MSJ Experimental Translational Clinical

Original Article

Cannabis-induced alterations in brain activation during a test of information processing speed in patients with MS

Multiple Sclerosis Journal – Experimental, Translational and Clinical

1: 1–10

DOI: 10.1177/2055217315588223

Bennis Pavisian, W Richard Staines and Anthony Feinstein

Abstract

Objective: The objective of this article is to determine the functional brain correlates of information processing speed in multiple sclerosis (MS) patients who smoke cannabis and those who are drug naïve.

Methods: Two neurologically and demographically matched samples of MS patients were enrolled, those who smoked cannabis daily ($n = 20$) and those who were cannabis naïve ($n = 19$). All participants completed the Brief Repeatable Battery of Neuropsychological Tests and underwent fMRI testing during which they were administered a modified version of the Symbol Digit Modalities Test (mSDMT).

Results: The cannabis group responded slower in nine of 11 blocks of the mSDMT ($p < 0.001$), showing a trend toward a slower response time ($p < 0.08$), but did not differ in the accuracy of response ($p < 0.18$). Both groups displayed activation in a prefrontal cortex-parietal network associated with information processing speed. When compared to the cannabis-naïve group, cannabis users showed less activation in the right ($p = 0.009$) and left ($p = 0.001$) thalami and increased activation in the anterior cingulate ($p = 0.006$).

Conclusion: Regular cannabis use in MS patients is associated with slower information processing speed and a pattern of cerebral activity that differs from cannabis-naïve individuals, most notably in a bilateral reduction of thalamic activity.

***Keywords*:** Multiple sclerosis, cannabis, fMRI, information processing speed, Symbol Digit Modalities Test, thalamus

Date received: 6 March 2015; accepted: 28 April 2015

Introduction

A recent review from the American Academy of Neurology concluded that empirical data relating to the putative benefits of smoking or ingesting cannabis in a disease like multiple sclerosis (MS) were lacking.[1] Nevertheless, approximately 14–22% of people with MS continue to use cannabis for widely divergent reasons such as symptom management and recreation.[2,3] There is also emerging literature suggesting that smoking cannabis may further compromise cognition in this population. Three studies with three different samples of participants, albeit from the same research group, have reported that MS cannabis users have more cognitive difficulties than demographically and disease-matched MS patients who are cannabis naïve.[4–6] These deficits encompass information processing speed, verbal and visual-spatial memory, executive function and visual-spatial abilities. Given that 40–70% of people with MS are cognitively compromised to begin with, any other agent further compromising cognition must be cause for concern.

Tentative evidence also indicates that MS cannabis users have a more dysfunctional pattern of cerebral activation when performing a cognitive task. In a study exploring working memory, MS patients who tested positive for the presence of cannabis metabolites not only performed more poorly relative to cannabis-free individuals as the task became increasingly complex, they also demonstrated two notable differences on functional magnetic resonance imaging (fMRI), namely increased activation in neural networks implicated in working memory

Correspondence to:
Bennis Pavisian
Sunnybrook Health Sciences Centre, 2075 Bayview Ave., Toronto, Ontario, M4N 3M5 Canada.
bennis.pavisian@sri.utoronto.ca

Bennis Pavisian
Sunnybrook Research Institute, University of Toronto, Canada

W Richard Staines
Department of Kinesiology, University of Waterloo, Canada

Anthony Feinstein
Sunnybrook Research Institute, University of Toronto, Canada
University of Toronto, Canada

and a more diffuse pattern of cerebral activation in general. The present study looks to expand this focus of inquiry by exploring cerebral activation linked to the performance of the Symbol Digit Modalities Test (SDMT), one of the more sensitive markers of cognitive impairment in MS.[7,8]

Sample selection

Information on patient recruitment has been reported previously.[5] To summarize, two groups of right-handed individuals with a confirmed diagnosis of MS were enrolled. The first ($n = 20$) were daily cannabis users while the second ($n = 19$) were cannabis naïve. All 20 participants designated users smoked cannabis. There was no other method of use. The groups were matched on demographic and neurologic variables. All participants had normal or corrected-to-normal vision.

Cannabis assessment

Cannabis use was confirmed on urine testing by the presence of two metabolites, 11-nor-delta-9-THC-9-carboxylic-acid-B glucuronide (THC-COOH glucuronide) and 11-nor-delta-9-THC-9-carboxylic acid (THC-COOH). Participants were instructed not to smoke cannabis for at least 24 hours prior to testing. To ensure the patients were not acutely intoxicated during testing, saliva samples were collected to screen for Δ9-tetrahydrocannabinol (THC) using NarcoCheck, which detects cannabis use within four to six hours. Patients who were acutely intoxicated were excluded from the study. All participants in the cannabis group also completed the Cannabis Withdrawal Scale.[9] Total scores below 51 indicate the absence of withdrawal symptoms.

Demographic and neuropsychological testing

All participants were administered the MS Brief Repeatable Neuropsychological Battery,[10] which includes measures of verbal (Selective Reminding Test Revised) and visual (10/36 Spatial Recall Test) memory, information processing speed (Paced Auditory Serial Addition Test (2s and 3s) and SDMT), and attention and semantic memory (Word List Generation). In addition, dexterity was assessed with the Purdue Pegboard Test,[11] pre-morbid intellectual quotient (IQ) was assessed with the Wechsler Test of Adult Reading (WTAR),[12] anxiety and depression with the Hospital Anxiety and Depression Scale (HADS),[13] in which scores ≥ 8 denote clinically significant anxiety and depression, respectively,[14] and fatigue with the modified Fatigue Impact Scale (mFIS).[15]

Ethics

All participants in the present study provided informed consent prior to participation. The study was also approved by the research ethics board at Sunnybrook Health Sciences Center and the St. Michael's Hospital.

