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Altered cerebellar-cortical resting-state functional connectivity in cannabis users

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Abstract

Background: Cannabis use has been associated with abnormalities in cerebellar mediated motor and non-motor (i.e. cognition and personality) phenomena. Since the cerebellum is a region with high cannabinoid type 1 receptor density, these impairments may reflect alterations of signaling between the cerebellum and other brain regions.

Aims: We hypothesized that cerebellar-cortical resting-state functional connectivity (rsFC) would be altered in cannabis users, relative to their non-using peers. It was also hypothesized that differences in rsFC would be associated with cannabis use features, such as age of initiation and lifetime use.

Methods: Cerebellar-cortical and subcortical rsFCs were computed between 28 cerebellar lobules, defined by a spatially unbiased atlas template of the cerebellum, and individual voxels in the cerebral regions, in 41 regular cannabis users (20 female) and healthy non-using peers (N = 31; 18 female). We also investigated associations between rsFC and cannabis use features (e.g. lifetime cannabis use and age of initiation).

Results: Cannabis users demonstrated hyperconnectivity between the anterior cerebellar regions (i.e. lobule I-IV) with the posterior cingulate cortex, and hypoconnectivity between the rest of the cerebellum (i.e. Crus I and II, lobule VIIb, VIIIa, VIIIb, IX, and X) and the cortex. No associations were observed between features of cannabis use and rsFC.

Conclusions: Cannabis use was associated with altered patterns of rsFC from the cerebellum to the cerebral cortex which may have a downstream impact on behavior and cognition.

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Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

Keywords

Cannabis; cerebellum; MRI; posterior cingulate cortex; connectivity; resting-state

Introduction

Cannabis (CB) is the most widely used illicit substance in the world (Johnston et al., 2012; ONDCP, 2008; SAMHSA, 2011). CB intoxication generates psychotomimetic effects, cognitive dysfunction, and psychomotor deficits (Radhakrishnan et al., 2014), and has been linked to increased risk for development of psychosis (Di Forti et al., 2014; Sherif et al., 2016). The psychoactive effects of CB on the brain are primarily due to delta-9-tetrahydrocannabinoid (Δ-9-THC), a partial agonist which binds to cannabinoid type 1 receptors (CB1r) (Malone et al., 2010; Mechoulam, 2005). Because CB1r density varies among brain regions, effects of CB are likely to be most apparent in regions with high densities of CB1r.

The cerebellum is one of the highest regions of CB1r density in the brain, although CB1r is also heavily expressed in the cingulate and middle frontal gyrus, medial temporal lobes, and basal ganglia (Glass et al., 1997; Tsou et al., 1998). Not only is the cerebellum rich with CB1r it also accounts for about 80% of total brain neurons (Herculano-Houzel, 2011). Measures sensitive to cerebellar dysfunction are often affected in CB users, including eyeblink conditioning (Skosnik et al., 2008; Steinmetz et al., 2012), postural sway (Bolbecker et al., 2018) time perception (Atakan et al., 2012; Sewell et al., 2013), and neurological soft signs related to motor control (Dervaux et al., 2013). In addition to disturbances of motor control and associative learning, extensive anatomical, and functional connections of cerebellum to cerebral networks suggest that the cerebellum optimizes cortical control of diverse cognitive, motor, and sensory domains (Koziol et al., 2012; Middleton and Strick, 2000; Stoodley and Schmahmann, 2009; Stoodley et al., 2012; Strick et al., 2009). Consistent with this model, cerebellar activation has been associated with modulation of blood oxygenation level dependent (BOLD) activity in functional magnetic resonance imaging (fMRI) resting-state networks, such as the default mode network (DMN) (Halko et al., 2014) and dorsal attention network (Salmi et al., 2018). Although the cerebellum has rarely been the focus of prior resting-state fMRI studies in CB users, it is thus highly likely that CB use would impact cerebellar-cortical interactions.

In addition to the specific susceptibility of the cerebellum to cannabinoids, rodent models and human research have implicated cerebellar circuits with other drugs of abuse and alterations in reward processing, a key component related to the development and maintenance of addiction (Koob and Volkow, 2010). Chronic use of heroin, nicotine, alcohol, and cocaine have frequently been associated with reduction of cerebellar gray matter volume, and acute administration of stimulants, nicotine and Δ-9-THC cause cerebellar activation (Moulton et al., 2011). The computational role of the cerebellum in prediction, sequential behaviors, and associative conditioning have been linked to craving and cue-responses in humans and rodent models of addiction (Carbo-Gas et al., 2014; Miquel et al., 2016; Moreno-Rius and Miquel, 2017). Cerebellar granule cells signal reward

prediction across different contexts, with cells that selectively respond to reward delivery, expectation, and omission (Wagner et al., 2017). In aggregate, these studies suggest that interactions between cerebellar circuits and other brain regions may play a key role in addiction.

