

ORIGINAL RESEARCH

Impaired awareness: Why people with multiple sclerosis continue using cannabis despite evidence to the contrary

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Abstract

Background: With widespread moves toward legalization of cannabis, increasing numbers of people with multiple sclerosis (pwMS) are using the drug. Emerging MS-related data show that cannabis can cause or exacerbate cognitive dysfunction.

Objective: To understand why people with MS continue using cannabis despite adverse cognitive consequences. It was hypothesized that lack of awareness, a component of metacognition, could explain this decision, in part.

Method: Forty pwMS who smoked cannabis almost daily were assigned by odd–even case number selection to either a cannabis continuation (CC) or cannabis withdrawal (CW) group. Both groups were followed for 28 days. All participants completed, at baseline and day 28, the brief repeatable battery of neuropsychological tests (BRNB) in MS for measures of processing speed, memory and executive function; Modified fatigue impact scale (mFIS) for self-report indices of cognitive functioning.

Results: No significant baseline differences between the groups on the BRNB and mFIS. At day 28, significant improvement within group was seen on all measures of the BRNB, but only in the CW group ($p = .0001$ for all indices). A repeat measure ANOVA did not find any significant group (CC vs. CW) \times time (baseline and day 28) interactions for the self-report cognitive measures on the mFIS. Cannabis abstainers did report less ability to function away from home. All 19 participants in the CW group reverted to using cannabis on study completion despite being informed individually of their cognitive improvement.

Conclusions and relevance: The inability of pwMS to accurately appraise their memory and executive function can help explain, in part, why they continue to smoke cannabis despite objective evidence of the deleterious cognitive side effects of this behavior.

KEYWORDS

cannabis, meta-cognition, multiple sclerosis

1 | INTRODUCTION

Cannabis is a very popular drug. Worldwide, only alcohol and tobacco are used more frequently (United Nations Office on Drugs & Crime

[UNODC], 2009). This general enthusiasm for the drug cannot, however, explain its standout acceptance among people with multiple sclerosis (pwMS). A 2017 survey hosted by the National MS Society and the Michael J. Fox Foundation (for Parkinson's research) reported

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that two thirds of people with MS were currently using cannabis, almost double the figure for those with Parkinson's disease (Kindred et al., 2017). Neurology and neuropsychiatry clinics in Canada confirm the high frequency of use (Banwell et al., 2016; Schabas et al., 2019). What is equally notable about these numbers is that pwMS find cannabis helpful despite limited supportive, empirical evidence for therapeutic benefits (Koppel et al., 2014) and in the face of emerging data suggesting problematic side effects like global cognitive impairment (Honarmand et al., 2011).

PwMS report using cannabis for multiple reasons, the most frequent being managing pain, spasticity, depression, anxiety, insomnia, and fatigue (Nielsen et al., 2018). For some it is a lifestyle or recreational choice. Significantly, users divulge that taking cannabis has allowed them to reduce their use of prescription medications (Kindred et al., 2017). The perception that a treatment could help is clearly a major factor accounting for ongoing use. Legalization has also contributed to a wider embrace (Banwell et al., 2016; Hildebrand et al., 2020). However, there is another factor that might explain, in part, this disconnect between the absence of objective therapeutic benefits and a subjective conviction that smoking, vaping, or ingesting cannabis is symptomatically beneficial. Self-awareness may be inaccurate.

Metacognition refers to the knowledge a person has about his or her own cognitive processes. In its broadest sense it refers to "thinking about thinking" and is considered integral to successful learning, self-regulation, and self-reflection of strengths and weaknesses (Flavell, 1979). There is evidence that metacognition is impaired in pwMS (Goverover et al., 2018; Mazancieux et al., 2018), particularly in those individuals with executive dysfunction and memory deficits (Beatty & Monson, 1991), two domains frequently impaired in MS (Chiaravalloti & DeLuca, 2008).