MRI scanning parameters

MRIs were collected on a 3T MRI scanner (GE HealthCare, Milwaukee, WI, USA) using a standard birdcage head coil. Prior to the functional scans, high-resolution anatomical scans were acquired for each participant (repetition time (TR) = 8.1 ms, echo time (TE) = 3.2, flip angle (FA) = 8 degrees, field of view (FOV) = 22 cm, 190 slices, slice thickness = 1 mm) for later co-registration with functional maps. Proton density (PD)/T2 (TR = 2500 ms, TE = 11.1/90, FA = 90 degrees, FOV = 22 cm, 48 slices, slice thickness = 3 mm) and fluid-attenuated inversion recovery (FLAIR) (TR = 9700 ms, TE = 140, FOV = 22 cm, 48 slices, slice thickness = 3 mm) images were also collected.

Details pertaining to the methods used to determine lesion, gray-matter (GM) and white-matter (WM) volumes have been reported previously.[5] To summarize, the T1 and PD/T2 images were used for brain extraction and generation of a brain mask encompassing the full intracranial cavity. Segmentation of brain tissues were divided into GM, WM and cerebral spinal fluid (CSF) using the brain mask. The fully automatic segmentation algorithm is histogram based and uses an expectation maximization algorithm to model a four-Gaussian mixture both for global and local histograms. The means of the local Gaussians for GM, WM, and CSF are used to set local thresholds for tissue classification. fMRI acquisitions used T2-weighted gradient echo imaging to obtain blood oxygenation level-dependent (BOLD) images, from which maps of inferred neuronal activation were derived. The current protocol involves single-shot spiral k-space acquisitions with in-out readout, as developed at Stanford University (FA/TE/TR = 70 degrees/30 ms/2000 ms, 20 cm FOV, 5 mm thick, 26 slices, effective matrix size 90×90). The duration of the SDMT fMRI scan was nine minutes and 26 seconds.

fMRI paradigm

The SDMT,[16] a test of information processing speed, was modified for fMRI presentation to avoid verbal responses.[17] Participants responded to each visual stimulus via a two-button response pad (Current Designs Inc) with accuracy and response times recorded in E-prime 2.0 Professional. The SDMT

Table 1. Demographic and disease characteristics of MS cannabis and noncannabis groups.

	MS cannabis $n = 20$ *M (SD)*	MS noncannabis $n = 19$ *M (SD)*	*t*-test/X^2	*p* value
Demographics				
Age	41.30 (11.28)	43.89 (9.09)	−0.78	0.44
Females, *n* (%)	6.00 (30.00)	6.00 (31.60)	0.01	0.92
EDSS total score	2.83 (2.20)	2.47 (1.52)	−0.62	0.54
Disease-modifying drugs, *n* (%)	7.00 (35.00)	9.00 (47.40)	0.62	0.43
Disease duration, years	9.50 (7.24)	9.90 (9.60)	−0.79	0.44
Relapsing–remitting	16.00	17.00	0.67	0.88
Purdue Peg, Right Hand	10.5 (2.46)	10.2 (2.85)	−0.40	0.69
Urine concentration of cannabis metabolite (μg/l)	246.00 (90.00)	0.00	–	–
Neuropsychological tests				
Estimated IQ (WTAR)	110.85 (9.13)	110.57 (8.21)	0.97	0.92
Selective Reminding Test (long-term storage)	44.30 (16.60)	45.37 (13.6)	−0.22	0.95
10/36 Spatial Recall Test (total learning)	**16.40 (7.40)**	**20.79 (4.10)**	**–2.29**	**0.03**
PASAT-2 (total # correct)	**28.35 (13.30)**	**39.47 (15.35)**	**–2.41**	**0.02**
SDMT (total score)	41.55 (9.70)	43.53 (10.00)	−0.63	0.54
HADS - Depression	11 (5.5)	8 (4.0)	0.85	0.42
HADS – Anxiety	13 (6.5)	11 (5.8)	0.21	0.65
mFIS, total score	42.9 (20.1)	39.2 (20.1)	0.58	0.57
CWS, mean total score	15.05 (18.36)	0.00	–	–
SDMT fMRI behavioral data				
SDMT response time (ms)	2139 (347)	1978 (383)	1.79	0.08
SDMT accuracy (out of 66)	53.3 (10)	58.2 (6.6)	−1.38	0.18

MS: multiple sclerosis; EDSS: Expanded Disability Status Scale; IQ: intellectual quotient; WTAR: Wechsler Test of Adult Reading; COWAT: Controlled Oral Word Association Test; PASAT: Paced Auditory Serial Addition Test; SDMT: Symbol Digit Modalities Test; HADS: Hospital Anxiety and Depression Scale; mFIS: Modified Fatigue Impact Scale; CWS: Cannabis Withdrawal Scale.

is a simple substitution task. Using a reference key, patients were asked to determine if a pair of geometric symbols and numbers matched a key of two rows of nine boxes that are shown in the middle of the screen, where the top row contains geometric symbols and is matched with the bottom row, which contains numbers 1 through 9. Each stimulus contained a lone pair of boxes presented below the key that also contained a geometric symbol in the top box and the number below. Patients were instructed to press the ''green'' button when the lone pair of geometric symbol and number matched the key presented on the current slide, and the ''red'' button when the presented lone pair did not match the presented key. The mSDMT was presented in 26-second blocks with intermittent 26-second ''resting'' blocks where only a fixation symbol was present in the middle of the screen.