Functional neuroimaging studies have found increases in cerebellar activation in healthy controls during acute exposure to marijuana or Δ-9-THC (Volkow et al., 1991, 1996). CB users were observed to have lower relative cerebellar metabolism but increased cerebellar metabolism in response to acute administration of Δ-9-THC (Mathew et al., 1998, 2002; Volkow et al., 1996). Further, cerebellar metabolism during Δ-9-THC intoxication was correlated with subjective intoxication (Volkow et al., 1996), and inversely correlated with impaired sense of time (Mathew et al., 1998).

Since preclinical animal models indicate that the endocannabinoid system is important for synaptic plasticity and modulating interactions within neural circuits (Rubino et al., 2009), connectivity among brain regions may be especially sensitive to CB use. Resting-state functional connectivity (rsFC) investigations have often found increases in cortical connectivity (Cheng et al., 2014; Filbey et al., 2014; Pujol et al., 2014; Vergara et al., 2018), and altered connectivity within the cerebellum of CB users (Cheng et al., 2014) and in response to Δ-9-THC (van Hell et al., 2011). Altered cerebellar-cortical connectivity has also been observed, including increases in functional connectivity between the cerebellum and the sensorimotor network (Klumpers et al., 2012) and between bilateral inferior parietal lobules and the left cerebellum (Behan et al., 2014), as well as decreases in connectivity between the cerebellum and posterior cingulate cortex (PCC) as a proxy of the DMN (Wetherill et al., 2015). Additionally, CB users have been observed to have decreased interhemispheric connectivity in the cerebellar pyramis and increases in fractional amplitude of low-frequency fluctuations in the right inferior semilunar lobe of the cerebellum (Orr et al., 2014). Notably, some studies also failed to detect alterations in functional connectivity between the cortical and/or subcortical regions and the cerebellum (Camchong et al., 2017; Pujol et al., 2014; Zimmermann et al., 2018). It is important to acknowledge that the literature lacks consistency in how CB use has been defined, which may have important implications for the inconsistencies observed in the literature. For instance, some studies defined their CB use group based on the number of uses per week, such as once a week over the past month (Cheng et al., 2014), 4 times a week over the past 6 months (Filbey et al., 2014) or greater than 14 times per week over the 2 years (Pujol et al., 2014). Additionally, other studies chose to define their CB group based on meeting diagnostic standards of dependence and/or treatment for CB dependence (Behan et al., 2014; Camchong et al., 2017; Orr et al., 2013; Wetherill et al., 2015; Zimmermann et al., 2018).

Given the heterogeneous findings, limited number of studies and lack of systematic investigation of cerebellar connectivity further investigation is needed to better understand the role of the cerebellum while the brain is at rest in CB users. Moreover, previous studies largely used cortical seed-based analyses, such as the PCC or insula, for the primary goal of assessing functional connectivity within cortical networks. The present study assessed rsFC with fMRI, from the cerebellum to cortical and subcortical regions of the brain. Unlike previous studies, we used the spatially unbiased atlas template of the cerebellum (SUIT),

which is a pre-defined cerebellar parcellation scheme, as seeds in our connectivity analysis. It was hypothesized that rsFC in CB users would be altered relative to their non-using peers. Also, as previous research suggests that CB use features are important potential moderators of the impacts of CB use (Anglin et al., 2012; Crean et al., 2011; Fontes et al., 2011; Gruber et al., 2012; Hides et al., 2009; Stefanis et al., 2004, 2013; Weinstein et al., 2016; Wilson et al., 2000), it was hypothesized that differences in rsFC would correlate with CB use features, such as age of initiation and lifetime use.

Methods

Subjects

Forty-one CB users (20 female) and thirty-one healthy controls (18 female) participated in the study. After detailed explanation of research procedures, subjects provided verbal and written informed consent. Study procedures were approved by the Institutional Review Board of Indiana University for protection of human subjects and carried out according to guidelines of the *Declaration of Helsinki*.

Subjects were determined to be free of any current axis I disorder based on the Structured Clinical Interview for DSM-IV-TR (SCID), Research Version (First et al., 2002). Subjects were excluded if they met criteria for lifetime dependence on any substance (excluding nicotine and CB). All participants were at least 18 years of age, and free of any neurological disorder, loss of consciousness, learning disability, family history of a first degree relative with psychosis, and contraindication to MRI. While subjects were considered CB users if their rate of CB use was ⩾ once per week, the mean rate of use of CB users was 30 times per month (Table 2). Controls were not required to be CB naïve (six subjects reported distant and minimal lifetime CB use: 4.17 ± 4.23 lifetime uses, range 1 to 12.5 total uses), but were not permitted to have used CB within past 3 months, or to meet lifetime diagnostic criteria for CB abuse or dependence, as per the DSM-IV SCID. Subjects underwent urine toxicology to validate self-reported CB and other substance use.

