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Empathy-related differences in the anterior cingulate functional connectivity of regular cannabis users when compared to controls

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Abstract

It has been reported that cannabis consumption affects the anterior cingulate cortex (ACC), a structure with a central role in mediating the empathic response. In this study, we compared psychometric scores of empathy subscales, between a group of regular cannabis users (85, users) and a group of non-consumers (51, controls). We found that users have a greater Emotional Comprehension, a cognitive empathy trait involving the understanding of the "other" emotional state. Resting state functional MRI in a smaller sample (users = 46, controls = 34) allowed to identify greater functional connectivity (FC) of the ACC with the left somatomotor cortex (SMC), in users when compared to controls. These differences were also evident within the empathy core network, where users showed greater within network FC. The greater FC showed by the users is associated with emotional representational areas and empathy-related regions. In addition, the differences in psychometric scores suggest that users have more empathic comprehension. These findings suggest a potential association between cannabis use, a greater comprehension of the other's affective state and the functional brain organization of the users. However, further research is needed to explore such association, since many other factors may be at play.

KEYWORDS
cognitive empathy, emotional comprehension, fMRI, posterior insula, somatomotor cortex

1 | INTRODUCTION

United Nations estimate that in 2018, 3.9% of the global population aged 15–65 had used cannabis, of them 9.9% correspond to daily or near-daily cannabis users. Chronic cannabis use has widely been associated with effects on brain structure and function (Batalla et al., 2013; Battistella et al., 2014). Cannabis dependence has been linked to the binding mechanism between Δ9-tetrahydrocannabinol

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(THC), the primary psychoactive component of cannabis, and Cannabinoid CB1 brain receptors. In humans, the anterior cingulate cortex (ACC) is one of the main areas in which CB1 receptors have been identified (Burns et al., 2007; Eggan & Lewis, 2007), even more, it has been suggested that chronic cannabis use decreases CB1 receptors availability in this area (Ceccarini et al., 2015). In murine models, the administration of cannabinoid agonists on ACC CB1 receptors modulate responses involved in regulating cost–benefit decision making (Khani et al., 2015). In addition, an acute oral dose of THC on healthy subjects has proven to attenuate functional brain activity of the subgenual anterior cingulate cortex (sgACC) during the induction of negative affect (Rabinak et al., 2012).

The ACC has been proposed as a cortical hub of the salience network, involved in the processing of external and internal stimuli to maintain homeostasis, assigning positive or negative valences (Seeley, 2019). In this sense, the ACC is involved both in cognitive and affective functions, for example, conflict detection (Carter & van Veen, 2007), and empathy (Fan et al., 2011). A recent multimodal meta-analysis study performed by Yan et al. (2023) has identified that substance use disorder is highly associated with decreased resting-state functional brain activity in the bilateral anterior cingulate cortex and the medial prefrontal cortex (ACC/mPFC), also these authors found structural changes associated with reduced gray matter volume in these brain regions extending to the insula, thalamus, striatum, and left sensorimotor cortex. fMRI studies in regular cannabis users have reported lower functional activation of the ACC when performing cognitive tasks including inhibition control, awareness error detection, and reward anticipation (Batalla et al., 2013). In contrast, affective domains have been less investigated, whereas most studies including regular cannabis users have reported deficits in emotional evaluation and recognition (MacKenzie & Cservenka, 2023). Regular users, when compared to controls, have reported decreased functional activation in the ACC during masked affective stimuli perception (Gruber et al., 2009) and lower activation of the ventromedial prefrontal cortex/ACC during the evaluation of positive and negative stimuli (Wesley et al., 2016). Although it has been reported small to moderate associations between regular cannabis use and, physical violence, partner aggression perpetration, and violence among people with severe mental disorders (Beaudoin et al., 2020; Dellazizzo et al., 2020); regular cannabis use has also been related to increased positive affect and decreased hostile and anxious affect (Testa et al., 2019). In this sense, the therapeutic effects of cannabis use on mood and anxiety disorders had also been reported (Crippa et al., 2018; Elsaid et al., 2019). Moreover, Vigil et al. (2022) recently reported non-significant differences on levels of physical aggression, verbal aggression, anger, and hostility between cannabis users and controls, however, cannabis users report higher levels of prosocial behaviors, benevolence, fairness, and empathy when compared to non-users.