Image pre-processing and statistical analyses were performed using BrainVoyager QX 2.8 (Brain Innovation, Maastricht, The Netherlands). Prior to co-registration, the fMRI data were pre-processed by linear trend removal, Gaussian spatial smoothing with a full-width half-maximum value of 6 mm, and a three-dimensional motion correction using trilinear interpolation to detect and correct for small head movements during the scan by spatially realigning all subsequent volumes to the fifth volume. Functional data sets were transformed into Talairach space by co-registering the functional data with the anatomical data for each participant. Subsequent analyses were performed within individual participants and across the groups. The first five of 289 volumes of each time series were deleted to remove transient signal changes related to the steady magnetization.

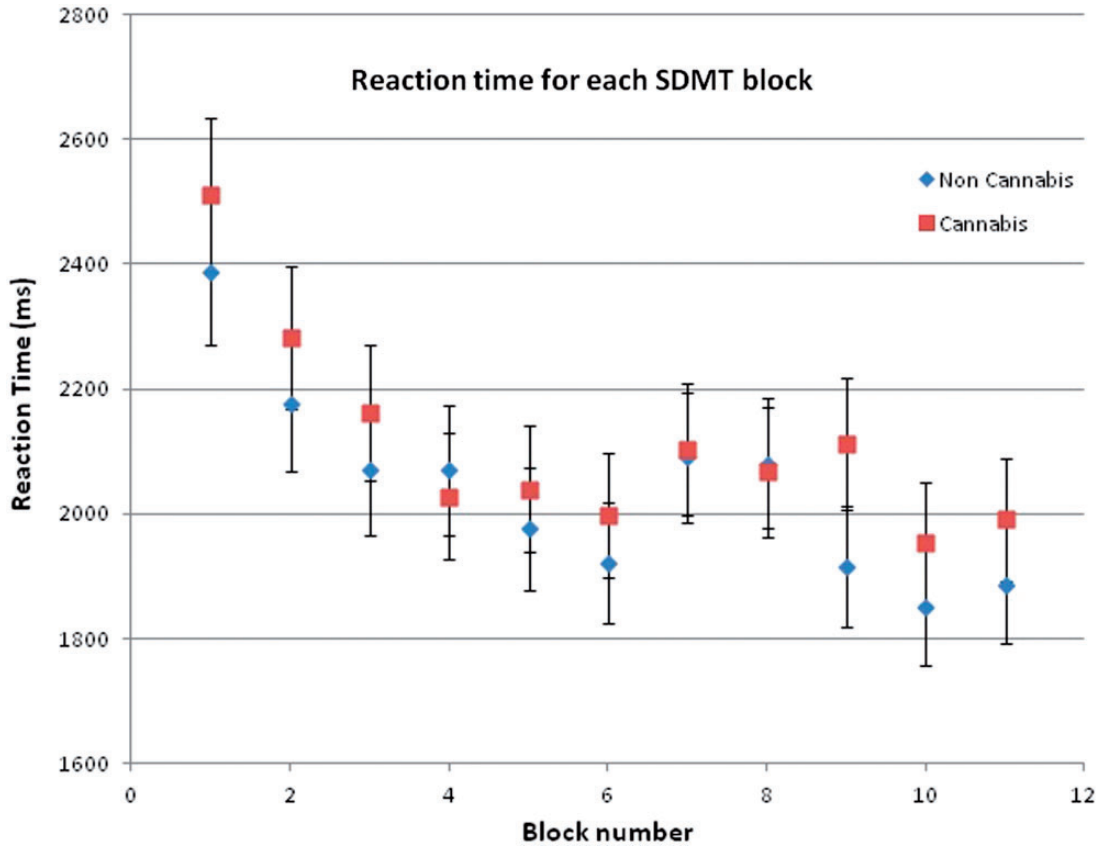

Figure 1. Reaction times for each mSDMT block.
mSDMT: modified Symbol Digit Modalities Test; SDMT: Symbol Digit Modalities Test.

In order to statistically evaluate the cerebral activation during the SDMT task, a multiple regression method was used using the task blocks as predictors with the resting blocks serving as a baseline. The stimulation protocol was convolved with a boxcar hemodynamic response function[18] to account for the expected shape and temporal delays of the physiological response and was used in the general linear model. A random-effects analysis was used within groups to generate activation maps. A random-effects analysis was also used to compare activations across the groups. Contrast maps were created using a voxel-based approach to show relative changes between tasks (SDMT > Rest) and across groups (Noncannabis > Cannabis). Activated voxels in the with-in group analysis were considered significant if the threshold exceeded a Bonferroni correction, while activated voxels in the between-group analysis were considered significant if they exceeded a threshold of $p < 0.001$ and forming 33 contiguous voxels, based on a cluster size threshold estimator stimulation (BrainVoyager QX 2.6 software, Brain Innovation, corresponding to a corrected threshold of $p < 0.05$.[19] The center of gravity and *t*-statistics were extracted for each significant cluster. All functional imaging analysis was conducted blind to the cognitive results.