Procedure

Recruitment and screening procedures have been previously reported (Bolbecker et al., 2018). In brief, subjects were recruited via local advertisements and word of mouth and completed a phone screen to assess general eligibility. Potentially eligible subjects then completed in-person oral and written informed consent, diagnostic interview, urine toxicology, and self-report measures assessing lifetime substance use. Subjects returned a second day for imaging data collection and were required to abstain from alcohol, illicit drug use, and smoking CB at least 12 h before their MRI session. Subjects were compensated $12 per h for the initial interview and $60 for the imaging day. A Substance Use Questionnaire was used to collect information about lifetime substance use including tobacco, alcohol, CB, and synthetic marijuana (Fridberg et al., 2011; Skosnik et al., 2012). The Short Michigan Alcohol Screening Test (SMAST) (Selzer et al., 1975) was used to characterize alcohol use as scores >2 are indicative of problematic drinking.

MRI acquisition

MRI data were collected on a 3T Siemens TimTrio MRI scanner (Magnetom TimTrio, Siemens). Eyes open resting-state fMRI was collected using an echo-planar image (EPI) sequence with multi-banded RF pulses (multi-band factor = 3) and the following parameters: TR = 813 ms, TE = 28 ms, flip angle = 60°, field of view = 221 × 221 mm, slice thickness = 3.4 mm, and acquisition matrix = 65 × 65 × 43, 3.4 mm^3 isotropic voxels. Scans for the first 10 s were omitted from analysis to allow the T1-magnetisation equilibrium, resulting in a total of 1000 volumes (= 13 min 33 s). High-resolution T1-weighted anatomical images were acquired in the sagittal plane using a Magnetization Prepared Rapid Gradient Echo sequence: TR = 1.8 s; TE = 2.67 ms; inversion time = 0.9 s; flip angle 9°; acquisition matrix = 256 × 256 × 192; voxel size = 1 × 1 × 1 mm^3. Subjects were asked to remain awake, and to keep their eyes open looking at a fixation-cross on the screen inside the scanner.

MRI preprocessing

Preprocessing of the functional and anatomical MRIs was done with AFNI (https://afni.nimh.nih.gov) and Freesurfer software (http://fresurfer.net). Functional scans were preprocessed with despiking (to exclude signal intensity outliers introduced by excessive head movement), slice timing correction, rigid-body motion correction (with three translation and three rotation parameters), linear and trend removal, within-run intensity normalization to a whole-brain mode value of 1000, linear regression of nuisance variables, and temporal band-pass filtering ($0.009 < f < 0.08$ Hz). Nuisance parameters for linear regression included six rigid-body motions, cerebrospinal fluid (CSF), and white-matter (WM) signals, along with their temporal derivatives. A whole brain signal was not included in nuisance covariates given on-going controversy (Saad et al., 2012). Functional scans were then co-registered to each individual's anatomical MRI and normalized to the Talairach space. Volumes with high motion in functional scans were censored to minimize potential motion-artifacts (Power et al., 2014). We used a frame-wise displacement (FD) threshold of 0.5 mm and a percentage of BOLD signal changes over the whole-brain (DVARS; D referring to temporal derivative of time-courses, VARS referring to root-mean-square variance over voxels) of 0.5, above which scans (including one backward and two forward volumes) were removed (Power et al., 2012). No group differences were found in the head motion defined by averaging FD values across scans (FD_{HC} : FD_{CB} = 0.12 ± 0.04: 0.14 ± 0.05 mm, $t = 1.52$, $p = 0.13$) and the number of censored scans (N_{HC} : N_{CB} = 18.61 ± 40.08 : 30.49 ± 73.04, $t = 0.82$, $p = 0.42$), respectively.

