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Coming off cannabis: a cognitive and magnetic resonance imaging study in patients with multiple sclerosis

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Cognitive dysfunction affects 40–80% of patients with multiple sclerosis. Smoking cannabis may add to these deficits. It is unclear whether coming off cannabis results in cognitive improvement. To address this question, 40 patients with multiple sclerosis who started using cannabis after the onset of multiple sclerosis and who used it for at least 4 days a week over many years were divided by odd-even number selection into two groups: cannabis continuation and cannabis withdrawal. Assessments took place at baseline and after 28 days and included serial versions of the Brief Repeatable Neuropsychological Battery for multiple sclerosis containing tests of verbal and visual memory, processing speed and executive function; structural and functional MRI, the latter entailing a compatible version of the Symbol Digit Modalities Test; urine for cannabinoid metabolites to detect compliance with abstinence. Only those participants deemed globally impaired at baseline (failure on at least two cognitive domains) were enrolled. The results revealed that the two groups were well matched demographically and neurologically. One subject was removed from the withdrawal group because of failed abstinence. Urine analysis revealed the cannabinoid consumed was predominantly tetrahydrocannabinol (THC). There were no baseline between group cognitive differences, but by Day 28 the withdrawal group performed significantly better on every cognitive index ($P < 0.0001$ for all). Significant within group differences were present for every test over time, but only in the abstinent group ($P < 0.0001$ for all tests). There were no between group baseline or Day 28 differences in structural MRI indices (global atrophy, total T_1 and T_2 lesion volume). At index assessment the two groups had a similar performance on the functional MRI-compatible Symbol Digit Modalities Test and there were no group differences in brain activation. However, by Day 28, the withdrawal group completed more trials correctly ($P < 0.012$) and had a faster reaction time ($P < 0.002$), associated with significantly increased activation in brain regions known to be associated with performance of the test (bilateral inferior frontal gyri, caudate and declive/cerebellum, $P < 0.001$ for all regions). These results reveal that patients with multiple sclerosis who are frequent, long-term cannabis users can show significant improvements in memory, processing speed and executive function after 28 days of drug abstinence. The absence of similar improvements in a matched multiple sclerosis group that remained on cannabis shows that beneficial cognitive change after stopping cannabis is not solely attributable to the effects of practice.

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Abbreviations: BNRB = Brief Repeatable Neuropsychological Battery; CC = cannabis continuation; CW = cannabis withdrawal; SDMT = Symbol Digit Modalities Test; THC = tetrahydrocannabinol

Introduction

For the purpose of this article, cannabis refers to the drug that is smoked, vaped or ingested. It is estimated that 20% of patients with multiple sclerosis use it in this fashion, typically multiple times per week and over many years (Clark *et al.*, 2004; Chong *et al.*, 2006; Banwell *et al.*, 2016). The reasons for using the drug vary widely and may include more than one factor, such as relief from pain, spasticity, anxiety, depression and insomnia or combinations thereof. However, there is little empirical support for this behaviour, notwithstanding the user's conviction that cannabis is beneficial. The dearth of objective evidence supporting the medical use of cannabis is confirmed in a systematic review by the American Academy of Neurology (Koppel *et al.*, 2014).

Similarly, there is little data that describe possible side effects of cannabis when taken in association with neurological disease. However, four studies, three from one research team, suggest that patients with multiple sclerosis who smoke cannabis may experience greater cognitive compromise (Ghaffar and Feinstein, 2008; Honarmand *et al.*, 2011; Pavisian *et al.*, 2014) associated with altered brain activation when completing tasks of information processing speed and working memory (Pavisian *et al.*, 2015). These results are potentially important because cognitive dysfunction can affect 40–80% of patients with multiple sclerosis (Ruano *et al.*, 2017) leading to greater difficulty maintaining work, sustaining relationships and pursuing leisure activities (Prager *et al.*, 2017). Any substance that might add to this burden should be viewed with added scrutiny.

There is another pressing reason why clarity on the potential benefits and side effects of cannabis use is needed. Political and economic considerations in some countries are driving a momentum to legalize use of the drug. Data show that a sizeable proportion of law-abiding Canadians with multiple sclerosis who are not using cannabis because of concerns about breaking the law, would reconsider their decision if the drug became legal (Banwell *et al.*, 2016). With legalization having come into effect in Canada in 2018, it is anticipated the number of users will increase (Banwell *et al.*, 2016). A similar outcome can be predicted in other countries too.

The present study addresses an equally important question: are cognitive deficits in patients with multiple sclerosis who use cannabis potentially reversible, at least in part, with abstinence? To date this too has not been investigated. Evidence from healthy subjects is equivocal (Pope *et al.*, 2001; Meier *et al.*, 2012). This uncertainty comes with numerous caveats and cautionary notes reflecting heterogeneous factors that might influence outcome, with studies varying in their attention to them. These include duration and frequency of use, potency of the cannabis strains used, duration of follow-up, controlling for the potentially confounding effects of cannabis withdrawal on cognition and whether subjects were cognitively impaired or not before being enrolled in a withdrawal study.

Clarity is therefore required as healthcare professionals grapple with what to advise their patients with multiple sclerosis with respect to cannabis use or discontinuation. The present study is an attempt to provide additional insights by investigating the potential for cognitive improvement in patients with multiple sclerosis who come off the drug.

Materials and methods

Subject selection

A sample of 40 patients with a confirmed diagnosis of multiple sclerosis (Thompson *et al.*, 2018) was recruited from a hospital based multiple sclerosis clinic. Subjects were reimbursed for travel and parking expenses, but were not paid for their involvement in the study. Only those subjects who had begun using cannabis after their diagnosis of multiple sclerosis were considered in order to avoid the possibility of recruiting subjects who may have been cognitively impaired from cannabis use before the onset of their disease. In addition, subjects were only enrolled if they were deemed to have global cognitive impairment, defined in our study, by convention, as failure on two or more cognitive domains comprising the Brief Repeatable Neuropsychological Battery (BRNB) for multiple sclerosis (Rao, 1990). Additional exclusion factors were another disease of the CNS, a significant mental illness (psychosis, bipolar disorder), intellectually disability, an inability to give informed consent, a previous neuropsychological assessment within the past 18 months, steroid treatment within the past 3 months, visual acuity of less than 20/70 and a positive urine test for an illicit substance other than cannabis. The latter included drugs such as morphine, codeine, heroin, phencyclidine, lysergic acid diethylamide and amphetamines.