We have previously shown that discontinuing cannabis can bring about a significant improvement in numerous indices of cognition and depression in pwMS (Feinstein et al., 2019, 2020). The current study expands on these earlier findings by assessing the self-awareness of MS cannabis users with respect to their own cognition on and off cannabis. We hypothesize that an impaired awareness of cognitive abilities can explain, in part, a predilection for the drug.

2 | METHODS

A group of 40 people with MS who were longstanding, frequent users of cannabis were enrolled in the study. The group was divided into those who were withdrawn from cannabis ($n = 20$) and those who continued on the drug ($n = 20$). Demographic details of the group and the odd-even group selection process has been described previously (Feinstein et al., 2019). Given that the study focused primarily on the potential cognitive benefits of cannabis discontinuation, only cognitively impaired individuals were enrolled. Both groups were followed for a month. Baseline and follow-up assessments included the following:

1. Cognition: All participants underwent a 30-minute cognitive battery, the brief repeatable battery of neuropsychological tests

(BRNB) in MS (Rao, 1990). This battery focuses on measures of information processing speed, working memory, learning and attention. It consists of the selective reminding test revised, 10/36 spatial recall test, PASAT, symbol-digit modality test (SDMT) and controlled oral word association test (COWAT). Global impairment was defined as failure (scores of 1.5 standard deviations below normative data controlling for age, sex and education) on two or more tests. Alternate versions of the tests were given to minimize practice effects. The Wechsler test of adult reading (WTAR; Wechsler, 2001) was administered at baseline only to obtain a measure of pre-morbid intelligence.

2. Self-perception of cognition was elicited with the modified fatigue impact scale (mFIS; "Measuring the Functional Impact of Fatigue: Initial Validation of the Fatigue Impact Scale on JSTOR," 2011.). The mFIS contains three subscales, physical, cognitive and psychosocial. The cognitive subscale has 10 questions encompassing attention, concentration, slowed thinking, clarity of thought, memory, organizing thoughts, decision making, and task completion. Each question contains five responses scored in a simple Likert fashion. A total score is obtained by adding the scores from the three subscales.
3. Symptoms of anxiety and depression were recorded with the hospital anxiety and depression scale (HADS; Zigmond & Snaith, 1983), validated for use in MS research (Honarmand & Feinstein, 2009).
4. Cannabis: The duration and frequency of cannabis use were recorded at baseline. The reasons for using cannabis were also noted and they included pain, spasticity, depression, anxiety, insomnia, bladder dysfunction, lifestyle choice, and combinations of these. The long half life of cannabis introduces a challenge in monitoring withdrawal. In order to distinguish residual excretion from new use of cannabis a ratio of the cannabis metabolite 11-nor-9-carboxy- Δ^9 -tetrahydro-cannabinol (THCCOOH) to urinary creatinine was obtained. All subjects completed the cannabis withdrawal scale which quantifies symptoms of cannabis withdrawal according to these scores: < 51 none; 52–66 mild to moderate; > 66 severe. The CW group was contacted on a weekly basis during their 28-day withdrawal period to monitor symptoms and reminded participants of the need for abstinence.

2.1 | Statistical analysis

Comparisons between the cannabis continuation (CC) and cannabis withdrawal (CW) groups' self-perception of cognition over time (Baseline and Day 28 assessments) were undertaken using repeat measure analysis of variance (rmANOVA) controlling for the effects of depression and baseline demographic/disease mismatch, when present.

2.2 | Ethics

Informed consent was obtained from all participants and ethic's approval for the study was obtained from the host institution's Research Ethics Board.

TABLE 1 Demographic and MS-related data

	Cannabis-C		Cannabis-W		t-test/ χ^2	Sig. (2 = tailed)
	Mean/frequency (N = 20)	SD	Mean/frequency (N = 19)	SD		
Age (years)	39.30	8.473	36.26	11.690	$t = 0.36$	0.36
Sex (% female)	9 (45.0%)	-	11 (57.89%)	-	$\chi^2 = 0.648$	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%)	-	$\chi^2 = 0.219$	0.72
SPMS	4 (20%)	-	5 (26.32%)	-	-	-
Disease duration (years)	9.61	5.67	5.62	5.10	$t = 2.31$	0.03
Disease modifying drug, n (%)	5 (25%)		10 (52.63)		$\chi^2 = 3.143$	0.07

Abbreviations: Cannabis-C = cannabis continuation group; cannabis-W = cannabis withdrawal group; EDSS-expanded disability status scale; SD = standard deviation; Sig-statistical significance; χ^2 = chi square test.

