Multiple sclerosis, cannabis, and cognition: A structural MRI study

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Abstract

Objective: A subset of patients with multiple sclerosis (MS) smoke cannabis to relieve symptoms including spasticity and pain. Recent evidence suggests that smoking cannabis further impairs cognition in people with MS and is linked to impaired functional brain changes. No such association, however, has been reported between cannabis use and structural brain changes, hence the focus of the present study.

Methods: Twenty patients with MS who smoke cannabis for symptom relief, and 19 matched non-cannabis-smoking MS patients were given the Brief Repeatable Neuropsychological Battery and structural MRI scans. Images were segmented into gray matter and white matter, and subsequently analysed with Partial Least Squares, a data-driven multivariate technique that explores brain-behaviour associations.

Results: In both groups, the Partial Least Squares analysis yielded significant correlations between cognitive scores and both gray matter (33% variance, \(p < .0001\)) and white matter (17% variance, \(p < .05\)) volume. Gray matter volume in the thalamus, basal ganglia, medial temporal, and medial prefrontal regions, and white matter volume in the fornix correlated with cognitive deficits. Crucially, the analysis indicated that brain volume reductions were associated with more extensive cognitive impairment in the cannabis versus the non-cannabis MS group.

Interpretation: These results suggest that cannabis use in MS results in more widespread cognitive deficits, which correlate with tissue volume in subcortical, medial temporal, and prefrontal regions. These are the first findings demonstrating an association between cannabis use, cognitive impairment and structural brain changes in MS patients.

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1. Introduction

Cognitive impairment occurs in approximately 40–60% of patients with multiple sclerosis (MS), and is associated with structural and functional brain changes (Hulst et al., 2013; Lansley et al., 2013). Approximately 14–18% of MS patients use cannabis for symptomatic relief from pain, spasticity and insomnia (Chong et al., 2006; Page et al., 2003). Evidence for enduring effects of cannabis on cognition and cerebral integrity in non-MS samples is equivocal, with negative studies offset by others revealing deficits in episodic memory, attention, and executive functioning (Crane et al., 2013), gray matter atrophy in the hippocampus and basal ganglia (Battaglini et al., 2012), and decreased white matter integrity in hippocampal efferent connections (Zalesky et al., 2012). Given the effects of MS on the brain, patients who smoke cannabis may be particularly vulnerable to similar cerebral changes and associated cognitive deficits.

Recent evidence confirms this: MS patients who smoke cannabis show further deterioration in processing speed, memory, and executive functioning (Ghaffar and Feinstein, 2008; Honarmand et al., 2011). Moreover, cannabis use is linked to less-efficient recruitment of brain regions during a working memory task (Pavisian et al., 2014). However, no MRI data to date show a specific association between structural brain changes and cognitive deficits in MS patients who smoke cannabis (Pavisian et al., 2014). Whether this reflects the absence of structural change or the limitations of the MRI analyses is unclear. Given the diffuse nature of MS-related cerebral pathology, and the wide distribution of cannabis receptors in the brain, it is possible that multivariate analyses may uncover underlying effects not observable using standard univariate approaches. To this end, the present study explored whether there is a structural basis for the cognitive differences present between MS patients who smoke cannabis and those who do not.