Subjects were assigned to either the cannabis withdrawal (CW) or cannabis continuation (CC) groups based on odd or even case number designation. The tester was unaware of pending group allocation prior to the index assessment. All subjects underwent a neuropsychological assessment and brain MRI at baseline and 28 days after the index assessment. Subjects in the withdrawal group were offered appointments as needed for the duration of the study to discuss alternative medications to cannabis in the event of symptoms deterioration.

The following data were collected at baseline:

(i) Basic demographic information and neurological variables that included Expanded Disability Status Scale (EDSS) (according to neurologists' ratings), disease duration and course and use of disease modifying drugs.

(ii) Cannabis history, which included amount in grams per day, duration of use, reason for use and frequency of use.

(iii) To assess compliance with cannabis withdrawal urine samples for cannabis metabolites were checked from both groups at entry and completion of the study. This was done for the two main cannabinoids, Δ^9-tetrahydrocannabidol (THC) and cannabidiol, with respective metabolites, 11-nor-9-carboxy-Δ^9-tetrahydro-cannabinol (THCCOOH) and total cannabidiol. Ratios of the two metabolites to creatinine were obtained to control for alterations in fluid intake that can affect metabolite concentrations in the urine (Huestis and Cone, 1998). Details of metabolite determination can be found in the Supplementary material. In addition, all subjects were asked to refrain from using cannabis for at least 12 h prior to cognitive testing to avoid assessing individuals who were acutely intoxicated. An objective marker of cannabis abstinence for up to 6 h was obtained from a saliva sample using NarcoCheck© prior to cognitive testing at baseline and Day 28 in all subjects.

(iv) Symptoms of cannabis withdrawal were noted with the self-report Cannabis Withdrawal Scale (CWS). Total CWS Scores indicate the following: <51 none; 52–66 mild to moderate; and >66 severe withdrawal symptoms (Allsop *et al.*, 2011).

(v) To control for nicotine use or abstinence as a potential confounder of the cognitive results, we obtained carbon monoxide (CO) levels in breath using a piCO^{TM} Smokerlyzer®. The Smokerlyzer can detect CO concentrations in a range between 0 and 150 ppm with the level interpreted as follows: non-smoker 0–6 ppm, borderline 7–9 ppm, low addicted 10–15 ppm, moderately addicted 16–25 ppm, heavily addicted 26–35, and very heavy addicted 36+.

(vi) Medications taken for symptom management.

(vii) A measure of pre-morbid intelligence was obtained with the Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001).

(viii) Cognitive data were obtained with the BRNB (Rao *et al.*, 1991). Serial versions of the BRNB were used to offset practice effects at the follow-up assessment. By convention, failure on any one test was based on a score of 1.5 standard deviations (SD) below age, sex and education matched normative data. In keeping with BRNB approach, subjects were considered globally impaired if they failed two or more cognitive domains. The full battery comprised the following: (a) verbal memory: the Selective Reminding Test (SRT) (Larrabee *et al.*, 1986); (b) visual memory: the 10/36 Test (Buschke *et al.*, 1974); (c) processing speed: the Paced Auditory Serial Addition Test (PASAT) with 2- and 3-s administrations (Gronwall, 1977), and the Symbol Digit Modalities Test (SDMT) (Smith, 1982); and (d) executive function: the Controlled Oral Word Association Test (COWAT) (Benton, 1994). In addition, all subjects completed a functional MRI compatible version of the SDMT (Genova *et al.*, 2013). Modified to avoid verbal responses, subjects must decide if a stack of paired geometric shapes and numbers (displayed in the middle of the screen) matched any of the nine-geometric/number pairs (reference key) placed above it. Using a two-button response keypad (Current Designs Inc., ©2018) subjects are required to press the red button for 'no' (there is no match), and the green button for 'yes' (there is a match). The full test consists of one block of eight trials, each running for 24 s. Each trial is allocated a maximum time window of 3000 ms for subjects to make a response. There is a rest period of 26 s between each block, during which a fixation cross is displayed in the middle of the screen. Accuracy and response times were recorded in E-prime 2.0.

(ix) Symptoms of depression and anxiety were recorded with the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), validated for use in multiple sclerosis research (Honarmand and Feinstein, 2009). Psychotropic medication use was also recorded.

Brain imaging

MRI scanning parameters

The Siemens Prisma 3 T system was used to collect MRI images, using a 32-channel head coil at index assessment and Day 28. High resolution anatomical brain scans were acquired using a sagittal 3D T_1 MPRAGE sequence with the following parameters: echo time = 1.94 ms, repetition time = 2300 ms, inversion time = 900 ms, flip angle = 9 degrees, GRAPPA × 2, field of view = 256 mm × 248 mm, 192 slices 1-mm thick, matrix = 256 × 248 (1.0 mm × 1.0 mm × 1.0 mm voxels).

Axial proton density (PD)/T_2 turbo spin echo (TSE): Images were acquired with the following parameters: echo time = 11 ms/95 ms, repetition time = 3050 ms, flip angle = 165 degrees, GRAPPA × 2, field of vierw = 224 mm × 189 mm, 48 slices 3.0-mm thick, matrix = 256 × 216 (0.875 mm × 0.875 × 3.0 mm voxels).

SDMT functional MRI data were acquired using T_2-weighted axial gradient echo planar imaging (EPI), echo time = 30 ms, repetition time = 2000 ms, flip angle = 40 degrees, field of view = 204 mm × 204 mm, 38 slices 3.5-mm thick, 1.0 mm gap, matrix = 68 × 68 (3.0 mm × 3.0 mm × 3.5 mm voxels), scan time 9:26 (+0:06) to obtain blood oxygen level-dependent contrast. A total of 283 volumes and 38 slices were collected for each subject.

SDMT functional MRI acquisition

BrainVoyager QX software (version 2.8, Brain Innovation, Maastricht, the Netherlands) was used to preprocess functional and anatomical image files. To remove transient signal changes related to the steady magnetization the first five of the 283 volumes from the SDMT functional image files were skipped. Preprocessing of functional files included; removal of drift in the signal times course, linear trend removal, Gaussian spatial smoothing with a full-width half-maximum value of 8 mm, and a 3-dimensional motion correction using trilinear interpolation to detect head movement. To reduce noise related to head motion further, the output from the 3D motion correction (consisting of six estimated motion parameters: three translation and three rotation) were added to the general linear model (GLM) design matric as confounds, to improve statistical tests. Before co-registering functional data onto the anatomical brain, intensity inhomogeneity correction was applied to the anatomical image files. The correction included: setting voxels outside the brain to an intensity of 0, brain extraction from skull, white/grey matter detection, and bias field estimation within white matter. Functional data were then superimposed on to an anatomical brain, aligned and transformed into standard Talairach space for each subject. The stimulation protocol was convolved with a boxcar hemodynamic response function to account for the expected shape and temporal delays of the physiological response and was used in the GLM. A multi-study GLM, random effects analysis was used to generate activation maps for each group. Regions

of interest were then defined to run further statistical analysis (e.g. *t*-test, pair *t*-test). Activated voxels were considered significant if the threshold exceeded $P < 0.001$ uncorrected and formed a cluster of 34 contiguous voxels, based on a cluster threshold estimator (BrainVoyager QX version 2.8 software, Brain Innovation), corresponding to a corrected threshold of $P < 0.05$. The centre of gravity and *t*-statistics were extracted for each significant cluster resulting in a text file and the Talairach client© was used to determine appropriate brain label based on the Talairach coordinates (Lancaster *et al.*, 1997, 2000).