The bilateral anterior insula and the anterior cingulate cortex including its anterior middle (aMCC) and posterior portion (pACC) have been proposed as the empathy core network (Bernhardt & Singer, 2012; Fan et al., 2011). Empathy can be defined as an umbrella term that encompasses all the processes that influence our own representation of the other person's affective state (de Waal & Preston, 2017; Olalde-Mathieu et al., 2022), this includes, the experience and comprehension of negative feelings when perceiving others suffering (Batson, 2009; Decety & Lamm, 2009; Hoffman, 2001) and processes that promote prosocial behavior (de Waal, 2008; de Waal & Preston, 2017), engaging several brain areas and the interaction of other networks, for example, empathy core network, somatosensory, and the default mode network (DMN) (Engen & Singer, 2013; Gallo et al., 2018; Weisz & Cikara, 2020). Although, there are no studies in regular cannabis users related to the neural correlates of empathy, Roser et al. (2012), studied functional brain activation in cannabis users during the execution of a perspective taking task, a cognitive component of empathy. Regular users showed greater activation in the left cuneus and the right anterior cingulate gyrus compared to a group of non-users. Even though, the authors associated these findings with possible alterations in social cognition related to the attribution of others' mental states, the ACC was a region with differentiated functional activation on cannabis users.

Taking into account that the ACC is a region characterized by having a high concentration of CB1 receptors, susceptible to regular cannabis use, playing a major role in empathy, and considering the reported positive effects of cannabis in mood and positive affect (Crippa et al., 2018; Elsaid et al., 2019), we went to assess empathy-related psychometric differences and the functional connectivity of the ACC in a group of regular cannabis users and compared them to a group of non-users. Expecting greater scores in empathy and differences in the functional connectivity of the ACC and the empathy core network.

Significance

Cannabis use has generally been associated with negative mental health and behavioral outcomes. Using fMRI connectivity and psychometric methods, this study found that regular cannabis users have a greater understanding of the emotions of others. Furthermore, the anterior cingulate, a region generally affected by cannabis use and related to empathy, had stronger functional connectivity with brain regions related to sensing the emotional states of others within one's own body. These findings highlight positive effects of cannabis on interpersonal relationships and potential therapeutic applications.

2 | METHODS

2.1 | Participants

A sample of 85 regular cannabis users and a control group of 51 participants completed the psychometric tests and consumption questionnaires (Table S1). Of these, 46 users and 34 controls participated in a resting state fMRI acquisition (Tables S2 and S3). Exclusion criteria included neurological disorders, use of psychopharmaceuticals, depression assessed by interview and psychometric tests (Beck depression inventory, BDII) (Beck et al., 1961) and MRI contraindications. We also excluded other substance use disorders by semistructured interview and using a standard anti-doping urine test for detection of THC, cocaine, amphetamine, opioids, and methamphetamines. All participants signed an informed consent form. The experimental protocol was approved by the Ethics Committee of the Instituto de Neurobiología at the Universidad Nacional Autónoma de México (UNAM) and followed the guidelines of the Declaration of Helsinki.

2.2 | Psychometric test

We applied the Cognitive and Affective Empathy Test (TECA, in Spanish), developed by López-Pérez and Pinto (2009), which analyzes the empathic ability of the subject, assessing both cognitive and affective empathy. The TECA consists of 33 items, scored using a 5-option Likert scale, where 1 is "Strongly disagree" and 5 is "Strongly agree." The instrument has four subscales: Perspective Taking (PT), the capacity to place oneself in the shoes of another; Emotional Comprehension (CE), the ability to recognize and understand other people's emotions and impressions; Empathic Stress (ES), the ability to be in tune with others' negative emotions; and Empathetic Happiness scale (AE), the ability to feel others' positive emotions.