2. Materials and methods

2.1. Subjects

Details of patient recruitment and the descriptive data for this sample have been reported previously (Pavisian et al., 2014) and are...
summarized here. Thirty-nine patients (aged 18–60 years) with a diagnosis of MS were recruited from MS clinics. A diagnosis of MS was confirmed according to modified McDonald criteria (McDonald et al., 2001). Of these 39 subjects, 20 smoked cannabis on a regular basis (i.e. daily use, n = 17; 4–5 times/week, n = 2; 2–3 times/week, n = 1). With respect to the reason for use, 14/20 patients smoked cannabis for relief of physical symptoms, 2/20 for recreational purposes, and 4/20 smoked cannabis for both medicinal and recreational purposes. In terms of disease course, in the cannabis-smoking group 16/20 patients had relapsing–remitting, 2/20 patients had primary progressive, and 2/20 patients had secondary progressive MS. In the non-cannabis group, 17/19 patients had relapsing–remitting, 1/19 patients had primary progressive, and 1/19 patients had secondary progressive MS. Cannabis use was confirmed with a positive urine test for metabolites (a composite of THCCOOH glucuronide and THC-COOH). Twelve hours prior to testing, patients were asked to refrain from using cannabis in order to prevent any behavioural effects of acute intoxication. To ensure compliance, saliva samples were collected prior to testing to screen for Δ9-tetrahydrocannabinol (THC) use within the last 4–6 h (NarcoCheck). The 19 MS patients who had never used cannabis were matched to the cannabis group on all demographic and disease-related variables. All subjects in the non-cannabis group had negative urine and saliva tests.

2.2. Clinical variables

Age, sex, handedness, years of education, employment status, disease-related variables, and Expanded Disability Status Scale scores were obtained at the time of testing. Visual acuity was measured via Snellen chart. Estimates of premorbid IQ were obtained via the Wechsler Test of Adult Reading. All patients were given the Brief Repeatable Battery of Neuropsychological Tests (BRNB) in MS (Rao, 1990), consisting of tests measuring verbal memory (Selective Reminding Test; SRT) visual memory (10/36 Spatial Recall Test) processing speed (Paced Auditory Serial Addition Test; PASAT, 2 and 3 s; Symbol Digit Modalities Test; SDMT), and verbal fluency (Word List Generation; WLG). Mood and anxiety symptoms were measured using the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), using a cut-off score of 8 or greater to denote clinically significant anxiety or depression, respectively (Homanand and Feinstein, 2009). The modified fatigue impact scale was given to record subjective fatigue (Fisk et al., 1994).

2.3. Image acquisition

MRIs were collected on a 3 T MRI scanner (GE Healthcare, Milwaukee, WI) using an 8-channel head coil. T1-weighted anatomical scans (repetition time [TR] = 8.1 ms, echo time [TE] = 3.2, flip angle 5.8°, field of view [FOV] = 22 cm, 190 slices, slice thickness = 1 mm), PD/T2 scans (TR = 2500 ms, TE = 11.1/90, flip angle = 90°, FOV = 22 cm, 48 slices, slice thickness = 3 mm), and FLAIR images (TR = 9700 ms, TE = 140, FOV = 22 cm, 48 slices, slice thickness = 3 mm) were acquired for each subject. In addition, functional MRI scans were also acquired during a working memory task (n-back), as well as diffusion tensor imaging scans, which are reported elsewhere (Pavisi et al., 2014).

2.4. Imaging analysis

Images were preprocessed using SPM8, VBM8, and the Lesion Segmentation Toolbox (LST) (Schmidt et al., 2012), using standard settings. This process included first quantifying and subsequently filling WM lesions in order to limit segmentation error caused by the presence of WM lesions (Magon et al., 2014). After lesion filling, brain tissue was segmented and normalized to a common template space for voxel-wise testing. LST uses a lesion growth algorithm that considers information from T1 and FLAIR images simultaneously to identify white matter lesions. For the LST settings, a threshold value of κ = 0.2 was chosen and confirmed by visual inspection by a board-certified neurologist with expertise in MS, as a setting that captured the majority of white matter lesions without including non-lesion tissue in the calculation of overall lesion volume. Following identification, the resultant lesion tissue was quantified, and subsequently filled, using the average white matter intensity for each subject. This ensured an accurate estimate of gray matter (GM) volume, and that our analysis included only healthy tissue. Filled T1 images were then segmented via VBM8 using default parameters: images were co-registered using linear and non-linear transformations, and tissue segmented without tissue priors, using partial volume estimation. Segmented GM and WM images were normalized using high-resolution affine registration and the non-linear DARTEL algorithm to the DARTEL template provided with VBM8, in MNI space. Images were resampled to a resolution of 1.5 mm³ voxels and smoothed with an 8 mm full-width half-maximum Gaussian kernel.