Structural acquisition

Total hyperintense lesions volumes were obtained using a SPM segmentation tool, and hypointense lesion volumes were obtained using Lesion Mapper, a FSL script specifically designed for multiple sclerosis hypo-intense lesion analysis (Wetter *et al.*, 2016). Cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suite, which is available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in a prior publication (Dale *et al.*, 1999).

Statistical analysis and sample size justification

For the demographic and cognitive data, between group comparisons were undertaken using two-sided *t*-tests. Within group cognitive and behavioural change over time was assessed with paired *t*-tests. Predictors of cognitive impairment on each index were assessed with linear regression analyses. In addition to group membership (CW, CC), putative predictor variables entered were disease and cannabis related, which differed between the two groups. To control for multiple comparisons, significance was set at $P < 0.01$.

The sample size of 20 participants per group was based on estimates of the variability of regional task-related activity from our previous functional MRI experience with region of interest and whole-brain analyses in both healthy and clinical groups performing sensorimotor and attention tasks (Staines *et al.*, 2001, 2002; Ghaffar *et al.*, 2006; Meehan and Staines, 2007, 2009; Dionne *et al.*, 2010) a task effect size of 10%; power of 0.80 and α of 0.05. The group size of 20 accounts for an estimated 10% rate of data loss due to excessive head motion during scanning and withdrawal from the study.

Order of testing

Subjects completed the BRNB followed by the two psychometric scales (CWS, HADS) before undergoing brain imaging for the functional MRI-SDMT.

Consent and ethics approval

Informed consent was obtained from all subjects. The study was approved by the Research and Ethics Board at Sunnybrook Health Sciences Centre, affiliated with the University of Toronto.

Data availability

To promote data transparency, anonymized data will be available upon reasonable request.

Results

The demographic and neurological data for the CW and CC groups are shown in Table 1. The two groups were well matched for age, sex, EDSS and disease course. There were no group differences in use of disease modifying drugs ($\chi^2 = 3.14$, $P = 0.08$) or psychotropic medications ($\chi^2 = 0.81$, $P = 0.37$). Although the CW group had a shorter duration of illness this did not reach statistical significance. No subject in either group had an exacerbation during the study. Two subjects in the CW group requested a single appointment each to discuss alternative medication for their insomnia that worsened after they had discontinued cannabis. Both were prescribed zopliclone 3.75 mg every night at bedtime as required to good effect. CO levels denoting nicotine use were not statistically different between groups at index assessment [CC mean = 5.25 CO (SD = 6.09) versus CW mean = 4.89 CO (SD = 4.52), (t = 0.21; $P = 0.84$)], or at Day 28 [CC mean = 5.45 CO (SD = 6.35) versus CW mean = 5.53 CO (SD = 6.35), (t = −0.04; $P = 0.97$)].

Cannabis results

There was no difference in the frequency of cannabis use between the two groups [with 90% of the CC group, and 95% of the CW group using cannabis every day ($\chi^2 = 0.31$, $P < 0.58$)]. All subjects in both groups used the drug, on average, at least four times a week. The two groups did not differ in their reasons for using it with 100% of the CC group, and 84% of the CW group using it for a combination of reasons such as pain, spasticity, bladder, depression, insomnia, appetite, migraine and recreational. In addition, there was no difference in the amount of cannabis smoked each day between groups [CW mean = 2.05 g (SD = 1.27) versus CC mean = 2.30 g (SD = 1.35), t = 0.60; $P = 0.56$]. Although the CW group had been using cannabis for a shorter period of time this did not reach statistical significance [CW mean = 5.62 years (SD = 5.10) versus CC mean = 9.61 years (SD = 5.67), t = 2.31; $P = 0.03$]. There was a significant correlation between duration of multiple sclerosis and duration of cannabis use (r = 0.79; $P = 0.0001$). Serial urine-derived THC and cannabidiol metabolites to creatinine ratios for the two groups at baseline and Day 28 are shown in Fig. 1A and B. Baseline THCCOOH differences, albeit non-significant, were present with the CW group having a lower ratio to begin with [CW mean ratio = 80.37 (SD = 58.45) versus mean ratio = 156.94 (SD = 113.55), t = 2.51; $P = 0.02$]. Over the course of 28 days, the ratios in the CW group declined to almost zero (t = 4.505; $P = 0.0001$) whereas the CC group remained unchanged (t = −0.379; $P = 0.709$). One subject in the CW group showed a sharp increase in his ratio at Day 28 indicative of recent cannabis use and was withdrawn from the study. This reduced the sample size in the CW group at Day 28 to 19 subjects. The urine cannabidiol-creatinine ratios for both the CW and CC group

Table 1 Demographic and neurologic comparisons between CC and CW groups

	CC group		CW group		t-test/χ^2	Significance
	Mean/frequency (n = 20)	SD	Mean/frequency (n = 19)	SD		
Age, years	39.30	8.47	36.26	11.69	t = 0.36	0.36
Sex (% female)	9 (45.0)		11 (57.89)		χ^2 = 0.648	0.42
EDSS	2.90	1.85	2.45	2.05	t = 0.72	0.47
Disease course, n (%)						
RRMS	16 (80)		14 (73.68)		χ^2 = 0.219	0.72
SPMS	4 (20)		5 (26.32)			
Disease duration, years	9.61	5.67	5.62	5.10	t = 2.31	0.03

EDSS = Expanded Disability Status Scale; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

were noticeably lower than the respective THCCOOH-creatinine ratios. Changes in the cannabidiol-creatinine ratios over time were: for the CW group: index mean = 0.07 (SD = 0.19) versus Day 28 mean = 0.00 (SD = 0.00), t = 1.56; P = 0.79; and for the CC group: index mean = 1.94 (SD = 4.21) versus Day 28 mean = 2.06 (SD = 5.25), t = −0.28; P = 0.14.