For the MRI sample, we also applied two additional tests to control as covariates, alcohol and nicotine use. For alcohol consumption, we used the AUDIT (de Meneses-Gaya, 2009), this test consists of 10 questions about their alcohol consumption in the previous year. The scoring ranges from 0 to 40 points. A total score equal or higher than eight points is interpreted as an indicator of hazardous drinking and harmful consumption, while a score equal or higher than 15 reflects a potential alcohol dependence. For nicotine use, the Fagerström Test for Nicotine Dependence was applied, which comprises six items. There are three multiple-choice items scored from 0 to 3 and three yes/ no items scored 0 for no and 1 for yes. The minimum score available in the Fagerström test is 0, indicating no dependence and the maximum score is 10, indicating very high nicotine dependence (Becoña & Vázquez, 1998).

2.3 | Data analysis

The tests were scored as their respective authors advised (Becoña & Vázquez, 1998; de Meneses-Gaya, 2009; Pérez & Pinto, 2009). Differences between groups were evaluated by a two-sample *t*-test and the effect size by a Cohen's d. To evaluate the correlations between variables in each group we employed Pearson correlations. To control false positives due to multiple comparisons, false discovery rate (FDR) was applied. Sex and age were controlled as confounding variables in both the general and fMRI sample. For the fMRI sample, the differences between groups were done using sex, age, AUDIT scores, and Fagerström scores as confounding. All statistical analyses were done using R software (*R: A Language and Environment for Statistical Computing (ISBN 3-900051-07-0)—ScienceOpen*, n.d.).

2.4 | Imaging

MRI images were obtained using a 32-channel array head coil, in a 3T MR scanner (Philips Healthcare, Eindhoven, The Netherlands). For anatomical reference, high-resolution T1-weighted images were obtained using a 3D Turbo Field Echo (TFE) acquisition with a $1\times1\times1\,mm^3$ voxel size (TR = 8.1 ms, TE = 3.2 ms, flip angle = 12.0°). For the resting state images participants were instructed to close their eyes during the 10 min acquisition; a total of 300 volumes were obtained using a gradient recalled echo T2* echo-planar imaging sequence (TR = 2000 ms, TE = 30 ms, voxel size $3\times3\times3\,mm^3$).

2.5 | Image analysis

Resting state fMRI (rsfMRI) analysis was performed mainly with FMRIB's Software Libraries (FSL v.4.1.9) (Jenkinson et al., 2012; Smith et al., 2004) and R (*R: A Language and Environment for Statistical Computing (ISBN 3-900051-07-0)—ScienceOpen*, n.d.) using in-house developed scripts. A standard preprocessing procedure was applied: slice timing correction, inhomogeneity correction, physiological noise and head motion correction, brain extraction, spatial normalization, and high band-pass temporal filtering (.01–.08 Hz). Afterward, images were registered to the corresponding structural image using rigid body transformation, after that, non-linear transformations were applied to normalized images to the Montreal Neurological Institute (MNI) standard space. Transformations were concatenated and applied only once to reduce interpolation effects on the datasets. Motion parameters were estimated for each volume within the fMRI dataset, the root mean squares (rms) of the displacement relative to the precedent volume were obtained (Satterthwaite et al., 2013). Participants were to be removed if they had over 30 volumes that showed more than .25 mm of rms; none of the participants were discarded based on this criterion. We applied the aCompCor method to minimize physiological noise, that is, five principal components of WM and CSF were regressed out (Behzadi et al., 2007; Chai et al., 2012). A region of interest (ROI) analysis of the ACC related to the empathy core network was performed to assess its resting state functional connectivity (Bernhardt & Singer, 2012; de Waal & Preston, 2017). The empathy-related ACC was defined based on an automated meta-analysis within a large database of fMRI results, using NeuroSynth, with the search term Empathy (Yarkoni et al., 2011). From this analysis, two ACC clusters were obtained, using the association test maps to constrain cluster size and increase consistency, from these clusters two ACC Rois were obtained (Table S4 and Figure S1). For each subject, the functional connectivity (FC) of the ACC was obtained by estimating Pearson's correlations between its time series with those of the voxels of the rest of the brain (voxel-wise), after that, a Fisher's *z* transformation was applied. To compare the functional connectivity between the two groups, for each voxel, a two-sample *t*-test was applied (Winkler et al., 2014), with age, sex, AUDIT scores, and Fagerström scores as covariates. The family-wise error corrected p values for each cluster were estimated based on a null distribution of the maximum size of clusters obtained when randomly permuting the data (5000 times), clusters were defined based on the Threshold-Free Cluster Enhancement (TFCE) method (Smith & Nichols, 2009). To further explore the connectivity of the regions of the Empathy core network, we performed a ROI to ROI analysis (Table S5 and Figure S1). Specifically, the time series from each of the ACC and the ROIs of the empathy core network were extracted and the Pearson's correlation between all possible pairs was estimated, then a Fisher's z transformation was performed (ROI to ROI matrices in Tables S6 and S7). Then, we compared between the two groups, each of the possible six connections, using a two-sample *t*-test. In addition, we calculated the strength within the network, by summing the strengths of individual nodes (all of the node edges) and then obtaining the mean strength of all nodes (Gracia-Tabuenca et al., 2021; Wig, 2017). We compared the network strength of both groups using a two-sample *t*-test, all the analysis were done using age, sex, AUDIT scores, and Fagerström scores as covariates, all results were family-wise corrected with a False Discovery Rate (FDR) of $q<.05$.FDR corrected, referred as p values FDR-corrected.