Preprocessed GM and WM images were entered into a behavioural Partial Least Squares (PLS) analysis (Krishnan et al., 2011; McIntosh and Lobaugh, 2004). Generally, PLS is a data-driven, multivariate technique that finds independent latent variables which maximize the covariance between two sets of data via singular value decomposition. It has been used to characterize brain–behaviour associations in other patient groups where structural brain changes are more subtle, such as mild traumatic brain injury (Levine et al., 2013), and autism (Ecker et al., 2012).

Specifically, we employed behavioural PLS, which searches for latent variables that maximize the covariance between brain data (GM and WM voxels) and neuropsychological test scores. This analysis determines whether there exist patterns of regional brain volume change that are correlated with neuropsychological test scores and how these correlations may be similar or different across patient groups. Such an analysis would allow us to determine a) if regional GM and/or WM volume is associated with cognitive performance within each patient group, b) which brain regions and cognitive tests are correlated, and c) whether the pattern of those correlations differ between cannabis and non-cannabis groups. For this analysis, raw total scores from all 5 neuropsychological tests (SRT — total learning score across trials; 10/36 — total learning score across trials; WLG — total # of words generated across trials; SDMT — total correct; PASAT-2 — total correct) were entered simultaneously, each as individual variables of interest. We used raw scores as both groups were well-matched in terms of age, level of education, and estimated IQ.

The statistical significance of extracted variables was evaluated by 1000 permutation tests, using sampling without replacement. The robustness (i.e. salience) of each brain region’s contribution to the latent variable is determined through bootstrap resampling that resampled the data 500 times with replacement to estimate the standard error of the weight of each voxel on the latent variable. Brain regions were considered reliable if they had a ratio of weight to standard error (i.e. bootstrap ratio, equivalent to a z-score) greater than 4.5, corresponding to a probability of p < 0.0001. Because the mathematical procedure is completed in a single step, there is no need for correcting for multiple comparisons.

Furthermore, we also segmented T1-weighted images using FreeSurfer to obtain subcortical GM volumes, to conduct ancillary region of interest analyses. Specifically, we were interested in the thalamus and hippocampus, based on recent evidence demonstrating atrophy in these regions due to MS (Benedict et al., 2013; Pardini et al., 2014).

2.5. Ethics

All subjects provided informed consent prior to participation. In addition, the study was approved by the research ethics board at Sunnybrook Health Sciences Centre.

3. Results

There were no significant differences between the cannabis and non-cannabis groups in terms of age (cannabis M = 41.30, non-cannabis...
lobes, and both the lateral and medial prefrontal cortex (Fig. 1; dala, and fusiform gyrus), lateral temporal cortex, posterior parietal mus and basal ganglia, medial temporal regions (hippocampus, amyg-

dals M = 9.90, non-cannabis M = 110.85, non-cannabis M = 2.83, non-cannabis M = 2.47, 

showed a signi
c significative performance (33% of the variance). Brain regions where GM was 

diated patterns of brain–behaviour correlations: In the non-cannabis group, GM volume in the aforementioned regions was associated only with tests of processing speed (i.e. SDMT, PASAT-2), and WLG, a test of executive control that is timed and thus has a speeded component. However, in the cannabis group, GM volume was associated with performance on measures of processing speed (SDMT, PASAT-2) and verbal memory (SRT).

The second latent variable (17% of the variance, p < 0.05) represented the association between WM volume and cognitive performance, and showed a similar pattern of results: in the non-cannabis group, WM volume correlated with tests where processing speed contributes to task performance (SDMT, PASAT, WLG) whereas in the cannabis group, WM volume correlated with all five cognitive measures, including both verbal (SRT) and visual memory (10/36 recall) (Fig. 2). Regions of white matter correlating with cognition included the fornix continuing into the left fimbria, as well as WM in superior parietal and middle frontal regions (Table 3). Collectively, these results provide robust evidence to suggest that in cannabis-smoking patients, GM and WM volume reduction is associated in more widespread cognitive deficits.