Cognitive results

There were no between group differences at the index assessment on any of the individual indices of the BRNB. By Day 28, however, subjects in the CW group had a significantly better performance on every cognitive index (Table 2). Within group comparisons revealed no significant change over time for the CC group apart from visual memory deteriorating. In the CW group significant improvement took place over time in all cognitive domains (Table 3). To determine whether differences in disease duration, duration of cannabis use and baseline THCCOOH-creatinine ratios were influencing serial cognitive results, multiple regression analyses were undertaken in which these three potential predictive variables were added to the grouping (CW versus CC) variable. The results revealed that group membership was independently predictive of all cognitive indices at Day 28 [SRT_LTS (t = 5.84; P = 0.0001), 10/36 (t = 8.25; P = 0.0001), PASAT 3 (t = 7.36; P = 0.0001), PASAT 2 (t = 6.99; P = 0.0001), SDMT (t = 4.88; P = 0.0001), and COWAT (t = 3.24; P = 0.003)]. Disease duration also emerged as an independent predictor of performance on the SDMT at Day 28 (t = −4.64; 0.001).

By Day 28 the global cognitive failure rates in the CC and CW groups had decreased to 90% (18/20) and 21.1% (4/19), respectively (P = 0.003; McNemar test).

Patient report outcomes

There were no between group differences on the HADS at the index or Day 28 assessments. At Day 28, the CW group endorsed more withdrawal symptoms on the CWS, but this was not statistically significant (Table 2). Within group changes over time with respect to these three variables showed that while the CW group endorsed more withdrawal symptoms and fewer depressive difficulties over time, these changes fell short of statistical significance (Table 3).

MRI results

Structural MRI

There were no between group differences in total hyperintense and hypointense lesion volumes at index or Day 28 assessments. Similarly there were no between group differences in total white and grey matter volumes at index and Day 28 assessments (Table 4).

Functional MRI SDMT results

There were no between group differences at index assessment when it came to either the number of correct responses or reaction times on the SDMT. By Day 28 the CW group had a significantly better performance in terms of the number of correct responses and speed of response (Table 5). A within group analysis for the CC group revealed no differences over time for correct responses or reaction times (Table 5). The CW group, however, showed significant improvement in the number of correct responses. Speed of response was quicker too in the CW group, but fell short of statistical significance (Table 5).

Functional MRI results

A recent functional MRI meta-analysis has defined the SDMT neural network in healthy subjects to include the middle frontal gyrus (BA6), superior parietal lobule (BA7), precuneus (BA7), inferior frontal gyrus (9), cuneus (BA17), lingual gyrus (BA17), declive and caudate nucleus (Silva *et al*, 2018). Our initial analyses focused on these regions and revealed no between group differences at index assessment. By Day 28, however, significantly higher activations in four regions were observed in the CW versus the CC groups. These were the right inferior frontal gyrus (t = −3.868; P = 0.000), left inferior frontal gyrus (t = −3.649; P = 0.001), right declive cerebellum (t = −4.408; P = 0.000) and right caudate nucleus (t = −3.983; P = 0.000) (Fig. 2).

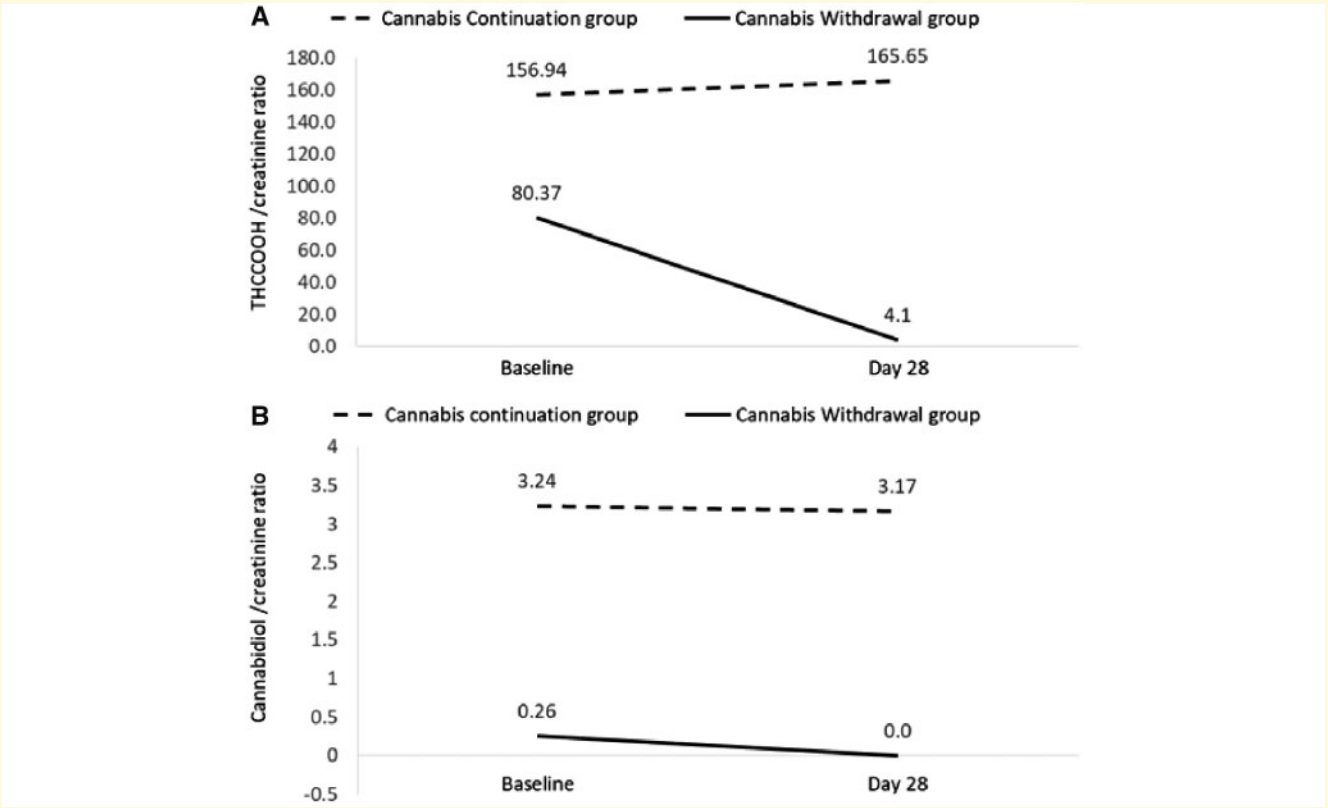

Figure 1 Longitudinal urine THCCOOH/creatinine analysis (A) and longitudinal urine cannabidiol/creatinine analysis (B).