3 | RESULTS

3.1 | Psychometric tests

In the general, sample of 85 regular cannabis users and 51 controls, cannabis users showed higher scores in the Emotional Comprehension scales of the TECA (Table S8 and Figure S2). These differences were greater in the sample that participated in fMRI (Table 1 and Figure 1). Given that the groups showed differences in age (general sample $t=2.75$, $p<.01$; fMRI sample $t=2.20$, $p<.05$) and sex (general sample $t=-2.71$, $p<.01$; fMRI sample $t=-1.45$, $p=.15$ ns), we used these factors as confounding variables in all the contrasts. Similarly, there were differences between the two groups in the AUDIT scores ($t=5.68$, $p<.01$) and the Fagerström scores ($t=6.43$, $p<.01$) both sets of scores were used as confounding variables in all of the fMRI sample contrasts (Table S9). There were no statistical differences in years of education between cannabis users and controls in the psychometric ($t=.30$, $p=.034$) and the fMRI sample ($t=.32$, $p=.74$ ns).

TABLE 1 TECA scores (fMRI sample).

	Users ($M\pm SD$)	Controls ($M\pm SD$)	t Value	*p*-Value*	Cohen's *d*
PT	26.7 ± 3	26.7 ± 3	−.54	.74	.01
EC*	**30.9 ± 3**	**28.6 ± 3**	**3.05**	**.01**	**.74**
ES	21.3 ± 4	21.6 ± 4	−1.05	.74	−.1
EJ	29.0 ± 4	28.8 ± 3	.15	.88	.04
Total	107.9 ± 8	105.8 ± 8	.53	.74	.26

Note: Cognitive and affective empathy test (TECA) scales: PT, perspective taking; EC, emotional comprehension; ES, empathic stress; EJ, empathic joy.

*In bold constructs that showed statistically significant differences (**$p<0.05$**, FDR-corrected).

3.2 | rsfMRI

The voxel-wise FC analysis showed differences between users and controls when contrasting the FC network identified using the ACC ROI (Table 2 and Figure 2). Regular cannabis users showed greater connectivity between the anterior cingulate cortex (ACC) and the pre-posterior central gyrus (pr-pCG) (Table 2 and Figure 2). In the within empathy network analysis, the users showed greater connectivity between the left anterior insula (lAi) and the ACC (Table 3), and greater network strength when compared to controls ($t=2.27$, $p=.02$). There were no correlations between the functional connectivity findings and the TECA scores (Table S10).