Results

Demographic, neurologic and cognitive data

Demographic and neurologic findings did not differ between the two groups (see Table 1). There were no group differences in terms of weekly alcohol consumption ($t = -0.69$; $p = 0.95$) or smoking cigarettes ($x^2 = 0.27$; $p = 0.61$). Cannabis smokers were more impaired on the 10/36 Spatial Recall Test and the 2-second PASAT relative to noncannabis users (see Table 1). On the mSDMT there was no difference in the accuracy of response, but cannabis users responded slower. Our block design involved 11 sequential groups of symbols and numbers. In nine of these, the cannabis group had slower response times than the noncannabis group (chi square = 36.00; $p < 0.001$; see Figure 1). This translated into a trend for an overall slower response time in the cannabis group for the entire test (see Table 1). There were no group differences on the HADS and mFIS.

Table 2. Brain activation for the within-group contrasts using a Bonferroni correction.

Brain region	*x*	*y*	*z*	*z* score	Number of voxels
CANNABIS					
Left inferior frontal gyrus	−43	3	26	8.94	652
Left medial frontal gyrus	−8	11	47	8.50	449
Left superior frontal gyrus	−10	10	48	8.57	467
Right precentral gyrus	40	−1	33	8.19	530
Left precentral gyrus	−43	1	27	9.27	927
Right superior parietal lobule	26	−62	48	11.6	2893
Left superior parietal lobule	−31	−59	45	12.91	2402
Right inferior parietal lobule	42	−36	38	8.08	1339
Left inferior parietal lobule	−46	−37	45	8.01	1451
Left angular gyrus	−30	−59	38	11.24	911
NONCANNABIS					
Right inferior frontal gyrus	−46	4	31	11.3	501
Right medial frontal gyrus	6	2	50	12.0	488
Left medial frontal gyrus	−7	9	41	11.77	407
Left middle frontal gyrus	−43	−3	47	9.54	1022
Left superior frontal gyrus	−7	10	48	10.96	2441
Right precentral gyrus	38	−5	30	9.69	2249
left precentral gyrus	−40	−5	48	12.34	2155
right posterior cingulate gyrus	5	−50	27	−9.20	447
Right precuneus	23	−63	31	8.91	612
Left precuneus	−22	−65	49	11.89	786
Right inferior parietal lobule	37	−44	49	11.51	1110
Right thalamus	17	−20	12	9.69	1147
Left insula	−34	16	3	11.65	2536
Left superior parietal lobule	−25	−63	51	12.2	1745

Structural MRI

The two MS groups did not differ in T2 ($t = 0.56$; $p = 0.58$) and T1 ($t = 0.25$; $p = 0.81$) lesion volumes and whole-brain gray- ($t = -0.29$; $p = 0.78$) and white- ($t = 0.51$; $p = 0.62$) matter volumes.

fMRI results

Common areas of activation within the cannabis and noncannabis groups were found in the left medial frontal, left superior frontal, right and left precentral gyri, the left superior parietal lobule, and right inferior parietal lobule, but some regional differences were present too (see Table 2 and Figure 2). Between-group analysis revealed significantly reduced activation in the cannabis group in the following regions: the left and right thalamus, the parahippocampal gyrus, the superior temporal gyrus, the left inferior gyrus, and the left and right precuneus (see Table 3 and Figure 3). Increased activation in the cannabis group was observed in the right and left superior frontal gyri, left middle temporal gyri, right anterior cingulate, and the right posterior cingulate gyrus.

Discussion

The most notable results to emerge from this study were cannabis-smoking MS patients relative to those who were cannabis naïve had slower reaction times on the mSDMT and displayed a different pattern of cerebral activation when completing the mSDMT. Before discussing the functional imaging findings, a closer inspection of the mSDMT results is necessary.

The slower response of the MS cannabis group on the mSDMT cannot be attributed to cannabis withdrawal as our results reveal. They also cannot be explained by greater impairments in fine motor coordination or motor speed because the two groups performed similarly on the Purdue Pegboard task. The cannabis users did not, however, make more errors on the mSDMT and traditional paper versions of the SDMT. The latter result is at odds with findings from two of our previous studies in which cannabis users were found to be more impaired. While a bigger sample size may have tipped the present result