Table 2 Cognitive data: comparisons between CC and CW groups at baseline and Day 28

	CC group		CW group			
	Mean	SD	Mean	SD	t-test	Significance
Baseline						
SRT-LTS	29.70	10.65	29.95	13.17	t = −0.07	0.95
10/36	16.90	5.95	18.47	5.99	t = −0.82	0.42
PASAT3	32.25	6.03	35.21	10.53	t = −1.08	0.29
PASAT2	23.60	4.43	25.47	8.85	t = −0.84	0.41
SDMT	37.30	7.21	34.42	12.51	t = 0.89	0.38
COWAT	37.05	4.70	39.37	5.90	t = −1.36	0.18
CWS	42.25	31.97	42.68	28.09	t = −0.05	0.96
HADS-A	8.30	5.22	8.42	4.62	t = −0.08	0.94
HADS-D	6.75	3.84	7.16	4.59	t = −0.30	0.76
Day 28						
SRT_LTS	26.90	10.81	44.89	8.58	t = −5.74	0.000
10/36	13.25	5.34	24.68	3.13	t = −8.10	0.000
PASAT3	31.25	5.96	48.05	7.36	t = −7.85	0.000
PASAT2	23.15	5.10	37.26	6.62	t = −7.48	0.000
SDMT	37.30	6.47	51.89	10.95	t = −5.10	0.000
COWAT	37.45	4.81	45.21	6.60	t = −4.22	0.000
CWS	37.70	31.72	61.74	34.59	t = −2.26	0.030
HADS-A	7.00	4.05	5.42	2.99	t = 0.53	0.598
HADS-D	8.50	4.24	7.79	4.09	t = 1.37	0.176

10/36 = Spatial Total Recall Test; COWAT = Controlled Oral Word Association Test; CWS = Cannabis Withdrawal Scale; HADS-A = Hospital Anxiety and Depression Scale – Anxiety; HADS-D = Hospital Anxiety and Depression Scale – Depression; PASAT = Paced Auditory Serial Addition Test (2 and 3 s); SRT-LTS = Selective Reminding Test-Long Term Storage.

Table 3 Cognitive data: within group comparisons for CC and CW groups at baseline and Day 28

	Baseline Mean	Versus SD	Day 28 Mean	SD	t-test	Sig
CC group						
SRT-LTS	29.70	10.65	26.90	10.81	t = 1.48	0.16
10/36	16.90	5.95	13.25	5.34	t = 3.68	0.00
PASAT3	37.30	7.21	37.30	6.47	t = 0.00	1.00
PASAT2	32.25	6.03	31.25	5.96	t = 0.70	0.49
SDMT	23.60	4.43	23.15	5.10	t = 0.30	0.77
COWAT	37.05	4.70	37.45	4.81	t = −0.44	0.67
CWS	42.25	31.97	37.70	31.72	t = 0.73	0.48
HADS-A	8.30	5.22	8.50	4.23	t = −0.30	0.77
HADS-D	6.75	3.84	7.00	4.05	t = −0.55	0.59
CW group						
SRT-LTS	29.95	13.17	44.89	8.58	t = −5.76	0.000
10/36	18.45	5.99	24.68	3.13	t = −4.42	0.000
PASAT3	34.42	12.51	51.89	10.95	t = −7.68	0.000
PASAT2	35.21	10.53	48.05	7.36	t = −6.90	0.000
SDMT	25.47	8.85	37.26	6.62	t = −7.18	0.000
COWAT	39.37	5.90	45.21	6.60	t = −4.90	0.000
CWS	42.68	28.09	61.74	34.59	t = −2.36	0.030
HADS-A	8.42	4.62	7.79	4.09	t = 0.66	0.517
HADS-D	7.16	4.59	5.42	2.99	t = 2.12	0.048

10/36 = Spatial Total Recall Test; COWAT = Controlled Oral Word Association Test; CWS = Cannabis Withdrawal Scale; HADS-A = Hospital Anxiety and Depression Scale – Anxiety; HADS-D = Hospital Anxiety and Depression Scale – Depression; PASAT = Paced Auditory Serial Addition Test (2 and 3 s); SRT-LTS = Selective Reminding Test-Long Term Storage.

Table 4 Structural MRI data: Comparison between CC and CW groups at baseline and Day 28

	CC group Mean (SD)	CW group Mean (SD)	t-test	Significance (2-tailed)
Baseline				
Hyperintense lesion volume	0.0054 (0.0044)	0.0068 (0066)	t = −0.793	0.433
Hypointense lesion volume	0.0047 (0.0030)	0.0056 (0.0054)	t = −0.603	0.551
Total white matter volume	0.3044 (0.0300)	0.2924 (0.0409)	t = 1.045	0.303
Total grey matter volume	0.4020 (0.0271)	0.3968 (0.0351)	t = 0.519	0.607
Day 28				
Hyperintense lesion volume	0.0056 (0.0044)	0.0065 (0.0064)	t = −0.477	0.636
Hypointense lesion volume	0.0048 (0.0031)	0.0050 (0.0047)	t = −0.184	0.855
Total white matter volume	0.3022 (0.0301)	0.2906 (0.0294)	t = 1.215	0.232
Total grey matter volume	0.3993 (0.0272)	0.4055 (0.0293)	t = −0.691	0.494

All values refer either to lesion or grey and white matter volumes/total intracranial volume.

A within group analysis for the CC group revealed no significant change over time with regard to brain activation from index assessment. The CW group, however, revealed significantly increased blood oxygen level-dependent related activations in the following brain regions: right middle frontal gyrus (t = −3.872; $P = 0.001$), left cuneus (t = −5.327; $P = 0.000$), left inferior frontal gyrus (t = −3.661; $P = 0.002$), and right precuneus (t = −3.996; $P = 0.001$) (Fig. 3).

Ancillary-functional MRI results

Apart from the SDMT-task related neural network, there were additional blood oxygen level-dependent activations present during a within group random-effect analysis at a threshold setting of $P < 0.001$. At initial assessment both the CC and the CW groups had similar brain activations. By Day 28 these regions were still present in the CC group (Supplementary Table 1). However, in the CW participants, fewer ancillary areas activated at Day 28 leaving a pattern of activation more closely aligned to regions that activate in people with multiple sclerosis who are cannabis naive, namely, the precentral gyrus, anterior cingulate, thalamus, insula, and middle temporal gyrus (Genova *et al.*, 2013) (Supplementary Table 2).