Functional connectivity analysis

After the spatial smoothing with 6-mm full width at half maximum in the gray matter mask was applied, BOLD time-series were extracted in a set of 28 cerebellar lobules acquired from a SUIT(Diedrichsen et al., 2009). Notably, due to its small size (4 mm^3, which is approximately equivalent to only 1 voxel in the 2 × 2 × 2 mm resting-state voxel resolution), the vermis Crus I was omitted from the analyses. Pearson's correlation coefficients were then computed between the principal component (PC) within each cerebellar lobule and individual voxel time-series in the cerebral regions. Correlations were converted to z-scores, using Fisher's *r*-to-*z* transformation, and group differences were investigated with

independent samples t-tests using age, sex, and education as covariates. To control for multiple comparisons, we performed 10,000 Monte Carlo simulations using 3dClustSim program in AFNI (http://afni.nimh.nih.gov) with an individual voxel level threshold of $p < 0.005$, cluster connection radius, 3.4 mm (edge connected), individual smoothing kernel by 3dFWHMx with -acf option in AFNI, individual voxel resolution, $2 \times 2 \times 2$ mm^3, and a gray matter mask based on group averaging T1-weighted image. According to the simulations, a corrected significance level of $p < 0.05$ with an extent threshold of 69 contiguous voxels (i.e. $p < 0.05$, cluster-corrected) was used.

Statistical analysis

Statistical analyses were performed with IBM SPSS statistical software (Version 25.0) from IBM (CORP, 2020). A student's *t*-test was used to assess for differences in age, BMI, and education, and a chi-square test was used to assess for differences in sex, ethnicity and race. After the computation of rsFC values, values were extracted at the peak voxel of each cluster with significant group differences found in the functional connectivity analysis above, and partial correlations, controlling for education, as groups differed on this demographic feature (Table 1), were computed with FDR correction to assess associations with CB-related features (i.e. age of CB initiation and total lifetime use) in the CB group alone ($n = 41$) as well as across the entire sample ($n = 41 + 31$).

Results

Subjects

Groups did not differ in age, sex, race or BMI ($p > 0.05$), but were significantly different in completed education ($p < 0.05$), see Table 1, and thus partial correlations between rsFC and CB use features were completed controlling for education. The CB group reported 30.67 ± 24.69 uses over the past month, and an average of 7.33 ± 15.07 uses of wax, a formulation with a high concentration of Δ-9-THC, over the past 6 months. Groups did significantly differ in average drinks per week (over the past month) ($p < 0.05$). Further characterization of alcohol use and problems with the SMAST, indicated that groups did not differ in risk of problematic drinking ($p > 0.05$). Table 2 provides comprehensive information regarding CB and alcohol use features of both groups.

Group differences in functional connectivity

Several regions were identified in which groups differed in rsFC (Figure 1). CB users had increased rsFC between the right lobule I to IV of the cerebellum to the left posterior cingulate ($Z = -4.380$, $p < 0.0001$) and right fusiform gyrus ($Z = -3.766$, $p = 0.0002$). CB users also had decreased rsFC from the left Crus I to the left middle frontal gyrus ($Z = 4.202$, $p < 0.0001$) and right medial frontal gyrus ($Z = 3.675$, $p < 0.0001$), cerebellar left Crus II to the right inferior frontal gyrus ($Z = 4.273$, $p < 0.0001$) and left superior frontal gyrus ($Z = 3.780$, $p = 0.0002$), left cerebellar VIIb to the right insula ($Z = 4.154$, $p < 0.0001$), right cerebellar VIIIa to the right insula ($Z = 4.432$, $p < 0.0001$), cerebellar vermis VIIIb to the left inferior frontal gyrus ($Z = 4.129$, $p < 0.0001$), right cerebellar VIIIb to the right putamen ($Z = 4.090$, $p < 0.0001$), left cerebellar IX to the left caudate ($Z = 4.235$, $p < 0.0001$), left cerebellar X to the left superior frontal gyrus ($Z = 4.547$, $p < 0.0001$) and left

middle temporal gyrus ($Z = 4.485$, $p < 0.0001$), and finally, from the right cerebellar X to the left middle temporal gyrus ($Z = 3.916$, $p < 0.0001$) and right middle temporal gyrus ($Z = 3.387$, $p = 0.0007$). For a summary of observed group differences see Table 3, and additional figures in Supplemental Materials.

No other group differences in rsFC were observed, as no significant group differences in rsFC were observed between the cerebral cortex and cerebellar regions including the left cerebellum I to IV, left V, right V, left VI, vermis VI, right VI, right Crus I, vermis Crus II, right Crus II, vermis VIIb, right VIIb, left VIIIa, left VIIIb, Vermis IX, right IX, and vermis X.

Functional connectivity and CB use features

There were no significant associations between CB use features, such as lifetime CB use and age of CB initiation, and regions of group difference in rsFC from the cerebellum that survived correction for multiple comparisons. For all partial correlations between rsFC and CB use features see Table 4. Similar to associations observed for the CB group alone, there were no significant associations between CB use features and measures of rsFC from the cerebellum.