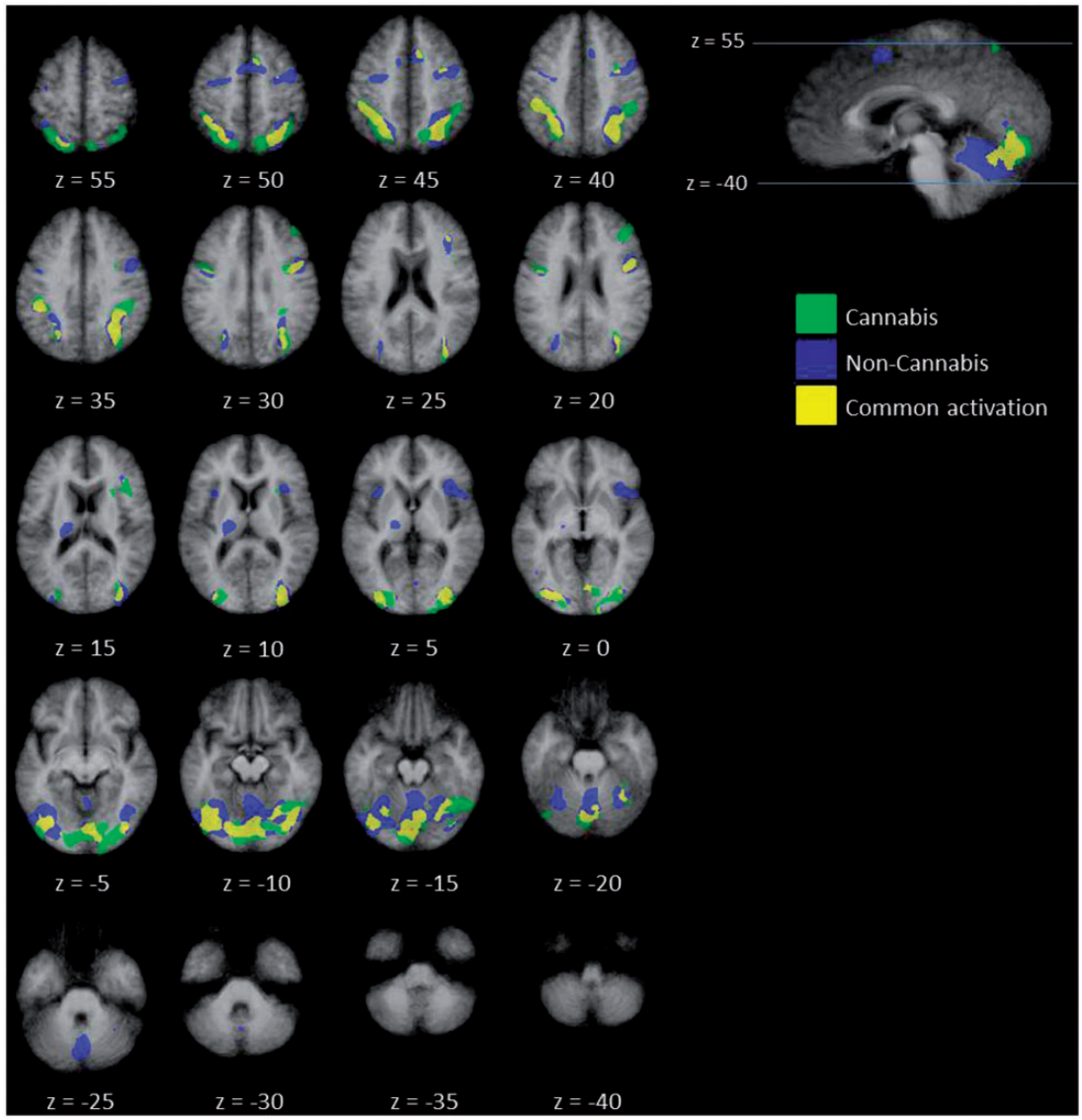

Figure 2. Within-group activations of the SDMT >Rest contrast using a Bonferroni correction.
SDMT: Symbol Digit Modalities Test; Rest: resting state.

into significance by removing the possibility of type II error, it is germane to note that the SDMT, while indisputably a sensitive test of cognition in MS[20] does not always reveal group differences. To begin with, SDMT comparisons between MS patients and healthy controls have, on occasion failed to find differences, even in the presence of robust sample sizes.[21,22] Of particular relevance to our data are two fMRI studies using a similar paradigm to the one we adopted in which no differences were found between people with MS and healthy controls in their accuracy of response,[23,24] although the MS group members were again slower in their response times.

The absence of significant differences in performance accuracy on the mSDMT in our study was not matched by the fMRI data. Here a different pattern of cerebral activation emerged between the two groups. Given that there are no mSDMT-fMRI data in either people with MS or healthy controls who smoke cannabis, we need to look elsewhere to place our results in a broader context. A useful place to start is the information processing speed-fMRI literature uncontaminated by cannabis use. A consistent finding to emerge here irrespective of the cognitive test used is the central role played by a prefrontal cortex (PFC)-parietal network.[25,26] In the study referenced earlier in which MS patients were

Table 3. Brain activation for the between-group contrast (Noncannabis > Cannabis) at a threshold of $p < 0.05$ corrected.

Brain region	*x*	*y*	*z*	*z* score	*p* value	Number of voxels
CANNABIS						
Right superior frontal gyrus	17	28	51	−2.74	0.009	696
Left superior frontal gyrus	−10	55	−18	−3.92	>0.001	520
Left middle temporal gyrus	−43	−65	27	−2.82	0.008	706
Right anterior cingulate	2	28	−6	−2.93	0.006	2064
Right posterior cingulate gyrus	−4	−41	33	−2.81	0.009	1719
Cerebellum	−40	−59	−33	−2.83	0.008	471
NONCANNABIS						
Left inferior frontal gyrus	−28	13	−15	3.37	0.002	948
Left middle frontal gyrus	−46	13	24	2.74	0.009	585
Left superior temporal gyrus	−49	4	3	3.34	0.002	1064
Right cuneus	5	−98	15	3.70	>0.001	1771
Right precuneus	11	−59	57	2.50	0.017	596
Left precuneus	−31	−47	48	2.77	0.009	904
Right thalamus	14	−20	12	2.76	0.009	999
Left thalamus	−16	−17	0	3.64	>0.001	865
Right parahippocampal gyrus	35	−23	−21	3.42	0.002	559
Left parahippocampal gyrus	−16	−14	−30	3.31	0.002	588
Left culmen	−1	−56	−6	2.81	0.008	913
Cerebellum	23	−65	−33	4.05	>0.001	5809

slower, but equally accurate in their responses relative to healthy individuals, reduced cerebral activation in the PFC-parietal network was seen in the MS group.[24] Surprisingly, however, the MS group displayed no signs of compensatory activity, a finding at odds with results from another study also probing information processing speed, albeit with the Computerized Test of Information Processing.[27] Here, increased activation was discernible in the MS group in the prefrontal cortex and right temporal gyri. As it is unlikely that these contradictory findings are due to differences in the cognitive paradigm used, further research will be needed to clarify the situation. Greater certainty, however, pertains to the cerebral response to more demanding tests of processing speed. Reducing the inter-stimulus interval produces not only more activation within the well described fronto-parietal regions, but also the recruitment of additional brain regions that extend from the presupplementary motor area into the cingulate gyrus.[25]