3 | RESULTS

- Demographic and MS-related data: Demographic and MS-related comparisons between the CC and CW groups are shown in Table 1. The CW group had a shorter disease duration ($t_{2.31}, p = .03$). The baseline THCCOOH/creatinine ratios for the two groups were: CW = 80.37 (SD = 58.45) versus CC = 156.94 (SD = 113.55), $t = 2.51; p = .02$. Over the course of 28 days, the ratios in the CW group approached zero ($t = 4.505; p = .0001$) whereas the CC group remained unchanged ($t = -0.379; p = .709$). A single person in the CW group was withdrawn from the study because of cannabis use. There were no group differences in the frequency ($\chi^2 = 0.31, p < .58$) or amount of cannabis smoked daily (CW mean = 2.05 g (SD = 1.27) versus CC mean = 2.30 g (SD = 1.35), $t = 0.60; p = 0.56$).
- Self-awareness of cognition, physical abilities and psychosocial functioning: The comparisons between group (CW vs. CC) over time (Baseline and Day 28) are shown in Table 2 in a rmANOVA. We controlled for three covariates, namely depression, disease duration, and baseline THCCOOH/creatinine ratios. Depression was included given the well described association between mood and self-awareness of cognition (D'hooghe et al., 2019) while the latter two variables were added because they differed between the two groups at baseline. The group \times time interactions were not significant for any of the cognitive or physical variables on the mFIS. The only significant group \times time interaction was for the variable "psychosocial activities" in which the CW group reported to being less likely to do things away from home once they had discontinued their cannabis. This interaction remained unchanged after controlling for the effects of depression, disease duration, and baseline THCCOOH/creatinine ratio. Of note is that depression was significantly associated with every variable on the mFIS, but there were no group \times depression interactions. Thus, while depression influenced how participants perceived their cognitive, physical and psy-

chosocial abilities, it did not do so selectively in one group more than the other. The only other statistically significant covariate finding of note was that baseline THCCOOH/creatinine ratios were associated with motivation for psychosocial activities. A closer look at the raw data for this variable at baseline and day 28 showed that scores over time remained identical for the CC group and increased marginally in the CW group.

- Cognition: The cognitive results and their functional MRI correlates have been reported previously; to summarize, there were no cognitive differences between the two groups at baseline. By day 28, the CW group performed significantly better than the CC group on all the BRNB indices, namely SRT, 10/36, PASAT3, PASAT2, SDMT ($p = .0001$ for all). Within group comparisons showed no change over time for the CC group across all cognitive indices, whereas in the CW group, significant improvement was found on all indices, namely SRT, 10/36, PASAT3, PASAT2, SDMT ($p = .0001$ for all). Linear regression analyses revealed that group membership (CW versus CC) was a significant, independent predictor of cognitive performance on every BRNB variable at day 28 after controlling for group differences in disease duration, baseline THCCOOH/creatinine ratios, duration of cannabis use, and frequency of disease modifying drug use. Depression scores in those pwMS who were using cannabis to manage their depression remained statistically unchanged in the CC group ($n = 11$), but declined in the CW group ($n = 9; p = .006$).
- All 19 subjects in the CW withdrawal group returned to using cannabis after being given their results showing significant cognitive improvement after 28 days of abstinence. The reasons cited were the same as those given for using it in the first place, namely pain, spasticity, depression, insomnia, bladder dysfunction, migraine, and recreational. The only symptom that worsened over time was insomnia in two individuals in the CW group. This was managed by low-dose hypnotic prescription.