Discussion

As hypothesized, significant group differences in rsFC between the cerebellum and the cortex were observed between CB users and their non-using peers. The most robust group differences indicated hypoconnectivity in the CB group relative to control subjects that were observed between the left lobule X of the cerebellum to the left superior frontal gyrus and to the left middle temporal gyrus, from the right VIIIa of the cerebellum to the right insula, and from the left Crus II of the cerebellum to the right inferior frontal gyrus. In contrast, CB users had increased functional connectivity compared to controls from the right I to IV of the cerebellum to the left posterior cingulate and to the right fusiform gyrus. While speculative, these alterations in connectivity may be secondary to downregulation and desensitization of CB1 receptors after chronic exposure (González et al., 2005; Sim-Selley, 2003). Contrary to our hypotheses, CB use features, such as age of CB initiation and total lifetime use were unrelated to rsFC.

Our results indicated that most differences reflected hypoconnectivity in CB users, while previous studies suggested hyperconnectivity between cerebellar regions and specific cortical regions in CB users (Behan et al., 2014; Cheng et al., 2014; Klumpers et al., 2012; Orr et al., 2013). Hypoconnectivity in CB users observed in this study was significant for three areas: prefrontal gyri, the insula, and the dorsal striatum. These regions are particularly relevant for processes involved in habitual substance use. The prefrontal cortex is critical for many processes involved in addictive behaviors including decision making, salience attribution, response inhibition, and planning (Goldstein and Volkow, 2011). The functions of the insula likely include risk prediction and incorporation of interoceptive and emotional states into decision making (Gogolla, 2017; Uddin et al., 2017). Finally, the dorsal striatum plays a central role in learning habitual behavioral sequences such as those involved in craving and drug-seeking (Yin et al., 2008). Hypoconnectivity between these cortical regions

and the cerebellum may contribute to failures and/or disruptions in information flow that is necessary for cognitive control, emotional regulation, and planning which results in impulsive behaviors and drug-seeking habits. More broadly, given the hypoconnectivity observed involved modules of the cerebellum implicated in non-motor functions (i.e. Crus I and Crus II), it is possible that these findings may reflect potential deficiency of non-motor cognitive cerebellar functions due to CB use. It is also notable that altered functional connectivity in similar regions has been implicated in attention-deficit hyperactivity disorder (Fair et al., 2013), a disorder that has been associated CB use (Ameringer and Leventhal, 2013; Lee et al., 2011).

With respect to observed hyperconnectivity to the left posterior cingulate, it is possible that the cerebellum is exerting more efferent output, relative to controls, to influence activity at the posterior cingulate, a region involved with sensory integration and a hub of the resting-state DMN (Fransson and Marrelec, 2008; Greicius et al., 2009). Further this increased effort may potentially be at the cost of neural effort between the cerebellum and other regions of the cerebral cortex. This conceptualization is consistent with the model of Moulton et al. (2014), in which he proposed that decreased cerebellar inhibition resulted in an overall net excitatory effect in regions associated with reward, motivation, memory, and interoception (Moulton et al., 2014), many of which were observed in this study. If this interpretation were true, it may have multiple explanations.

Firstly, since the posterior cingulate is associated with self-representation and body awareness (Guterstam et al., 2015) and the cerebellum is thought to maintain an internal model of current and predicted movements (Ito, 2006), this connectivity may reflect a person's awareness of body position and movements. Also, increased activity in the anterior lobules of the cerebellum (lobules I–IV), which are associated with motor control (Strick et al., 2009), and decreases in activity in other lobules (including Crus I and II) related to cognitive function, may suggest differential cerebellar involvement related to CB. For instance, increased cerebellar output may be required to inhibit excessive movement. Secondly, CB users may require additional cerebellar influence on the DMN, via the posterior cingulate, in order to maintain a resting state similar to that of controls. Interestingly, acute Δ-9-THC administration generated decreased deactivation of the DMN and possible interference with subjects' ability to perform a cognitive task (Bossong et al., 2013). Although this study did not include a traditional DMN analysis or cognitive task, the findings of elevated activity to a hub region of the DMN are consistent with these previous findings. Acute cannabinoid intoxication has also been observed to disrupt PCC connectivity within the DMN, although with mixed observations of increased and decreased PCC activation (Klumpers et al., 2012; Orr et al., 2013; Rzepa et al., 2016; Wall et al., 2019).

Preclinical and human research has suggested possible dopaminergic influence via reciprocal midbrain to cerebellar neural circuits that implicate the cerebellum in psychomotor functioning and reward processing (Ikai et al., 1994; Mittal et al., 2020; Volkow et al., 2013). Also, the anterior cerebellum has been associated with motor memory, and specifically within a motor network including the premotor cortex and putamen (reinforcement learning) (Bostan and Strick, 2018). The anterior cerebellum has also

been associated with rewards and reward prediction errors (Garrison et al., 2013). While speculative, these collective findings suggest that the altered rsFC between the anterior cerebellar lobules and the PCC observed in this study may contribute to the disruption of conditioned responses and goal-directed behaviors which may result in drug-seeking activities.

