized in adolescents, with prevalence reported as high as 33% (Lewinsohn, Hops, Roberts, Seeley, & Andrews, 1993; Merikangas et al., 2011). Depression is also common in persons with MS (Chwastiak et al., 2002; Patten, Beck, Williams, Barbui, & Metz, 2003). Depression has been shown to relate to reduced resting activation of the right dorsolateral prefrontal cortex (Koenigs & Grafman, 2009) and so could have influenced our results. However, while depression may be very relevant at the individual level, the impact on our findings may have been limited given that CES-DC scores did not differ between groups at the mean level, nor when examined as a function of proportion of participants in each group showing elevated depressive symptoms.

In summary, pediatric MS patients with age-expected performance on an information processing task, the SDMT, demonstrate less activation of prefrontal networks than non-MS individuals, raising the possibility that MS interferes with activation of neural networks maturing during the period of MS onset. In addition, faster performance was associated with greater activation of key posterior brain regions, potentially implicating a compensatory process required for enhanced performance in MS patients.

### Declarations of interests

B.B. serves as a consultant to Novartis to review magnetic resonance imaging (MRI) studies for a clinical trial, also as a consultant/advisor on the safe conduct of clinical trials for Biogen-IDEC and Sanofi, for which she is not remunerated. All other authors (N.A., C.T., J. G.S., M.A.B., S.M.D., B.R., M.L.) report no disclosures.

### Disclosure statement

No potential conflicts of interest was reported by the author.

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