TABLE 2 Modified fatigue impact scale: comparisons between cannabis continuation (CC) and cannabis withdrawal (CW) groups

	Baseline				Day 28 assessment				rmANOVA F[df], Sig.	HADS-D	THCCOOH-creatinine	Duration
	CC		CW		CC		CW					
	Mean	SD	Mean	SD	Mean	SD	Mean	SD				
Cognitive subscale												
Alertness	1.85	1.04	1.37	1.26	1.70	.865	.89	.658	F[33] = .75, p = .391	p = .002	p = .145	p = .482
Vigilance	1.75	.967	1.53	1.12	1.60	.883	1.00	.882	F[33] = 2.47, p = .124	p = .017	p = .758	p = .859
Thinking clearly	1.80	1.01	1.84	1.21	1.65	1.04	1.42	.838	F[33] = .89, p = .352	p = .003	p = .4487	p = .213
Memory	1.70	.979	2.21	1.03	1.45	.999	1.79	.855	F[33] = .67, p = .417	p = .002	p = .283	p = .443
Decision making	1.95	.999	2.21	.976	1.60	1.04	2.26	1.24	F[33] = .91, p = .347	p = .003	p = .447	p = .769
Motivation ^a	1.75	1.25	2.21	1.13	1.45	.945	2.53	1.38	F[33] = 1.4, p = .244	p = .002	p = .386	p = .529
Task completion	1.85	1.18	2.21	.976	1.45	.887	1.89	1.04	F[33] = .03, p = .869	p = .001	p = .139	p = .475
Organizing thoughts	1.95	1.28	2.00	1.29	1.50	1.05	1.53	.772	F[33] = .09, p = .763	p = .003	p = .191	p = .666
Slowed thinking	1.70	1.17	2.00	1.29	1.40	.995	1.16	.958	F[33] = 3.56, p = .067	p = .002	p = .439	p = .859
Concentration	1.75	1.16	1.53	1.07	1.70	.801	1.05	.911	F[33] = 2.34, p = .134	p = .002	p = .454	p = .597
Physical subscale												
Uncoordinated	2.35	1.23	2.26	.806	2.15	1.10	2.05	1.08	F[33] = 0, p = 1.0	p = .002	p = .659	p = .347
Physical speed	2.25	1.21	1.68	1.06	2.15	1.27	2.11	1.10	F[33] = 2.24, p = .143	p = .000	p = .438	p = .683
Motivation ^b	2.15	1.39	1.89	.994	2.35	1.31	2.21	.976	F[33] = .1, p = .758	p = .000	p = .783	p = .434
Stamina	2.25	1.16	2.00	1.00	2.20	1.20	2.00	1.20	F[33] = .11, p = .74	p = .000	p = .553	p = .256
Weakness	2.40	1.47	1.68	1.20	2.20	1.11	2.00	1.05	F[33] = 1.92, p = .174	p = .000	p = .814	p = .57
Discomfort	2.30	1.34	1.95	1.35	2.20	1.32	2.05	1.13	F[33] = .27, p = .605	p = .000	p = .93	p = .479
Physical effort	2.45	1.43	2.00	1.05	2.40	1.27	2.32	.885	F[33] = 1.25, p = .27	p = .000	p = .733	p = .881
Physical limitations	2.10	1.17	1.74	.872	2.40	1.10	1.89	1.24	F[33] = .20, p = .657	p = .000	p = .706	p = .196
Physical rest	1.85	1.23	1.79	1.18	2.20	1.06	1.95	1.03	F[33] = .29, p = .596	p = .000	p = .911	p = .164
Psychosocial subscale												
Motivation ^c	1.65	1.35	1.53	1.12	1.65	1.35	1.58	1.02	F[33] = .98, p = .328	p = .000	p = .03	p = .710
Activities	1.50	1.28	1.42	1.07	1.50	1.28	1.84	1.21	F[33] = 2.86, p = .007	p = .000	p = .067	p = .694

Abbreviations: CC = cannabis continuation group; CW = cannabis withdrawal group; df = degrees of freedom; duration = MS disease duration in years; HADS-D = hospital anxiety and depression scale-depression subscale; rmANOVA = repeat measures analysis of variance; SD = standard deviation; Sig = statistical significance; THCCOOH-creatinine = ratio of THC metabolite to creatinine in urine.