It was hypothesized that earlier age of onset of CB use and greater total lifetime exposure may be associated with increased resting-state abnormality compared to non-users; however, this relationship was not observed. It is possible that the observed differences are instead related to predispositional factors. While CB use features have been associated with other structural and functional changes in CB users (Gruber and Yurgelun-Todd, 2005; Harding et al., 2012), the observed group differences may be indicative of those likely to use CB, and not a result of use.

There are several limitations of this cross-sectional study. Future research should build on these findings with twin and/or longitudinal study designs to address the question of causality. Also, the lack of correlation between CB use features and rsFC may reflect the difficulty of accurately measuring THC and/or other cannabinoid intake from self-report measures, or due to the high heterogeneity of lifetime/recent CB use with limited report of heavy use. Given the difficulty of assessing the content of the CB used by participants, the current study included a self-report measure of wax to detect exposure to high concentrations of THC, the primary component of CB. Future research should consider the influence of various CB strains and individual compounds (i.e. THC, cannabidiol) within CB. Also, the development of objective biomarkers associated with proximal and remote use of CB may facilitate better estimates of exposure (Huestis and Smith, 2018; Meersseman et al., 2016). Additionally, to increase the generalizability of study findings, we did not exclude control participants based on lifetime CB exposure. Future research may be necessary to determine the influence of limited CB exposure on functional connectivity. The current study also only included CB users without current psychiatric problems or other types of substance use disorders. Since about 90% of persons with CB dependence have comorbid psychiatric disorders, this sampling approach likely excluded the most severely affected members of the user population (Agosti et al., 2002; Connor et al., 2013). Also, while this cohort of participants did not endorse regular cigarette use or dependence, future research should consider the potential impact of regular tobacco use. Finally, from a methodological perspective, it is possible that CB users have an altered hemodynamic response (Block et al., 2000; Sneider et al., 2006, 2008), and thus it is necessary that all functional connectivity dependent on a BOLD signal be interpreted cautiously.

With replication, these findings have the potential for broad impact. The influence of CB use on brain function has potential to inform the public at large, as CB legislation is increasingly being developed in the absence of scientific evidence on the psychophysiological consequences of its use. This is particularly relevant given the increasing rates of CB use (Carliner et al., 2017; Hasin et al., 2015) and perception of minimal risk (Azofeifa et al., 2016; Carliner et al., 2017; Zehra et al., 2018). Additionally, Δ-9-THC has been increasing over the past several decades (Mehmedic et al., 2010), and of consequence, has been associated with elevated psychotomimetic effects in users (Böcker et al., 2010; D'Souza et