4 | DISCUSSION

The ACC is a region that is prone to the effects of cannabis consumption and is also greatly involved in empathy, which is a multicomponent process that can be influenced in different ways. In the present study, regular cannabis users scored higher on emotional comprehension

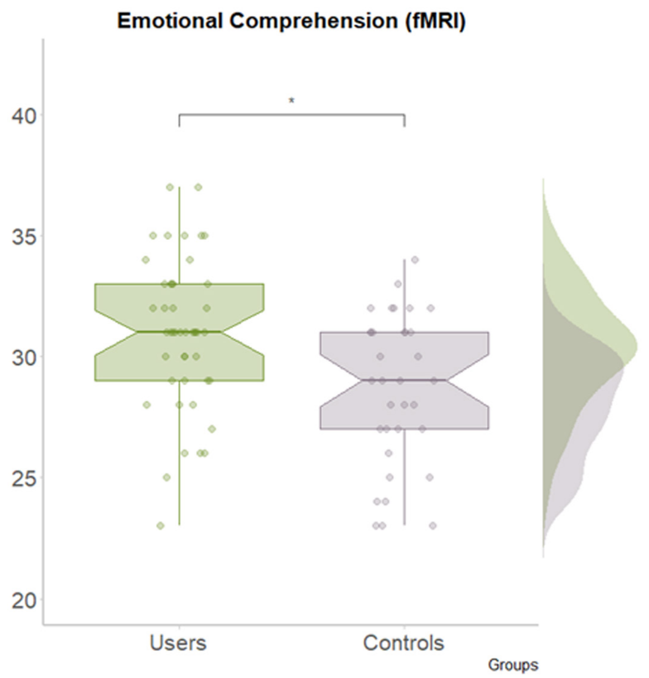

FIGURE 1 Psychometric differences between users and controls, fMRI sample. Boxplots of the differences between users (*N*=46) and controls (*N*=34) with age, sex, AUDIT scores, and Fargerstorm scores as covariates (*FDR-corrected*). Differences in the cognitive empathy scale of the TECA, Emotional Comprehension. At the right of the boxplot the density plot of each group is presented. In green users, in violet controls. In the *y*-axis, the scale of the test scores. * Statistically significant differences ($p<0.05$).

when compared to non-users. Emotional comprehension is a construct of cognitive empathy related to the capacity to recognize and comprehend others' emotional states (Pérez & Pinto, 2009). This difference is consistent with those reported by Vigil et al. (2022), where cannabis users report a higher ability to detect others' feelings compared to non-users. Additionally, previous research has shown that these types of psychometric results correspond with the subjective experience and behaviors of cannabis users related to a greater understanding of other emotions, less verbal hostility, enhanced prosociality and empathic predisposition to others' situations (Georgotas & Zeidenberg, 1979; Salzman et al., 1976; Tart, 1970). This greater emotional comprehension of the affective state of the other requires in part, a better vicarious representation of the emotional cues ostensively communicated by the other, and a reduction of the personal discomfort that those cues arise, so the emergence of such representation could be more adequate to that portrait by the other.

This difference in emotional comprehension related to their representation of the emotional state of the other, could be linked to the greater FC between the anterior cingulate cortex with the bilateral somatomotor cortex (SMC) in regular cannabis users when compared to non-users. Previous studies have suggested that the somatomotor cortex has been involved in processing our somatosensory states and in the vicarious representation of other people's somatosensory states (Craig, 2009; Keysers et al., 2010). Functional activation of the somatosensory cortex is related to increased attention toward our own emotional involvement (Straube & Miltner, 2011). Even more, the functional activation of these regions has been related to the simulation of others' actions and emotions (Borja Jimenez et al., 2020; Keysers et al., 2010). Thus, it could be suggested that a greater connectivity between the ACC and the SMC could add a somatosensory dimension to the representation of the emotions of others, in turn, this could be related to the greater emotional comprehension scores shown by the cannabis users. This suggestion could also be supported by the differences showed in the empathy core network (ECN) were cannabis users showed greater connectivity between the ACC and lAi and greater strength of the ECN, when compared to controls.