Table 5 Functional MRI-SDMT data

Comparisons between the CC and CW groups at baseline and Day 28						
	CC group		CW group			
	Mean	SD	Mean	SD	t-test	Significance
Baseline						
SDMT	75.05	8.96	78.42	4.32	t = −1.48	0.146
SDMT RT	1912.76	159.82	1823.88	251.80	t = 1.32	0.194
Day 28						
SDMT	74.35	15.68	84.05	3.22	t = −2.64	0.012
SDMT RT	1911.63	167.55	1718.43	190.83	t = 3.36	0.002
Within group comparisons for the CC and CW groups at baseline and Day 28						
	Baseline		Day 28		t-test	Significance
	Mean	SD	Mean	SD		
CC group						
SDMT	75.05	8.96	74.35	15.68	t = 0.20	0.847
SDMT RT	1912.76	159.82	1911.63	167.55	t = 0.03	0.975
CW group						
SDMT	78.42	4.32	84.05	3.22	t = −4.50	0.000
SDMT RT	1823.88	251.80	1718.43	190.83	t = 2.63	0.017

RT = reaction time in milliseconds; SDMT = Symbol Digit Modalities Test total correct responses.

Discussion

Our data reveal that patients with multiple sclerosis who have been using cannabis frequently and over many years show wide-ranging cognitive improvement should they abstain from use for at least 28 days. These cognitive improvements cannot be attributed solely to the effects of practice, for a matched group of patients with multiple sclerosis who continued smoking cannabis during this period showed significantly less serial improvement. Of note is that abstinence was associated with better performance on tests of information processing speed, learning and memory both verbal and visual, and executive function. The improvement in processing speed as recorded by the SDMT, in particular, was matched by significant increases in cerebral activation observed on functional MRI in the neural network known to underpin performance in healthy individuals.

Our findings should be viewed in the context of a paucity of cannabis-cognition data in the multiple sclerosis literature. This dearth is acknowledged by the American Academy of Neurology in evidenced-based guidelines for complementary and alternative medicine (Koppel *et al.*, 2014). Mention is made of a single Class III study for treatment of spasticity in 37 patients with multiple sclerosis in which a single cognitive test, the 3-s PASAT, was included as a secondary outcome measure. Subjects who smoked cannabis performed more poorly on the test (Corey-Bloom *et al.*, 2012). This finding is boosted by three multiple sclerosis studies in which the focus was exclusively on cognition. A retrospective analysis of data from a computerized variant of the SDMT found that performance was 50% slower in cannabis users relative to matched non-users (Ghaffar and Feinstein, 2008). A subsequent case control study in a larger sample and utilizing a more extensive neuropsychological battery confirmed that multiple sclerosis cannabis smokers had slower processing speed, but also more extensive executive and visuospatial deficits relative to non-smokers. As a result, the global cognitive impairment rate in cannabis users was twice that in the cannabis abstinent group (Honarmand *et al.*, 2011). A third study using demographically and neurologically matched cannabis and non-cannabis samples reported greater memory deficits in the former, both with respect to visual and verbal memory (Pavisian *et al.*, 2014).

In all three of the above studies, cognitive testing was completed when subjects were not acutely intoxicated, a procedure that was again followed with the present protocol. THC is absorbed into the bloodstream within seconds, reaching a maximum brain concentration in 15–30 min. This coincides with the most prominent physiological and psychological effects. THC concentrations decline by 50% 15 min after inhalation, but the acute physiological and psychological effects linger for ~2–4 h (Berghaus *et al.*, 1998; Grotenhermen, 2003). Our use of the NarcoCheck© saliva test ensured that testing took place outside this window of maximum drug effect.

When interpreting these results it is important to recognize that cannabis is not a unitary drug. It comprises over 60 cannabinoids of which two, Δ^9-tetrahydrocannabinol (THC) and cannabidiol have been the most frequently studied with respect to cognition in the general population. The former is psychoactive whereas the latter is not. Studies of healthy subjects show that it is THC that is