^aMotivation related to anything that required thinking.

^bMotivation related to physical effort.

^cMotivation related to social activities.

4 | DISCUSSION

Our data show that when people with MS who have been using cannabis on a daily basis over many years discontinue the drug and remain abstinent for at least 28 days, significant cognitive improvement occurs across multiple domains such as processing speed, learning, verbal and visual memory, and executive function. Most notably, cognitive improvement was not accompanied by a self-awareness of this positive cognitive change. In keeping with previous research (D'hooghe et al., 2019), we showed that depression influenced how participants perceived their own cognitive abilities, but this does not differ according to cannabis use or abstinence.

The inability of our study participants who had discontinued cannabis to accurately appraise their own cognition is indicative of a deficit in metacognition. Despite a burgeoning MS cognitive literature over the past two decades, metacognition (incorporating metamemory) has received relatively less attention. Twenty years ago, Beatty and Monson (1991) reported that impairments in recognition memory and executive function contributed independently and cumulatively to poor metamemory. They concluded that people with MS were unable to acknowledge their memory deficits. The importance of executive function in metacognitive skills was underscored by a study that looked at the use of imagery mnemonics in verbal learning tasks (Canellopoulou & Richardson, 1998). The ability of people with MS to use this

strategy and appraise its effectiveness in boosting their memory broke down in the presence of executive difficulties. Interestingly, motivational factors were also implicated in this metacognitive failure. This finding resonates, in part, with our data. While individuals who came off cannabis did not report less motivation when it came to thinking or physical activities, they were less likely than the CC group to pursue activities away from home.

Metacognition relies on executive functions and self-awareness. Definitions of the latter include not only the ability to recognize difficulties that can arise from abnormal brain function in the presence of an acquired brain insult (Crosson et al., 1989) but also the ability to accurately appraise past, present, and future behaviors (Hoerold et al., 2008). A three-part hierarchy to self-awareness has been proposed with intellectual awareness (i.e., recognizing that a particular function is impaired) propping up emergent awareness (i.e., being aware of a problem when it arises), which in turn supports anticipatory awareness (i.e., the ability to foresee problems arising because of current deficits) (Crosson et al., 1989). When viewed within this construct, the predilection for using cannabis in our participants despite significant cognitive side effects becomes easier to comprehend. At the base of the hierarchy is a lack of awareness of the deficits in executive function and memory. In this regard, while our follow-up data show significant objective improvements in these two cognitive domains off cannabis (Feinstein et al., 2019), these gains appear insufficient to bring about a subjective awareness of improvement in our participants. This in turn impedes their ability to appreciate the deficits that either arise from cannabis use, or are exacerbated by it, and the gains that come with abstinence. This failure in emergent awareness ensures that anticipatory awareness, namely the ability to realize that cognitive problems are likely to arise or worsen should cannabis be smoked, vaped, or ingested, is faulty. In short, there is a failure of self-awareness at every step in this hierarchy, thereby compromising metacognition and leading to decisions related to persistent cannabis use that are self-injurious. Not only does the determination to use cannabis override the demonstrable cognitive side effects of the drug, it is unsupported by concomitant data of physical benefits. This point is underscored in our study by the longitudinal data from the physical subscale of the mFIS which showed no deterioration over time in self-report symptoms. In addition, no participant who came off cannabis in our study had to consult a neurologist for worsening pain, spasticity, or behavioral difficulties. Indeed, as we have shown earlier, depression actually improved off cannabis, most notably in those individuals who reported having used it specifically to help with their low mood (Feinstein et al., 2020).

