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Short report

Cannabis and cognitive functioning in multiple sclerosis: The role of gender

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Abstract

Background: Cognitive function in people with multiple sclerosis (PwMS) is associated with gender differences and the use of smoked/ingested cannabis.

Objective: The objective of this report is to explore a possible gender-cannabis interaction associated with cognitive dysfunction in PwMS.

Methods: A retrospective analysis was undertaken of cognitive data collected from 140 PwMS. A general linear model was conducted to determine gender and cannabis effects on processing speed (SDMT), verbal (CVLT-II) and visual (BVMT-R) memory, and executive functions (D-KEFS), while controlling for age and years of education.

Results: Cannabis was smoked at least once a month by 33 (23.6%) participants. Cannabis users were more impaired on the SDMT ($p = 0.044$). Men, who comprised 30.7% of the entire sample and 42.2% of cannabis users, were more impaired on the CVLT-II (total learning, $p = 0.001$; delayed recall, $p = 0.004$). A cannabis-gender interaction was found with the CVLT-II delayed recall ($p = 0.049$) and BVMT-R total learning ($p = 0.014$), where male cannabis users performed more poorly than female.

Conclusion: Males with MS may be particularly vulnerable to the cognitive side effects of smoked cannabis use.

***Keywords*:** Multiple sclerosis, cognition, cannabis, gender

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Introduction

There is a small literature showing that non-synthetic cannabis is linked to more extensive cognitive abnormalities in people with multiple sclerosis (MS).[1] There are also MS data that reveal greater cognitive dysfunction in men than women.[2] Given that approximately one in five people with MS smoke, vaporize or ingest cannabis, with men using it more frequently than women,[3] the question arises as to a possible cannabis-gender interaction associated with impaired cognition. Given that no study to date has addressed this potentially injurious interaction, we turned to a current dataset for possible answers.

Methods

Sample

We have previously described the sample of 140 people with MS reported here as part of a series of studies devoted to psychometric development.[4] Exclusion factors included a history of another disease of the central nervous system, traumatic brain injury, psychosis, learning disability, substance abuse, neuropsychological testing completed within the past year and a corrected visual acuity of less than 20/70.

Demographic and neurological data

Demographic (age, gender and years of education) and neurological (disease duration, disease course, and physical disability) data were collected.

Cannabis use

All participants were asked if they were using natural (non-synthetic) cannabis on a regular basis, which was defined as monthly or more frequently. The monthly window was chosen given that cannabis metabolites remain in the system for up to 46 days following cessation of use.[5] From this we inferred that if a participant endorsed usage, there would be

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Table 1. Demographics, neurological and psychiatric comparison by cannabis use and gender.

	Cannabis users — mean (SD)/ frequency (%); $n = 33$	Cannabis non-users — mean (SD)/ frequency (%); $n = 107$	t-test/χ^2	p value
Age (years)	37.73 (10.08)	45.01 (10.44)	$t = 3.531$	$p = 0.001$
Sex (% female)	19 (57.8%)	78 (72.9%)	$\chi^2 = 2.782$	$p = 0.095$
Years of education	14.39 (2.16)	15.46 (2.24)	$t = 2.403$	$p = 0.018$
Illness duration (years)	9.18 (7.11)	10.39 (8.59)	$t = 0.731$	$p = 0.466$
EDSS	2.81 (2.02)	2.48 (1.85)	$t = -0.817$	$p = 0.416$
% on disease-modifying medication	11 (33.3%)	42 (39.3%)	$\chi^2 = 0.376$	$p = 0.540$
Disease course				
RRMS	27 (81.8%)	82 (76.6%)	$\chi^2 = 0.424$	$p = 0.515$
SPMS	5 (15.2%)	17 (15.9%)	$\chi^2 = 0.015$	$p = 0.903$
PPMS	1 (3.0%)	8 (7.5%)	$\chi^2 = 0.848$	$p = 0.357$
HADS depression	6.76 (3.90)	6.38 (4.08)	$t = -0.465$	$p = 0.642$
HADS anxiety	9.09 (5.27)	8.04 (4.28)	$t = -1.168$	$p = 0.245$
	Males — mean (SD) / frequency (%); $n = 43$	Females — mean (SD)/ frequency (%); $n = 97$	t-test/χ^2	p value
Age (years)	41.98 (9.82)	43.88 (11.17)	$t = -0.962$	$p = 0.338$
Years of education	15.49 (2.42)	15.08 (2.19)	$t = 0.979$	$p = 0.329$
Illness duration (years)	9.65 (7.31)	10.30 (8.67)	$t = -0.429$	$p = 0.669$
EDSS	2.74 (1.98)	2.48 (1.85)	$t = -0.693$	$p = 0.490$
% on disease-modifying medication	31 (72.1%)	56 (57.7%)	$\chi^2 = 2.612$	$p = 0.106$
Disease course				
RRMS	34 (79.1%)	75 (77.3%)	$\chi^2 = 0.027$	$p = 0.871$
SPMS	6 (14.0%)	16 (16.5%)	$\chi^2 = 0.107$	$p = 0.743$
PPMS	3 (6.9%)	6 (6.2%)	$\chi^2 = 0.044$	$p = 0.833$
HADS depression	5.65 (3.05)	6.84 (4.36)	$t = -1.613$	$p = 0.109$
HADS anxiety	7.26 (3.82)	8.74 (4.77)	$t = -1.803$	$p = 0.074$
Use cannabis regularly	14 (32.6%)	19 (19.6%)	$\chi^2 = 2.782$	$p = 0.095$