Returning to our study, we see that our data overlap to a degree with the studies reported above. Both the cannabis and noncannabis groups showed activation in the PFC and parietal regions when performing the mSDMT in keeping with this well-defined information processing circuit. There was also common activation in the precentral gyrus given the motor component to the task. However, a between group analysis confirmed thalamic activation in the cannabis naïve group only. The importance of the thalamus in mediating aspects of cognition in MS has long been recognized. Enlargement of the third ventricle, considered a proxy for thalamic atrophy, was the earliest finding on CT brain scan to correlate with impaired cognition.[28] Since then, numerous brain MRI studies have replicated and extended this finding.[29,30] In a study that explored the relationship between five brain MRI indices of pathology (T1 and T2 lesion volume, third ventricle width, bicaudate ratio and brain parenchymal fraction) and a host of cognitive variables, it was third ventricle width that emerged as the most robust predictor of cognitive impairment.[31] Moreover, the strongest correlation was found with the SDMT. More recently, subtle indices of thalamic pathology, such as resting state functional connectivity[32] and altered diffusion tensor imaging metrics such as mean diffusivity[33] have been linked to impaired cognition in MS patients.

A relative fall-off in thalamic activation may therefore explain, in part, why the reaction times are

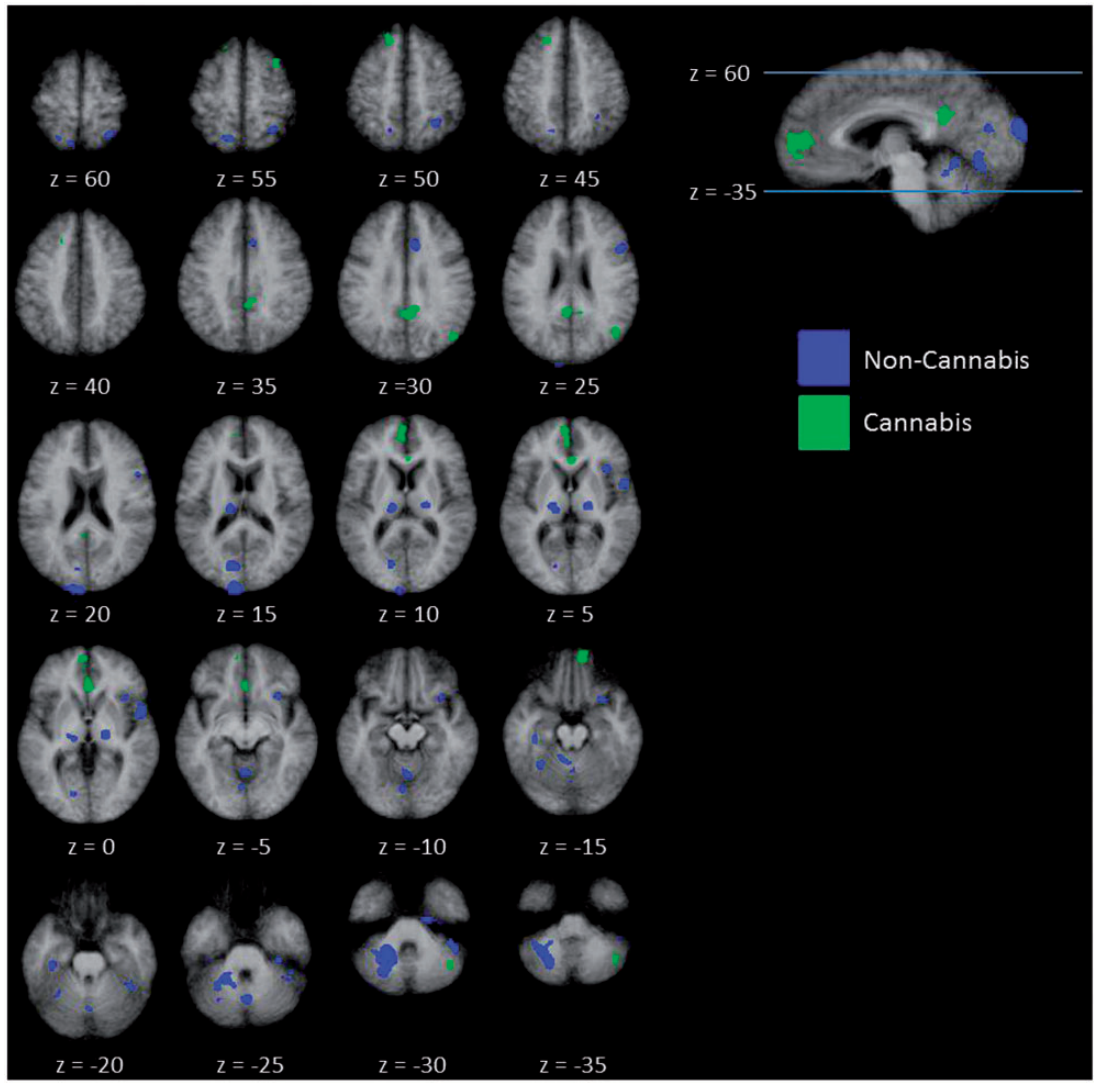

Figure 3. Between-group activations for the cannabis and noncannabis groups ($p < 0.05$).