As the PLS analysis revealed a significant correlation between subcortical GM and memory in the cannabis group but not the non-cannabis group, we ran additional region of interest analyses to test whether these correlations were significantly higher in the cannabis group, versus the non-cannabis group. Specifically, as the analysis identified left hippocampal involvement in cognitive performance, we computed correlations between verbal memory scores and left hippocampal volumes obtained via Freesurfer. There was a significant correlation between left hippocampal volume and verbal memory in the cannabis group (r = .52, p = .02), but not in the non-cannabis group (r = −.03, p = .90). Moreover, the magnitude of the correlation was significantly larger in cannabis group compared to the non-cannabis group (Fisher Zdifference = 1.73, p = .04, 1-tailed), suggesting that cannabis use moderated the association between cognition and hippocampal volume. As a comparison, we also examined correlations between left thalamic vol-

4. Discussion

To our knowledge, this is the first study in MS patients demonstrating a link between structural brain changes and cognitive deficits due to smoking cannabis. GM and WM volume in medial and lateral temporal regions, thalamus, basal ganglia, and prefrontal cortex was associated with more widespread cognitive deficits in cannabis-smoking MS patients, compared to patients who were cannabis-naïve. Specifically, decreased regional brain volume was associated with poorer performance on all neuropsychological tests in MS patients who smoked cannabis, whereas only speeded tasks correlated with brain volumes in non-

cannabis patients. Moreover, verbal memory was significantly correlat-
ed with hippocampal volume in the cannabis group, but not the non-
cannabis group, and cannabis-smoking MS patients also showed significantly lower performance on the 10/36 spatial recall test and the PASAT.

Taken together, this pattern of results raises the intriguing notion that MS patients who smoke cannabis may be less able to compensate for declines in memory, due to regional volume reductions. That is, given there were no group differences in terms of overall brain volume or subcortical structures, non-cannabis MS patients may be able to utilize other strategies to compensate to a degree for their memory, but not their processing speed deficits. Conversely, cannabis-smoking MS patients, who show significantly lower processing speed and visual memory scores, appear no longer able to compensate for either, and thus lower regional brain volumes in these patients was associated with poorer scores on all cognitive tests. These results complement the fMRI data elicited from the same sample of patients reported previ-

ously (Pavison et al., 2014), which revealed an increased and more anat-

omically diffuse pattern of cerebral activation during a working memory task in the cannabis group. Crucially, these functional and structural imaging findings cannot be explained by differences in demo-

graphic factors such as premorbid intelligence, disease severity, or in terms of differences in global measures of lesion, GM, or WM volumes as these were not significantly different between the two MS groups.

Given the absence of previous imaging studies in cannabis smoking MS patients, a review of data from non-MS samples is helpful in placing the current results in context. Notably, earlier systematic reviews pro-

vided mixed evidence linking structural brain changes to cannabis use in non-psychotic subjects (Martin-Santos et al., 2010). However, more recent studies are revealing a different picture. For example, Zalesky et al. (2012) found that effert hippocampal connections (i.e. fornix, fimbria) and white matter tracts in the corpus callosum were impaired in chronic cannabis users, with axonal integrity correlating with the age of onset for smoking cannabis. A meta-analysis of structural brain changes in healthy, long-term users concluded that selective brain re-

Table 1

<table>
<thead>
<tr>
<th></th>
<th>MS cannabis</th>
<th>MS non-cannabis</th>
<th>t-Test/χ²</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 20</td>
<td>n = 19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total brain tissue volume (mL)</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gray matter</td>
<td>680.37 (76.50)</td>
<td>675.18 (52.38)</td>
<td>0.25</td>
<td>0.81</td>
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<tr>
<td>White matter</td>
<td>514.26 (71.32)</td>
<td>493.76 (50.41)</td>
<td>1.03</td>
<td>0.31</td>
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<tr>
<td>Lesion</td>
<td>25.87 (21.19)</td>
<td>18.52 (21.82)</td>
<td>1.04</td>
<td>0.31</td>
</tr>
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</table>
highlighting once again the vulnerability of medial temporal and frontal regions to the deleterious effects of cannabis (Lorenzetti et al., 2014).