EDSS: Expanded Disability Status Scale; RRMS: relapsing–remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis; HADS: Hospital Anxiety and Depression Scale.

cannabis metabolites present at the time of testing. We did not record frequency of use and there was no corroborative urine testing.

Cognitive data

Based on previous research showing an association between cannabis use and deficits in processing speed, memory and executive function, we confined our analyses to the following cognitive tests:

1. Processing speed: Paced Auditory Serial Addition Test (PASAT), 3 and 2 second versions; The Symbol Digit Modalities Test (SDMT)
2. Verbal and visual learning and memory: California Verbal Memory Test-II (CVLT-II) and the Brief Visuospatial Memory Test-Revised (BVMT-R)
3. Executive function: Delis-Kaplan Executive Function System (D-KEFS) Sorting Test.

Anxiety and depression were assessed with the Hospital Anxiety and Depression Scale (HADS).[6]

Statistical analysis

A general linear model was conducted to determine gender and cannabis effects on cognitive variables while controlling for age and years of education. Statistical significance was set at $p < 0.05$.

Informed consent

Research ethics board approval from Sunnybrook Health Sciences Center was obtained for this study. Informed consent was received from all participants.

Table 2. General linear model assessing the effect of gender and cannabis on cognitive variables while controlling for age and education.

	F value	p value	η^2
SDMT			
Gender	$F = 0.019$	$p = 0.892$	$\eta^2 < 0.001$
Cannabis	$F = 4.153$	$p = 0.044$	$\eta^2 = 0.030$
Gender × cannabis	$F = 1.939$	$p = 0.166$	$\eta^2 = 0.014$
PASAT-3 seconds			
Gender	$F = 0.050$	$p = 0.824$	$\eta^2 < 0.001$
Cannabis	$F = 0.959$	$p = 0.329$	$\eta^2 = 0.001$
Gender × cannabis	$F = 2.584$	$p = 0.110$	$\eta^2 = 0.020$
PASAT-2 seconds			
Gender	$F = 1.517$	$p = 0.221$	$\eta^2 = 0.012$
Cannabis	$F = 2.175$	$p = 0.143$	$\eta^2 = 0.018$
Gender × cannabis	$F = 0.708$	$p = 0.402$	$\eta^2 = 0.006$
CVLT-II-Total learning			
Gender	$F = 11.453$	$p = 0.001$	$\eta^2 = 0.079$
Cannabis	$F = 3.503$	$p = 0.063$	$\eta^2 = 0.025$
Gender × cannabis	$F = 2.158$	$p = 0.144$	$\eta^2 = 0.016$
CVLT-II-Delayed recall			
Gender	$F = 8.740$	$p = 0.004$	$\eta^2 = 0.061$
Cannabis	$F = 2.988$	$p = 0.086$	$\eta^2 = 0.022$
Gender × cannabis	$F = 3.932$	$p = 0.049$	$\eta^2 = 0.029$
BVMT-R-Total learning			
Gender	$F = 3.547$	$p = 0.062$	$\eta^2 = 0.026$
Cannabis	$F = 2.064$	$p = 0.153$	$\eta^2 = 0.015$
Gender × cannabis	$F = 6.209$	$p = 0.014$	$\eta^2 = 0.044$
BVMT-R-Delayed recall			
Gender	$F = 0.233$	$p = 0.630$	$\eta^2 = 0.002$
Cannabis	$F = 3.136$	$p = 0.079$	$\eta^2 = 0.023$
Gender × cannabis	F = 2.617	$p = 0.108$	$\eta^2 = 0.019$
D-KEFS-Total sorts			
Gender	$F = 0.853$	$p = 0.357$	$\eta^2 = 0.006$
Cannabis	$F = 1.786$	$p = 0.184$	$\eta^2 = 0.013$
Gender × cannabis	$F = 0.912$	$p = 0.341$	$\eta^2 = 0.007$
D-KEFS-Total description			
Gender	$F = 1.229$	$p = 0.270$	$\eta^2 = 0.009$
Cannabis	$F = 2.594$	$p = 0.110$	$\eta^2 = 0.019$
Gender × cannabis	$F = 0.451$	$p = 0.503$	$\eta^2 = 0.003$