While our results differed from those studies reporting deficits in emotional detection on chronic cannabis users (MacKenzie & Cservenka, 2023; Troup et al., 2016), where the ACC in chronic cannabis users has been associated mainly with deficits in emotion perception (Gruber et al., 2009), emotional evaluation and theory of mind (Wesley et al., 2016). Our study indicates a greater emotional comprehension and a greater ACC functional connectivity associated with empathy-related areas in users when compared to controls. In this sense, the endocannabinoid activation due to chronic cannabis consumption may involve multimodal and context-dependent effects which may involve negative behaviors, such as emotional dysregulations or social stress, or positive behaviors such as social bonding and social reward (Wei et al., 2017).

Given that the ACC is one of the main areas that possess CB1 receptors and is heavily involved in the representation of the affective state of others, we believe that the differences shown by regular cannabis users in the emotional comprehension scores and their brain functional connectivity, could be related to the use of cannabis. However, we cannot discard that such differences were present before the users started their use of cannabis. Furthermore, the use of subjective reports related to cannabis and other substances consumption is marked as one limitation of the present

TABLE 2 FC differences of users > controls.

Seed	FC brain regions[b]	Abbrev.	No. voxels	*t* Value	1 − *p* value[c]	Coordinates MNI[a]		
						x	*y*	*z*
ACC								
	Left pre central gyrus	*lpr-CG*	20	4	.98	−54	−6	24
	Left posterior insula	*lpI*	1	4	.95	−42	−22	12

[a]Peak with the maximum (1 − *p*) value.

[b]Brain areas that showed significant differences in their functional connectivity with the ACC.

[c]All the *p*-values are *FWE corrected*.

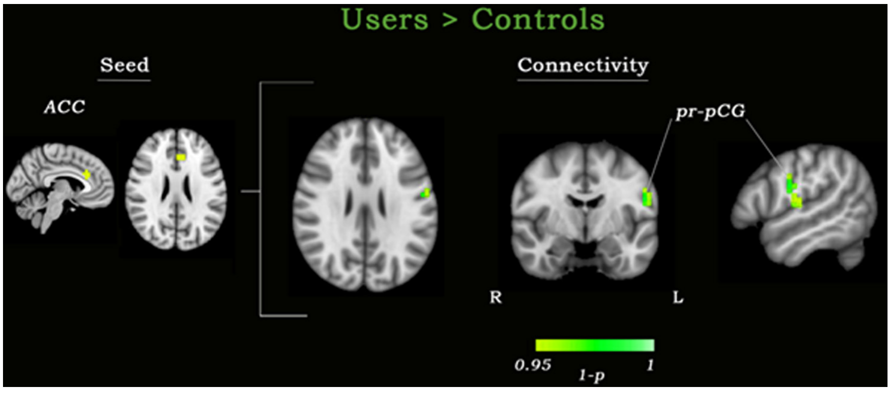

FIGURE 2 Functional connectivity differences. Seed anterior cingulate cortex (ACC) (yellow), greater connectivity with dorsomedial right posterior insula (rpI) and pre- and post-central gyrus (pr-pCG) (yellow-green; 1 − *p*-value > .95 *FWE corrected*, with age, sex, AUDIT, and Fargerström scores as covariates).

TABLE 3 Empathy core network ROI to ROI analysis (users > controls).