These imaging data are in turn helpful in explaining some of the cognitive findings to emerge from studies looking at long-term, non-psychotic cannabis smokers. As with the earlier structural neuroimaging data, initial findings were equivocal, with greater certainty regarding the adverse acute effects of Δ⁹-THC — one of the main cannabis metabolites — on verbal and working memory, but less clarity on whether the deficits endure beyond the period of intoxication (Schoeler and Bhattacharyya, 2013). A recent longitudinal study suggested that impairment may continue particularly if cannabis use started as an adolescent and continued for years. Of particular concern is the finding that in a situation such as this, multifocal cognitive deficits can persist even after cannabis cessation (Meier et al., 2012). While these conclusion have been called into question because of a failure to control for socio-economic status (Rogeberg, 2013), it is germane to note that recent findings of cognitive impairment in non-clinical samples of cannabis smokers (Thames et al., 2014), and a pattern of gender specific cognitive deficits (greater memory difficulties in females, more executive challenges in males) (Crane et al., 2013), fit with the structural brain MRI findings of selective hippocampal and prefrontal cortex atrophy. Moreover, in a recent systematic review, Batalla et al. (2013) noted a link between hippocampal volume and memory performance in cannabis users (Batalla et al., 2013). This region may be particularly sensitive to the effects of cannabis given its high concentration of endocannabinoid receptors (Glass et al., 1997; Herkenham et al., 1990).

The results from our MS sample dovetail with the findings summarized above. Notably, the regions that showed structural changes with cannabis use in the general population are the same as those associated with cognitive impairment in the present study. Specifically, we found correlations between GM volume in the hippocampus and poorer memory performance only in cannabis users. Furthermore, we found that

![Image of brain scan graphs]
WM volume in the fornix and connecting fimbria was associated with more widespread cognitive deficits in cannabis-smoking MS patients, the same WM tracts affected by long-term cannabis use in non-MS patients (Zalesky et al., 2012). Taken together, these results suggest that the hippocampus and its associated WM tracts are particularly vulnerable in MS patients who smoke cannabis.

Our findings are also consistent with cerebral atrophy due to MS-related pathology. It is now well-established that GM atrophy reliably occurs in the thalamus and putamen, with brain changes robustly linked to cognitive deficits (Benedict et al., 2013) and more extensive neurological disability (Riccitelli et al., 2012). Hippocampal atrophy also occurs to some extent in MS, and is associated with memory deficits (Pardini et al., 2014; Sicotte et al., 2008). Indeed, both patient groups showed significant correlations between thalamic volumes and tests of information processing speed. Interestingly, we found that GM volume reductions in the default-mode network (DMN; i.e. lateral temporal regions, precuneus, lateral parietal cortices, and medial prefrontal cortex) (Andrews-Hanna, 2012) was also correlated with poorer cognitive performance. Although the overall relevance of the DMN in MS requires further study, there is evidence that resting activity in this network predicts memory performance in MS patients (Sumowski et al., 2013). Furthermore, MS patients who are cognitively-impaired show decreased connectivity between DMN structures, compared to cognitively-intact MS patients (Louapre et al., 2014). Based on our findings that regional volume reductions in the DMN is associated with more widespread cognitive deficits in cannabis-smoking MS patients, one may posit that DMN integrity is necessary to mount any functional compensation for cognitive deficits, and thus volume loss in these regions would be associated with more global cognitive decline. This point is emphasized by the results of a study showing that in a sample of MS patients who received cognitive rehabilitation, the extent of functional connectivity within the DMN was predictive of lasting treatment gains (Parisi et al., 2014).