SDMT: Symbol Digit Modalities Test; PASAT: Paced Auditory Serial Addition Test; CVLT-II: California Verbal Learning Test-II; BVMT-R: Brief Visuospatial Memory Test-Revised; D-KEFS: Delis Kaplan Executive Function System.

Results

Demographic, neurologic and psychiatric comparisons between the 33 (23.6%) cannabis users and 107 (76.4%) non-users are displayed in Table 1. Cannabis users were younger (37.73 (SD: 10.08) vs. 45.01 (SD: 10.44) years, $t = 3.531$, $p = 0.001$) and less educated (14.39 (SD: 2.16) vs. 15.46 (SD: 2.24), $t = 2.403$, $p = 0.018$). The cannabis user group consisted of 14 men (42.4%) and 19 (57.6%) women. Ten out of 107 (9.3%) non-cannabis smokers used other medications for symptomatic relief of their pain and spasticity. Of the 33 cannabis users, two (6.06%) used other medications for similar purposes ($p = 0.732$).

There were no demographic, neurologic or psychiatric differences between men and women (Table 1). More men endorsed using cannabis, but the

difference fell short of significance (32.6% vs. 19.6%, $\chi^2 = 2.782$, $p = 0.095$).

The cognitive results from the general liner model are shown in Table 2. Cannabis users performed more poorly than non-users only on the SDMT ($F = 4.153$, $p = 0.044$). Men were more impaired on two indices of the CVLT-II; total learning ($F = 11.453$, $p = 0.001$) and long delayed free recall score ($F = 8.740$, $p = 0.004$). A gender X cannabis interaction was found on the latter ($F = 3.932$, $p = 0.049$) where men performed more poorly in the cannabis user ($t = -3.022$, $p = 0.005$), but not non-user ($t = 0.446$, $p = 0.659$) group. A significant gender X cannabis interaction was present on the BVMT-R total recall ($F = 6.209$, $p = 0.014$), where men performed more poorly than women in the cannabis user ($t = -2.370$, $p = 0.024$), but not non-user ($t = 1.537$, $p = 0.134$) group.

Discussion

The gist of our study is the novel finding that self-reported use of non-synthetic cannabis and gender interact in the pathogenesis of cognitive dysfunction in people with MS, with the negative effects most discernable when it comes to memory, both verbal and visual, in men. Our data bring together two independent strands reported previously in the MS-cognition literature. The first is the association between cannabis use on the one hand and impaired processing speed and verbal memory on the other. In this regard, further deterioration on the SDMT[1] and increasing memory difficulties on tasks such as the N-Back and 10/36 visual memory paradigm[7] have been reported previously in MS cannabis users. The second relates to a small yet increasingly consistent literature showing greater cognitive dysfunction in men[2] associated with more magnetic resonance imaging (MRI) visualized structural brain changes in men too.[8] In light of these earlier findings, the current cognitive results appear to mesh two synergistic causative influences. Interestingly, recent animal data show that cannabis has a localized effect on hippocampal dysregulation, but once more only in male rats.[9] The potential importance of this finding from a cognitive perspective is that hippocampal atrophy in people with MS has been linked specifically to impaired memory.

The result of this study was obtained from a secondary analysis of data collected for a different research purpose. We therefore lack objective confirmatory laboratory evidence of cannabis use or non-use, and the frequency and duration of use, which are limitations when it comes to data interpretation. Furthermore, the cross-sectional nature of our study means that association may not equal causality. As such our findings must be seen as preliminary. Nevertheless, they potentially reveal an intriguing congruence based on previous research. Looking to the future, as researchers continue to refine their understanding of the complex role played by cannabis in altering cognition in people with MS, attention should focus anew on the potentially modifying role played by gender.

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Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Viral Patel has nothing to declare.

Dr Anthony Feinstein has served on scientific advisory boards for Merck Serono and Avanir Pharmaceuticals; has received speaker honoraria from Merck Serono, Teva Pharmaceuticals Industries Ltd., Novartis, and Biogen Idec; serves on the editorial boards of *Multiple Sclerosis*; 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 and the Multiple Sclerosis Society of Canada.

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