Connectivity between regions	*t* Value	*p*-Value*
lAi-rAi	.93	.52
ACC- rAi	.52	.60
ACC- lAi	**2.94**	**.02**
ACC/MCC-ACC	1.85	.20
ACC/MCC-rAi	.79	.52
ACC/MCC-lAi	1	.52

Abbreviations: ACC, anterior cingulate Ctx; ACC/MCC, anterior cingulate Ctx/mid cingulate Ctx; lAi, left anterior insula; rAi, right anterior insula.
*Left Anterior Insula (lAi), Right Anterior Insula (rAi), Anterior Cingulate Ctx (ACC), Anterior Cingulate Ctx/Mid Cingulate Ctx (ACC/MCC). *In bold showed statistically significant differences (**$p < 0.05$**). All *p*-values are FDR corrected.

study. The implementation of biochemical markers in conjunction with subjective reports would have clarified the amount of cannabis metabolites to characterize the profile consumption of our participants. Also, compared to cannabis consumed in the US, the quality of cannabis consumed in Mexico is lower, containing approximately 2%–10% of THC on the illegal market (Pérez Correa & Ruiz Ojeda, 2018). These differences in THC concentrations between US and Mexican cannabis could have a differential impact on functional brain outcomes between the present study and those reporting emotional dysfunctions in cannabis users (Gruber et al., 2009; Wesley et al., 2016). Another limitation was the absence of a personality trait assessment, from which has been reported that substance consumption is correlated to certain personality profiles on users (Ferwerda & Tkalčič, 2020; Tartaglia et al., 2017). Due to the unbalanced distribution of gender in our cannabis group, gender comparisons on functional connectivity and empathic traits of cannabis users were not possible. This analysis would have contributed to the debate related to gender differences related to cannabis consumption (Fattore, 2013; Prieto-Arenas et al., 2022). Additionally, although we controlled age, alcohol consumption, and smoking as confounding variables in the contrasts, we cannot entirely discount the possibility of a comorbidity effect of these factors in the findings of this study.

In our study, regular cannabis users showed differences in emotional comprehension, showing greater connectivity of empathy-related areas, regarding the ACC with areas dedicated to somatosensory representation. Showing also greater connectivity within the empathy core network. Although these differences in the functional architecture of the brain might reflect the psychometric differences in empathy, we cannot discard the aforementioned limitations, however, given previous studies of the effect of cannabis on mood and emotional detection, we believe that these results contribute to open a pathway to study further the clinical applications of the positive effect that cannabis or cannabis components could have in affect and social interactions.

AUTHOR CONTRIBUTIONS

Sarael Alcauter, Fernando A. Barrios, and Víctor E. Olalde-Mathieu: Conceptualization. All authors: Methodology. Arafat Angulo-Perkins and Cesar Arturo Dominguez-Frausto: Investigation. Víctor E. Olalde-Mathieu, Daniel Atilano-Barbosa, Giovanna L. Licea-Haquet: Formal analysis. Fernando A. Barrios and Sarael Alcauter: Supervision and resources. Victor E. Olalde-Mathieu and Daniel Atilano-Barbosa: Writing- Original draft. Giovanna L. Licea-Haquet Writing - Review & Editing.

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CONFLICT OF INTEREST STATEMENT

None of the authors have a conflict of interest to disclose.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Access to the data can be obtained upon request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Table S1. General sample description.

Table S2. fMRI sample description.

Table S3. Users consumption measures fMRI sample.

Table S4. Anterior Cingulate Cortex empathy seeds.

Figure S1. Empathy ROIs. In (a) and (b), are shown the seeds for the Voxel-wise FC analysis of the ACC. In (a), (b), (c) and (d) are presented the regions for the ROI to ROI empathy core network analysis.

Table S5. ROIs of the ROI to ROI Empathy Core Network analysis.

Table S6. User's connectivity matrix of Empathy Core Network.

Table S7. Control's connectivity matrix of Empathy Core Network.

Figure S2. Psychometric differences between users and controls. Boxplots of the differences between users ($N=85$) and controls ($N=51$) with age and sex as covariates (*FDR-corrected*). Difference in the cognitive empathy scale of the TECA, Emotional Comprehension. At the right of the boxplot the density plot of each group is presented. In green users, in violet controls. In the y-axis, the scale of the test scores.

Table S8. TECA scores (general sample).

Table S9. Scores of Fagerstom and AUDIT test.

Table S10. FC ACC-pre central Gyrus (SMC).

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