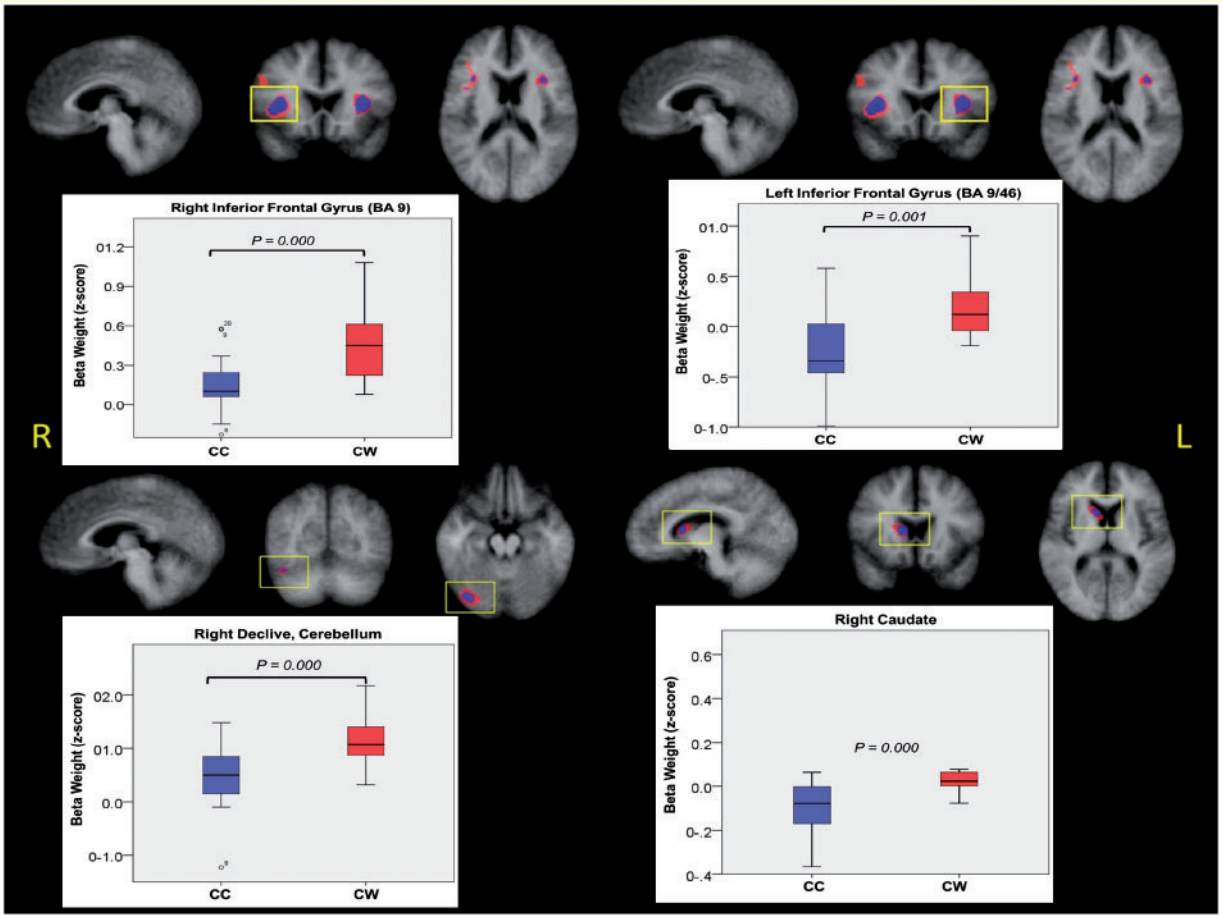

Figure 2 SDMT-functional MRI data: between group differences at Day 28.

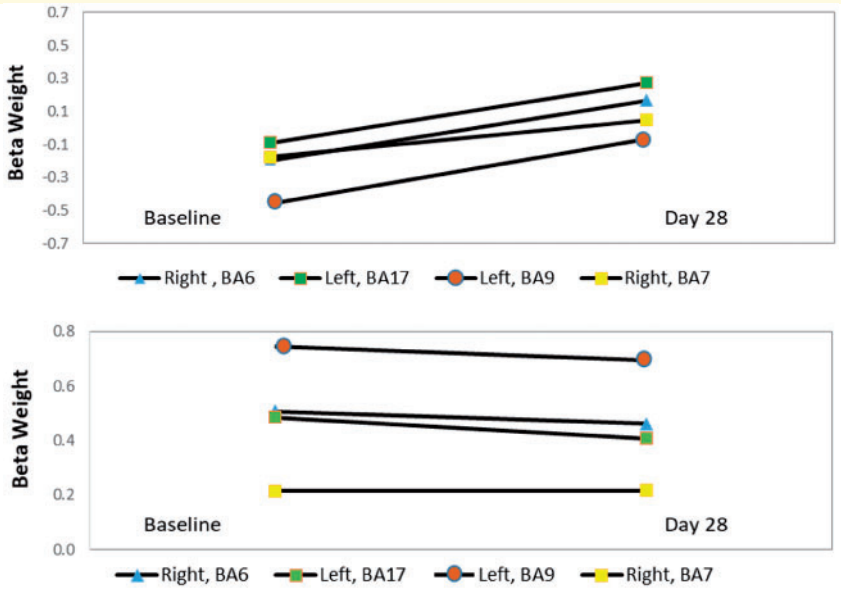

Figure 3 SDMT-functional MRI data: within group differences. BA6 = middle frontal gyrus; BA17 = left cuneus; BA9 = left inferior frontal gyrus; BA7 = right precuneus.

associated with euphoria and psychosis, and from a cognitive perspective linked to deficits in learning and memory in particular. Abnormalities affecting attention and executive function have also been noted, albeit less frequently. Cannabidiol, on the other hand, does not induce euphoria and purportedly has anxiolytic, anticonvulsant and anti-inflammatory effects (Rong *et al.*, 2017). While the putative cognitive effects of cannabidiol still need confirmation, preliminary evidence suggests it may be neutral (Gruber *et al.*, 2016), enhancing, (Colizzi and Bhattacharyya, 2017) or if given simultaneously with THC, potentially protective (Gruber *et al.*, 2018). The ameliorating effects when used with THC may be dose dependent for should the THC: cannabidiol ratio be skewed towards the psychoactive component, impaired cognition is more likely (Gruber *et al.*, 2018). This observation is particularly relevant to our study where the urine analyses revealed a predominant THC content. It is also germane to note, relative to our findings, that the composition of cannabis available in the province of Ontario, which is where we recruited our sample, has not only a high THC content, but one that is becoming more potent with time (Mammen *et al.*, 2017) in keeping world-wide trends (Colizzi and Bhattacharyya, 2017).

To date, there is only one neurological study exploring the relative benefits and side effects of both THC and cannabidiol in a sample of 24 subjects (18 with multiple sclerosis) who had a miscellany of neurological and psychological symptoms (Wade *et al.*, 2004). The methodology involved a consecutive series of double-blind, randomized, placebo-controlled single-patient cross-over trials with 2-week treatment periods of four treatment options administered by spray: THC, cannabidiol, THC + cannabidiol in equal parts and placebo. A single cognitive measure, The Short-Orientation-Memory-Concentration (SOMC) Test was used. Scores on the SOMC were significantly lower in the THC group relative to the other three treatment arms. Extrapolating from this result, and in light of the THC and cannabidiol findings in healthy individuals, it is reasonable to suppose that the additional cognitive deficits in patients with multiple sclerosis who use cannabis are THC related. Support for this comes from our study, where a decline to minimal levels of THCCOOH was associated with cognitive improvement. Significantly, the binding of THC to the CB1 cannabis receptor, which mediates the CNS effects of THC, takes 28 days to decline to zero with cannabis abstinence (Schreiner and Dunn, 2012). This timeline fits well with our serial cognitive data in the cannabis withdrawal group.

Our study is the first to show that cognitive deficits in patients with multiple sclerosis who use cannabis regularly over many years can improve with drug abstinence. Once more we have to turn to the cannabis literature in healthy subjects for comparisons. As with the prevalence data, results may be influenced by numerous factors such as frequency of use, potency of the drug, age of onset of usage and duration of follow-up, amongst others. Cognizant of these potential confounders a meta-analysis of adult data from 13 studies showed that cognitive deficits had for the most part resolved after 25 days of abstinence (Schreiner and Dunn, 2012). Not only did global indices of cognition revert to baseline, but individual cognitive metrics including executive function, attention, memory (learning and retrieval), perceptual motor abilities, simple reaction times and language, normalized as well. Support for this comes from more recent data in adolescents where abstinence for longer than 72 h resulted in cognition reverting to baseline levels (Scott *et al.*, 2018). This optimistic picture is, however, challenged by a 25-year longitudinal study that revealed that if cannabis use began in adolescence with subjects smoking or ingesting more than four times a week, cognitive deficits did not resolve with abstinence or reduced use in adulthood (Meier *et al.*, 2012). The critical variables influencing outcome would therefore appear to be the age of onset, coupled with duration of cannabis use. The deleterious interaction of THC with the developing adolescent brain in which neural networks are being pruned, reorganized and solidified has been cited as a cause for persistent deficits. This theory fits with diffusion tensor imaging data showing that long-term cannabis use is detrimental to the cerebral white matter in the developing brain (Zalesky *et al.*, 2012).