The MS-cannabis-behavioral literature is a small one and it is therefore helpful to look at the broader non-MS literature for insights into explaining the predilection for cannabis in our participants. Functional brain imaging has identified two networks that are relevant to different aspects of self-awareness. The default network has been implicated in bodily (somatic) awareness and its relationship to the external environment (Buckner et al., 2008). The insula network, on the other hand, is relevant to interoceptive awareness or inner body sensations that come from the gut, heart, sexual organs etc. This in turn can influence a person's subjective emotions (Craig, 2009). Pujol et al. (2014)

looked at resting state activity in these two networks in a group of heavy cannabis users and a control group of non-users and demonstrated a mix of increased and decreased functional connectivity in the former, in addition to showing enhanced anticorrelation between the two networks. These brain changes in the cannabis group were associated with a subtle modulation in anxiety and deficits in memory, specifically verbal recall, both of which are linked to a feeling enhanced wellbeing in psychoactive drug users. Of note is that these fMRI and behavioral changes were associated with the amount of cannabis used and, most importantly in the context of our study's methodology, persisted for one month after participants discontinued cannabis use.

Although these findings have not been demonstrated in people with MS who use cannabis, it is not unreasonable to suppose that similar mechanistic underpinnings are relevant. Here our mFIS data potentially provide some indirect supporting behavioral evidence. Individuals who came off cannabis and whose cognition improved substantially as a result appeared unaware of these changes, but what they did report was less of an ability to undertake activities away from home. This negative change, while subtle, gives a possible clue as to why all our study participants returned to using cannabis after a month of abstinence. The "reward" that comes with this recidivism is a less constrictive lifestyle, which in the context of a disabling illness like MS, cannot be underestimated. If this is indeed the case, we can see how the combined effects of being unable to perceive cannabis' cognitively harmful effects coupled with a subjective sense of being better able to function away from home, tip the scales in favor of continued drug usage.

Our study is not without limitations. The primary aim of the study was not on metacognition. This is reflected in our use of the modified fatigue impact scale as the only marker of meta-cognition.

While the scale is able to provide informative insights in this regard, it is not primarily a psychometric index of metacognition. Psychometric scales like the perceived deficits questionnaire (Sullivan et al., 1990) and the executive function index (Spinella, 2005) to give but two examples would have been preferable. Second, our sample size of 40 subjects divided into two groups is modest, but considered adequate for the functional imaging aspects of our inquiry, the results of which have been reported elsewhere (Feinstein et al., 2019). In addition our follow-up period of 28 days, while sufficient to allow for the THCCOOH levels to fall to zero, is relatively short. A longer duration may potentially have revealed an increase in self-perceived physical difficulties in the cannabis withdrawal group possibly matched by objective signs. Finally, as we have noted in our discussion, a failure in metacognition is not the only reason why people with MS continue to use cannabis in the face of demonstrable cognitive side effects. Our study was not designed to explore in greater details what these multifaceted reasons are, but they likely encompass placebo effects, the long reach of sophisticated marketing techniques and, at least in certain individuals, symptomatic benefits beyond those that our limited methodology could not detect.

If lack of awareness and abnormal metacognition explain in part the predilection for cannabis in people with MS, it may also offer a pathway to discontinuation. There is some evidence that using and improving metacognitive strategies can enhance cognitive rehabilitation in

people with MS (Goverover et al., 2018; Pöttgen et al., 2015). This potentially opens the door to assisting people with MS gain more awareness of how cannabis, predominantly THC-based, can harm their cognition. If successfully applied, such an approach has the potential to better inform an individual's decision when it comes to weighing the pros and cons of using the drug.

CONFLICT OF INTEREST

Anthony Feinstein has received speaker's honoraria from Sanofi-Genzyme, Roche, Biogen, Teva and Novartis, Advisory Board fees from Akili Interactive and book royalties from Cambridge University Press, Johns Hopkins University Press and Amadeus Press. The other authors have nothing to disclose.

AUTHOR CONTRIBUTION

Anthony Feinstein: Obtained grant funding, Study design, data analysis, and manuscript preparation

Cecilia Meza: Data acquisition, data analysis, and manuscript preparation

Cristiana Stefan: Study design, data analysis, and manuscript preparation

Richard W. Staines: Study design, data analysis, and manuscript preparation

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1002/brb3.2220>.

DATA AVAILABILITY STATEMENT

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

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