slower on the mSDMT in MS patients who smoke cannabis. The CB1 cannabinoid receptor is present in the thalamus, albeit in lower concentrations than in the basal ganglia and hippocampus (particularly the dentate gyrus, CA3 region), amygdala and hypothalamus.[34] Δ^9-THC induced decrease in neuronal firing is thought to modulate the memory impairment associated with cannabis use,[35] and the same mechanism may well be implicated when it comes to information processing speed. The challenge, however, when drawing an analogy between these data and our own is that we must first take into account the effects of MS on brain activity and from there factor in the potential effects of the Δ^9-THC. Confining our observations to the MS cannabis naïve group the pattern of cerebral activation seen resembles that reported in a study that used the same mSDMT paradigm albeit with a slightly slower speed of digit presentation, i.e. PFC-parietal plus ancillary ancillary responses from the thalamus, insula and anterior cingulate.[24] When we focus on the MS cannabis group we see a reduction in thalamic activation as mentioned above, but more prominent activity in the anterior cingulate. The effects of cannabis on the limbic system, of which the anterior cingulate is a part, are well described[36] and as such the activation that is apparent may possibly reflect a further attempt at brain compensatory activity as it pertains to processing speed. Here it is noteworthy that a critical review of the effects of cannabis on cognition and brain activation in healthy subjects observed that a common thread linked the 11 fMRI studies deemed methodologically worthy of inclusion, namely increased activation in anterior cingulate and PFC

regions.[37] While none of these 11 studies used the SDMT, the cognitive domains that were challenged were attention, memory and processing speed, hence the parallels with our cannabis imaging data. In keeping with this finding, and bolstering our data, a double-blind, placebo-controlled positron-emission tomography (PET) study of auditory attention in 12 healthy recreational cannabis users scanned before and after smoking cannabis and placebo cigarettes, reported significant between group differences. In particular, the cannabis group showed increased regional cerebral blood flow (rCBF) in the anterior cingulate and medial prefrontal regions and reduced rCBF in the thalamus, among other regions.[36] This raises the question of whether altered rCBF influenced the fMRI findings in our study. While our methodology cannot answer this, such an association has been reported,[38,39] albeit not in the cannabis literature.

Our study is not without limitations. For example, the inclusion of healthy, cannabis-smoking control individuals would have been helpful when it came to parsing the mSDMT fMRI data with greater accuracy. This would also have obviated our need to extrapolate findings from other imaging studies that used different information processing speed paradigms. Nevertheless, our mSDMT and fMRI data provide further clues as to the potentially negative effects of smoking cannabis of the mentation of patients with MS. In arriving at our conclusions we are cognizant of anecdotal evidence from MS patients who report that cannabis can alleviate some of their symptoms of the disease. As with any drug treatment, weighing the benefits and side effects is necessary in informing choice. Our data are in need of replication, but when seen alongside previous studies, introduces a cautionary note into the unfolding cannabis story.

Funding

This research was funded by the Multiple Sclerosis Society of Canada.

Conflict of interest

Bennis and Richard reports no conflicts of interest. Feinstein has served on scientific advisory boards for Merck Serono and Avanir Pharmaceuticals; has received speaker honoraria 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.

References

1. Koppel BS, Fife T and Youssof S. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2014; 82: 1556–1563.
2. Chong MS, Wolff K, Wise K, et al. Cannabis use in patients with multiple sclerosis. *Mult Scler* 2006; 12: 646–651.
3. Clark AJ, Ware MA, Uk M, et al. Patterns of cannabis use among patients with multiple sclerosis. *Neurology* 2004; 62: 2098–2100.
4. Honarmand K, Tierney MC, O'Connor P, et al. Effects of cannabis on cognitive function in patients with multiple sclerosis. *Neurology* 2011; 76: 1153–1160.
5. Pavisian B, MacIntosh BJ, Szilagyi G, et al. Effects of cannabis on cognition in patients with MS: A psychometric and MRI study. *Neurology* 2014; 82: 1879–1887.
6. Ghaffar O and Feinstein A. Multiple sclerosis and cannabis: A cognitive and psychiatric study. *Neurology* 2008; 71: 164–169.
7. Drake AS, Weinstock-Guttman B, Morrow SA, et al. Psychometrics and normative data for the Multiple Sclerosis Functional Composite: Replacing the PASAT with the Symbol Digit Modalities Test. *Mult Scler* 2010; 16: 228–237.
8. Benedict RH, Cookfair D, Gavett R, et al. Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *J Int Neuropsychol Soc* 2006; 12: 549–558.
9. Allsop DJ, Norberg MM, Copeland J, et al. The Cannabis Withdrawal Scale development: Patterns and predictors of cannabis withdrawal and distress. *Drug Alcohol Depend* 2011; 119: 123–129.
10. Rao SM, Leo GJ, Bernardin L, et al. Cognitive dysfunction in multiple sclerosis: I. Frequency, patterns, and prediction. *Neurology* 1991; 41: 685–691.
11. Tiffin J and Asher EJ. The Purdue Pegboard: Norms and studies of reliability and validity. *J Appl Psychol* 1948; 32: 234–247.
12. Wechsler D. *Wechsler Test of Adult Reading: WTAR*. New York: Psychological Corporation, 2001.