In our study, age of onset and duration of, cannabis use were found to differ, albeit not statistically, between the cannabis CC and CW groups. Neither variable, however, influenced cognition at the index or Day 28 assessments. The reasons for this may relate to our study design. By excluding subjects who had begun using cannabis before the onset of their multiple sclerosis, we ruled out individuals whose use dated back to adolescence, a period of development vulnerability. In our sample, the mean ages of onset of multiple sclerosis were 29.7 years and 30.6 years for the CW and CC groups, respectively, placing them well beyond the age of putative risk. The CW group had, however, been using cannabis for 3.9 years less than the CC group. Whether this conferred a greater cognitive advantage in the context of cannabis withdrawal cannot be ruled out, although it is considered unlikely. As discussed above, the cannabis withdrawal literature suggests that for duration of use to be a determinant of enduring cognitive impairment following cessation, first usage must date back to the teenage years and be frequent thereafter (Meier *et al.*, 2012).

When it came to analysing the SDMT-functional MRI data we had to account for two processes that could disrupt the neural network known to underpin the cognitive paradigm, namely the effects of multiple sclerosis and those due to cannabis. Our starting point was the well-defined SDMT core neural network in healthy subjects summarized in our methods section. (Silva *et al*, 2018). Our data show that elements of this network were intact at baseline and, as anticipated, there were no between group differences at that point in time. By Day 28, this network came into clearer focus, but only in the group off cannabis. The

data compliment an earlier functional MRI-SDMT study of patients with multiple sclerosis, half of whom were cannabis users and the other half cannabis naïve (Pavisian *et al.*, 2015). Findings from this study revealed cannabis-mediated network suppression associated with a trend for poorer test performance. The present study now demonstrates that as cannabis is withdrawn, network suppression abates and with it, performance on the SDMT not only speeds up, but becomes more accurate too. Notably, performances in the group remaining on cannabis stayed unchanged both for speed and accuracy of response indicating the absence of significant practice effects.

The second part to our imaging analysis looked at ancillary brain activations that can occur during the SDMT in response to the presence of both multiple sclerosis and cannabis. To tease apart these two putative influences, we made use of an already defined SDMT-neural network in patients with multiple sclerosis who are cannabis naïve. Pivotal brain regions involved include the insula, thalamus, anterior cingulate and middle temporal gyrus (Genova *et al.*, 2009). At baseline, we expected to find no between group differences, which was the case. In addition to the regions mentioned above, activations were seen in frontal and parietal regions not associated with the test. By Day 28, cerebral activation in the group off cannabis had reverted to that typically seen in cannabis-naïve patients with multiple sclerosis (Forn *et al*, 2009; Genova *et al.*, 2009; Pavisian *et al.*, 2014). No such improvement occurred in the group remaining on cannabis.

Our study is not without limitations. First, we did not know the precise composition and potency of cannabis used, which is likely to have varied across subjects. Of the 39 subjects who completed our study, 15 (38.5%) used medically prescribed cannabis and clues as to their components may be gleaned from a recent Canadian study from the province of Ontario (which is where we conducted our study), investigating the THC/cannabidiol concentrations in these prescriptions (Mammen *et al.*, 2017). A web-based content analysis was undertaken using the websites of all 36 licensed producers. After excluding 11 websites and 77 products with no information on the cannabinoid content, data were obtained from the remaining 25 licensed producers and their 277 products. The THC/cannabidiol content in each product ($n = 354$) were screened and revealed THC-dominant hybrids in 65%, pure THC in 11% and cannabidiol-dominant in 24%. Of note is that 91% of the THC-dominant hybrids contained only traces of cannabidiol. The overall conclusion was that the majority of the products contained potent levels of THC. While potency data are not available in our study, urine analyses confirmed that the cannabis used was predominantly THC.

A second limitation pertains to potential bias. Participants were assigned to the CW or CC groups based on odd and even case numbers, albeit with the tester unaware of pending group allocation prior to the index assessment. The tester, however, was responsible for following subjects over the course of the study to monitor for new symptoms and was thus aware of group membership at the time of the follow-up assessment. Tester expectations may influence cognitive results, even when the tester is unaware of this bias (Sodos *et al.*, 2018). These findings are in line with a neuropsychological literature that supports the influence of stereotype effects on cognitive performance in cannabis users (Looby and Earleywine, 2010). While this suggests the possibility of bias in the cognitive results obtained from the BRNB at Day 28, this limitation falls away when it comes to the functional MRI-SDMT data given that testing here was purely computerized with no tester input. The same point applies to the fully automated MRI analyses given that data are batch filed and machine analysed with group membership only added to the imaging data once completely analysed.

In summary, we have shown that cognitively impaired patients with multiple sclerosis who have used cannabis frequently over many years can show significant cognitive improvement should they discontinue cannabis use completely for a period of 28 days. When it comes to processing speed deficits, considered the quintessential feature of cognitive impairment in patients with multiple sclerosis, improvement is matched by a pattern of brain activation that is more closely aligned with that seen not only in patients with multiple sclerosis who are cannabis naïve, but also in healthy control subjects. From a clinical perspective, coming off cannabis was not associated with a significant worsening in symptoms. Cannabis withdrawal symptoms were transient and manageable.

Looking to the future, replication is needed with a methodology that removes the potential for tester bias and includes an analysis of the cannabinoid components and concentrations. To extrapolate the findings more generally, sample selection must extend beyond the demographic and multiple sclerosis characteristics of the group reported here, i.e. mainly young, mildly disabled and with a relatively short duration of disease. In addition future research should explore the potential benefits of cannabidiol on cognition and the degree to which this cannabinoid might offset the deleterious cognitive effects of THC in patients with multiple sclerosis. There are many questions about cannabis that remain unanswered, but moves towards widespread legalization and the likelihood of increasing numbers of patients with multiple sclerosis and other neurological disorders using the drug, suggest that greater attention be given to the risks and benefits of use in individuals with vulnerable brains. With this in mind, the promising data presented here should be viewed as first steps on a long and likely winding, road.

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Competing interests

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Supplementary material

Supplementary material is available at *Brain* online.

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