al., 2004; Ramaekers et al., 2006), and detrimental mental health effects, such as increased risk for the development of severe mental illness, like schizophrenia (Di Forti et al., 2014). Given the importance of the cerebellum in motor coordination, understanding cerebellar mediated neural circuits could shed insight into behavioral associations with CB use, and lead to innovations for testing motor incoordination, which is a pressing need given the lack of roadside CB intoxication assessment and increase in motor vehicle accidents as a result of CB use (Asbridge et al., 2012; Del Balzo et al., 2018; Li et al., 2011; Peterson et al., 2018; Ramaekers et al., 2004; Rogeberg and Elvik, 2016). Together, with the increase in CB use and Δ-9-THC content, which may be catalyzed by the decreased perception of overall risk and increased ease of access, it is urgent to understand the potential impact of CB on the brain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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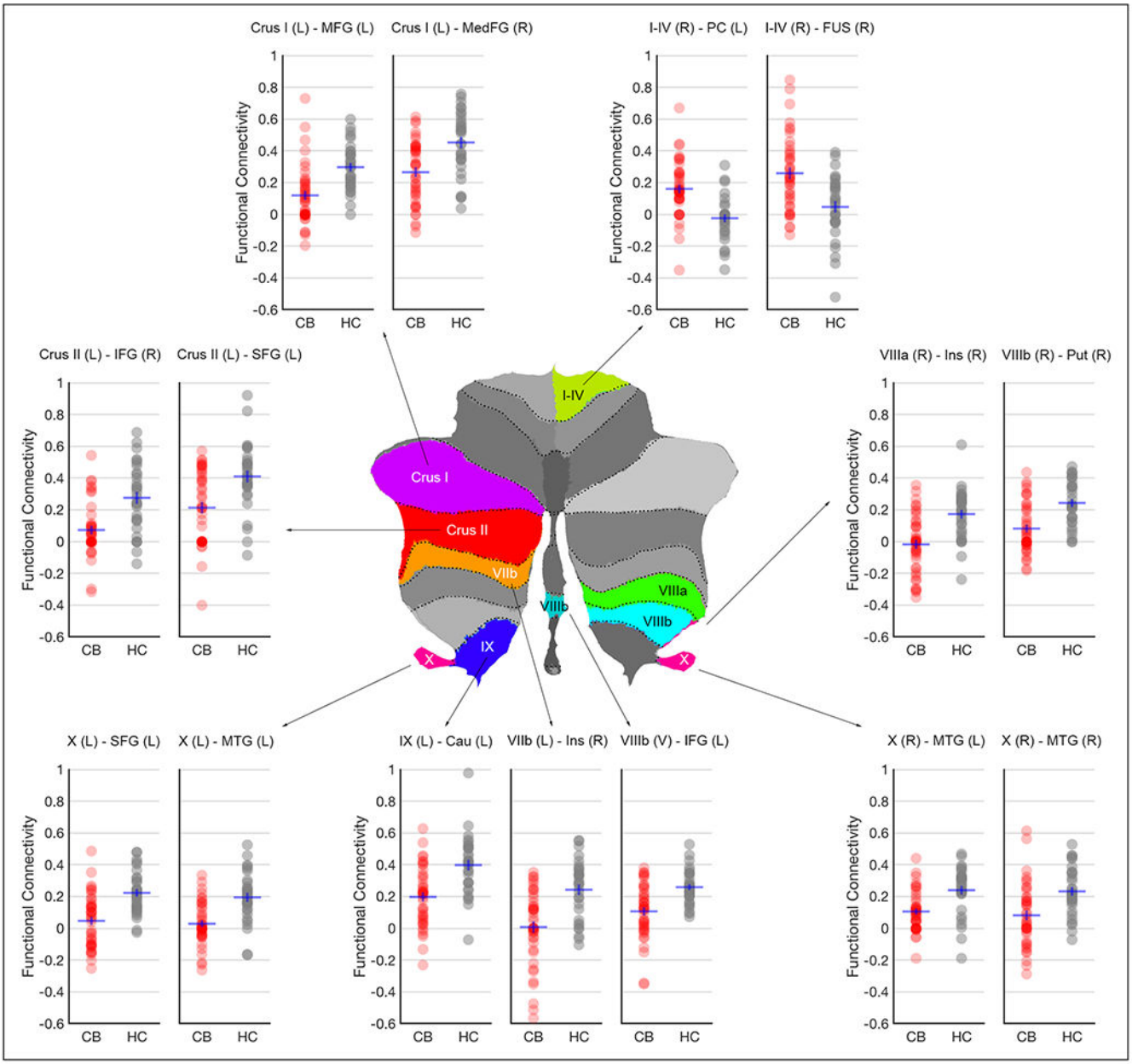

Figure 1.

Significant group differences of cerebellar-cortical functional connectivity. Red and gray dots represent cannabis (CB, $n = 41$) and healthy control (HC, $n = 31$) subjects, respectively. Horizontal and vertical blue lines represent mean and standard error in each group. Statistical significance was defined at the cluster-corrected $p < 0.05$ (>69 voxels). MFG, middle frontal gyrus; MedFG, medial frontal gyrus; PC, posterior cingulate; FUS, fusiform gyrus; IFG, inferior frontal gyrus; SFG, superior frontal gyrus; Ins, insula; Put, putamen; MTG, middle temporal gyrus; Cau, caudate; L, left; R, right; V, vermis.

Table 1.

Demographic information.

	HC (*n* = 31)	CB (*n* = 41)	*p*/Chi-square
Age (mean ± SD)	22.13 ± 3.52	20.88 ± 3.69	0.151
Sex (male:female)	13:18	21:20	0.435
Race (C:B/AA:A:M:UK)	18:4:6:2:1	27:7:5:2:0	0.669
Education (mean ± SD)	15.40 ± 2.10	13.79 ± 1.91	0.001 *
BMI (mean ± SD)	24.52 ± 4.73	24.06 ± 4.42	0.674
WASI	113.71 ± 10.42	110.07 ± 9.38	0.125

HC: healthy control group; CB: cannabis group; SD: standard deviation; C: Caucasian; B/AA: Black/African American; A: Asian; M: multiple races; UK: unknown.

* $p < 0.05$.

Table 2.

Cannabis and alcohol use features.