13. Zigmond AS and Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; 67: 361–370.
14. Honarmand K and Feinstein A. Validation of the Hospital Anxiety and Depression Scale for use with multiple sclerosis patients. *Mult Scler* 2009; 15: 1518–1524.
15. Fisk JD, Ritvo PG, Ross L, et al. Measuring of the functional impact of fatigue: Initial validation measuring the Functional Impact Scale. *Clin Infect Dis* 1994; 18(Suppl 1): S79–S83.
16. Smith A. *Symbol Digit Modality Test manual*. Los Angeles: Western Psychol Services, 1982.
17. Rypma B, Berger JS, Prabhakaran V, et al. Neural correlates of cognitive efficiency. *Neuroimage* 2006; 33: 969–979.
18. Boynton GM, Engel SA, Glover GH, et al. Linear systems analysis of functional magnetic resonance imaging in human V1. *J Neurosci* 1996; 16: 4207–4221.
19. Forman SD, Cohen JD, Fitzgerald M, et al. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): Use of a cluster-size threshold. *Magn Reson Med* 1995; 33: 636–647.
20. Parmenter BA, Weinstock-Guttman B, Garg N, et al. Screening for cognitive impairment in multiple sclerosis using the Symbol Digit Modalities Test. *Mult Scler* 2007; 13: 52–57.
21. Mainero C, Caramia F, Pozzilli C, et al. fMRI evidence of brain reorganization during attention and memory tasks in multiple sclerosis. *Neuroimage* 2004; 21: 858–867.
22. Mazerolle EL, Wojtowicz Ma, Omisade A, et al. Intraindividual variability in information processing speed reflects white matter microstructure in multiple sclerosis. *Neuroimage Clin* 2013; 2: 894–902.
23. Leavitt VM, Wylie G, Genova HM, et al. Altered effective connectivity during performance of an information processing speed task in multiple sclerosis. *Mult Scler* 2012; 18: 409–417.
24. Genova HM, Hillary FG, Wylie G, et al. Examination of processing speed deficits in multiple sclerosis using functional magnetic resonance imaging. *J Int Neuropsychol Soc* 2009; 15: 383–393.
25. Forn C, Ripollés P, Cruz-Gómez AJ, et al. Task-load manipulation in the Symbol Digit Modalities Test: An alternative measure of information processing speed. *Brain Cogn* 2013; 82: 152–160.
26. Smith AM, Walker LA, Freedman MS, et al. Activation patterns in multiple sclerosis on the Computerized Tests of Information Processing. *J Neurol Sci* 2012; 312: 131–137.
27. Smith AM, Walker LA, Freedman MS, et al. fMRI investigation of disinhibition in cognitively impaired patients with multiple sclerosis. *J Neurol Sci* 2009; 281: 58–63.
28. Rao SM, Glatt S, Hammeke TA, et al. Chronic progressive multiple sclerosis: Relationship between cerebral ventricular size and neuropsychological impairment. *Arch Neurol* 1985; 42: 678–682.
29. Benedict RH, Bruce JM, Dwyer MG, et al. Neocortical atrophy, third ventricular width, and cognitive dysfunction in multiple sclerosis. *Arch Neurol* 2006; 63: 1301–1306.
30. Houtchens MK, Benedict RH, Killiany R, et al. Thalamic atrophy and cognition in multiple sclerosis. *Neurology* 2007; 69: 1213–1223.
31. Benedict RH, Carone DA and Bakshi R. Correlating brain atrophy with cognitive dysfunction, mood disturbances, and personality disorder in multiple sclerosis. *J Neuroimaging* 2004; 14(3 Suppl): 36S–45S.
32. Tona F, Petsas N, Sbardella E, et al. Multiple sclerosis: Altered thalamic resting-state functional connevtivity and its effect on cognitive function. *Neuroradiology* 2014; 271: 814–821.
33. Benedict RH, Hulst HE, Bergsland N, et al. Clinical significance of atrophy and white matter mean diffusivity within the thalamus of multiple sclerosis patients. *Mult Scler* 2013; 19: 1478–1484.
34. Breivogel CS and Childers SR. The functional neuroanatomy of brain cannabinoid receptors. *Neurobiol Dis* 1998; 431: 417–431.
35. Ameri A. The effects of cannabinoids on the brain. *Prog Neurobiol* 1999; 58: 315–348.
36. O'Leary DS, Schultz SK, Andreasen NC, et al. Effects of smoking marijuana on brain perfusion and cognition. *Neuropsychopharmacology* 2002; 26: 802–816.
37. Martín-Santos R, Fagundo AB, Crippa JA, et al. Neuroimaging in cannabis use: A systematic review of the literature. *Psychol Med* 2010; 40: 383–398.
38. Ramsey NF, Kirkby BS, Van Gelderen P, et al. Functional mapping of human sensorimotor cortex with 3D BOLD fMRI correlates highly with H2(15)O PET rCBF. *J Cereb Blood Flow Metab* 1996; 16: 755–764.
39. Mechelli A, Price CJ and Friston KJ. Nonlinear coupling between evoked rCBF and BOLD signals: A simulation study of hemodynamic responses. *Neuroimage* 2001; 14: 862–872.