In arriving at our conclusions we are conscious that a relatively small sample may have obscured any subtle group differences in volume between the cannabis and non-cannabis groups. In addition, the lack of a matched healthy control group precluded our ability to determine whether patients' brains showed cerebral atrophy, relative to healthy brains. Nevertheless, we present evidence demonstrating the adverse effects of cannabis use on both GM and WM in MS: for patients who smoke cannabis, decreased GM and WM volume is associated with a wider array of cognitive deficits beyond that explained by MS alone.
Consequently, the potential clinical benefits of cannabis use in terms of symptom relief must be weighed against the negative impact on brain health and cognition, the full extent of which is only beginning to emerge. The findings also raise the intriguing question of what amount of cannabis use is required before such effects manifest, or whether cognitive deficits are reversible with cessation of cannabis use. Data from the general population suggest that this may be the case (Schreiner and Dunn, 2012). Whether this also holds true in MS subjects given the imaging data presented here must be questionable, but nevertheless worthy of future study.

**Author contributions**

Kristoffer Romero analysed and interpreted the results, and wrote the manuscript.

Bennis Pavisian collected the data, and contributed to analyzing the results, and reviewing the manuscript.

W. Richard Staines assisted in interpreting the results and reviewing the manuscript.

Anthony Feinstein assisted in interpreting the results and writing and reviewing the manuscript.

**Conflicts of interest**

Dr. Kristoffer Romero reports no disclosures.
Bennis Pavisian reports no disclosures.
Dr. W Richard Staines reports no disclosures.
Dr. Anthony Feinstein has served on scientific advisory boards for Merck Serono and Avanir Pharmaceuticals; has received speaker honouraria from Merck Serono, Teva Pharmaceutical Industries Ltd., Bayer Schering Pharma, and Biogen Idec; serves on the editorial boards of multiple sclerosis and the African Journal of Psychiatry; receives publishing royalties for the Clinical Neuropsychiatry of multiple sclerosis (Cambridge University, Press, 2007); chairs the Medical Advisory Committee for the Multiple Sclerosis Society of Canada; conducts...
neuropsychiatric evaluation, cognitive testing, and brain imaging in neuropsychiatry in his clinical practice; and receives research support from the Canadian Institute of Health Research, the Multiple Sclerosis Society of Canada and Teva Pharmaceutical Industries Ltd.

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References


Table 3

<table>
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<tr>
<th>Location label</th>
<th>Region</th>
<th>Location</th>
<th>Voxels (voxels)</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>BSR</th>
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<td>Frontal</td>
<td>R</td>
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<td>39</td>
<td>43.5</td>
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<td></td>
<td>R</td>
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<td>77</td>
<td>28.5</td>
<td>7.5</td>
<td>58.5</td>
<td>–5.23</td>
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<tr>
<td></td>
<td>R</td>
<td>Inferior frontal region</td>
<td>35</td>
<td>48</td>
<td>24</td>
<td>–13.5</td>
<td>–5.60</td>
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<tr>
<td></td>
<td>L</td>
<td>Superior frontal region</td>
<td>20</td>
<td>–22.5</td>
<td>37.5</td>
<td>–37.5</td>
<td>5.43</td>
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<tr>
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<td>–55.5</td>
<td>–61.5</td>
<td>–18</td>
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<td>27</td>
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<tr>
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<td>R</td>
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<td>30</td>
<td>6</td>
<td>–57</td>
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<tr>
<td>Other</td>
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<td>358</td>
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<td>13.5</td>
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<tr>
<td></td>
<td>L</td>
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<td>–34.5</td>
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<td>–15</td>
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<tr>
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<td>44</td>
<td>19.5</td>
<td>–31.5</td>
<td>37.5</td>
<td>4.69</td>
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BSR = bootstrap ratio.

Fig. 3. Correlations between gray matter Volumes in subcortical regions and cognitive performance in MS patients who do or do not smoke cannabis. A: Correlations between left hippocampal Volumes and verbal memory scores are significantly larger in the cannabis group. B: Correlations between left thalamic Volumes and processing speed scores are similar in patients who do or do not smoke cannabis.