CB use features	HC (mean ± SD)	CB (mean ± SD)	*p*
Age initiation	19.50 ± 1.97 (6 endorsing)	16.39 ± 2.21	0.002 *
Past month use	0.00 ± 0.00	30.67 ± 24.69	0.000 *
Total lifetime uses	0.81 ± 2.40	1092.09 ± 1760.66	0.000 *
Wax use over past 6 months	0.00 ± 0.00	7.33 ± 15.07	0.004 *
Alcohol use features			
Days since last use	111.34 ± 359.6262	19.78 ± 53.40	0.192
Average drinks per week over past month at screening	2.23 ± 2.82	4.41 ± 4.99	0.022 *

HC: healthy control group; CB: cannabis group; SD: standard deviation.

* $p < 0.05$.

Table 3.

Group differences in rsFC.

rsFC index #	Cerebellar lobule	Cortical region	Cluster size (voxel)	Talairach coordinates (mm)			Direction	*Z*-score/*p*-value
				X	Y	Z		
1	Right I-IV	Left posterior cingulate	249	22	64	11	CB > HC	−4.380/<0.0001
2		Right fusiform gyrus	77	−31	46	−9	CB > HC	−3.766/0.0002
3	Left Crus I	Left middle frontal gyrus	138	52	−43	8	HC > CB	4.202/<0.0001
4		Right medial frontal gyrus	70	−4	−46	38	HC > CB	3.675/<0.0001
5	Left Crus II	Right inferior frontal gyrus	145	−55	−43	2	HC > CB	4.273/<0.0001
6		Left superior frontal gyrus	79	28	−31	50	HC > CB	3.780/0.0002
7	Left VIIb	Right insula	178	−34	−25	11	HC > CB	4.154/<0.0001
8	Right VIIIa	Right insula	73	−34	−25	11	HC > CB	4.432/<0.0001
9	Vermis VIIIb	Left inferior frontal gyrus	139	37	−28	−6	HC > CB	4.129/<0.0001
10	Right VIIIb	Right putamen	85	−25	−13	8	HC > CB	4.090/<0.0001
11	Left IX	Left caudate	77	10	−7	8	HC > CB	4.235/<0.0001
12	Left X	Left superior frontal gyrus	291	4	−58	23	HC > CB	4.547/<0.0001
13		Left middle temporal gyrus	258	34	61	23	HC > CB	4.485/<0.0001
14	Right X	Left middle temporal gyrus	85	34	58	29	HC > CB	3.916/<0.0001
15		Right middle temporal gyrus	73	−58	43	−9	HC > CB	3.387/0.0007

rsFC: resting-state functional connectivity; CB: Cannabis group; HC: healthy control group.

The gray shading indicates where CB users were observed to have increased functional connectivity compared to the HC group.

Table 4.

Associations between rsFC and CB use features.

rsFC index #	CB users		Full sample	
	Age of CB initiation	Total lifetime CB use	Age of CB initiation	Total lifetime CB use
1	0.02 (0.91)	−0.02 (0.88)	0.03 (0.84)	0.14 (0.24)
2	0.002 (0.99)	0.04 (0.83)	−0.02 (0.90)	0.15 (0.22)
3	0.10 (0.55)	0.08 (0.62)	0.10 (0.51)	−0.09 (0.47)
4	−0.20 (0.21)	0.09 (0.58)	−0.20 (0.18)	−0.07 (0.58)
5	0.08 (0.61)	0.28 (0.08)	0.24 (0.12)	0.02 (0.87)
6	−0.002 (0.99)	0.10 (0.53)	−0.02 (0.91)	−0.05 (0.66)
7	0.06 (0.73)	−0.04 (0.81)	−0.01 (0.97)	−0.18 (0.13)
8	−0.01 (0.93)	0.12 (0.45)	−0.06 (0.67)	−0.05 (0.71)
9	−0.18 (0.26)	0.08 (0.64)	−0.13 (0.38)	−0.06 (0.60)
10	0.03 (0.83)	−0.17 (0.29)	−0.01 (0.93)	−0.27 (0.03)
11	0.14 (0.39)	0.16 (0.33)	0.22 (0.15)	−0.04 (0.77)
12	−0.38 (0.02)	0.01 (0.91)	−0.30 (0.04)	−0.14 (0.25)
13	−0.17 (0.31)	−0.05 (0.77)	−0.17 (0.25)	−0.18 (0.13)
14	−0.26 (0.10)	−0.05 (0.76)	−0.25 (0.10)	−0.16 (0.17)
15	−0.23 (0.16)	−0.03 (0.85)	−0.11 (0.45)	−0.14 (0.24)

rsFC: resting-state functional connectivity and is defined by the rsFC index # from Table 3; partial correlations with uncorrected *p*-values are depicted by $r(p)$; no correlations survived FDR correction for multiple comparisons.