

Are the effects of cannabis dependence on glucose metabolism similar to schizophrenia? An FDG PET understanding

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ABSTRACT

Background: Cannabis has been associated with transient psychotic states; however, the causal relationship between cannabis and schizophrenia continues to remain a matter of debate. Epidemiological and some biological studies hint at cannabis being an independent risk factor for schizophrenia; this has not been definitively proved.

Aims: We aimed to understand the patterns of glucose uptake in important brain regions among individuals with cannabis dependence and schizophrenia. Furthermore, we compared the interregional metabolic rates in pertinent neural circuits among individuals with cannabis dependence, schizophrenia and normal controls.

Setting and Design: This is a case-control cross-sectional study that was carried out by a general psychiatry department in collaboration with a nuclear diagnosis unit.

Materials and Methods: Male volunteers with cannabis dependence, schizophrenia and normal controls underwent FDG PET scanning. Glucose uptakes in pre-selected regions of interest were compared using MANOVA. Finally, Chow tests were used to compare interregional metabolic relationships in the mesocortical and cortical-subcortical-cerebellum circuits.

Results: Significant differences ($P < 0.05$) were noted among individuals with cannabis dependence and schizophrenia in the medial and lateral temporal regions. When the neural circuits were compared, significant interregional differences ($P < 0.05$) were noted between individuals with cannabis dependence and normal controls. However, among individuals with cannabis dependence and schizophrenia, no significant differences ($P > 0.05$) were noted in these patterns.

Conclusions: Our findings suggest that cannabis dependence can alter interregional relationships in a manner similar to schizophrenia. This indicates that cannabis could potentially play a role in the development of psychosis by altering neural circuits.

Key words: Cannabis dependence, FDG PET, interregional relationships, schizophrenia

INTRODUCTION

The cannabis–schizophrenia debate dates back almost four decades when Chopra and Smith^[1] first described paranoid psychosis among individuals with cannabis use.

Since then, cannabis has been consistently associated with transient psychotic phenomenon, exacerbation of psychotic symptoms, and precipitation of schizophrenia in vulnerable individuals. The ‘schizophrenogenic’ potential, i.e., a chronic psychotic state induced by cannabis, however, remains a matter of debate.^[2,3] Although epidemiological studies have

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reported an increased association between cannabis use and schizophrenia, causality^[4,5] remains unconfirmed due to various confounding issues.

The answer to this question may be buried under the neurobiological maze of schizophrenia and cannabis use. Chronic cannabis use has been associated with changes in gray and white matter densities (particularly in the parahippocampal regions)^[6] and also with reductions in the hippocampal and amygdalar volumes.^[7] Vorruganti *et al.*^[8] in a single case SPECT study of an individual with cannabis use concluded that cannabis can result in increase in synaptic dopamine release that can lead to psychosis after the initial euphoric-anxiety state associated with intoxication. In an attempt to unravel this dilemma, Ashtari *et al.*^[9] compared DTI images of individuals with cannabis dependence and individuals with schizophrenia. The study confirmed that cannabis dependence results in changes in the developing arcuate fasciculus that connects Broca's area in the frontal lobe and Wernicke's area in the left temporal lobe. These changes were similar to those noted in adolescent schizophrenia. They concluded that cannabis can affect developing neurons in a manner similar to that seen in schizophrenia; in other words, cannabis can have schizophrenogenic biological effects. Contrary to these findings, Delisi *et al.*^[10] failed to confirm any neurotoxic effects of cannabis on developing neurons, further adding to the ongoing debate.

A recent observation that merits consideration in the cannabis-schizophrenia debate is the potential role of cannabinoid receptors in the psychopathology of schizophrenia.^[11] Leroy *et al.*^[12] elucidated the possibility of a common genetic pathway for both cannabis use and schizophrenia. They noted that the cannabinoid receptor gene is associated with a type of schizophrenia thereby assigning a possible causal role for this gene in schizophrenia. The cannabinoid system is also closely linked to the dopaminergic system^[13,14] and the glutamatergic system;^[15] both of which have been implicated in schizophrenia.

Thus, while there appears to be a strong case for cannabis having a schizophrenogenic role, the fact is that mere hypotheses are not sufficient to dole out a clear decision. In an attempt to contribute to the neurobiological evidence for a causal role of cannabis in schizophrenia, we compared the brain glucose metabolic patterns in cannabis dependence to schizophrenia to explore for similarities among the two. We hypothesized that

1. If long-term cannabis use can lead to a psychotic process, glucose metabolism patterns in various brain regions would be similar in both cannabis dependence and schizophrenia.
2. Additionally, the pattern of metabolic changes in important neural circuits in cannabis dependence

would be similar to schizophrenia. We chose to explore circuits that are involved in emotional and cognitive processing, two key disturbances in schizophrenia.

- a. For emotion processing, we examined the relationship between the medial temporal and the frontal cortical regions (henceforth being called the temporo-frontal relationship). This is a dopaminergic circuit between the amygdala (medial temporal region) and the prefrontal cortex. This circuit along with connections with the nucleus accumbens and the ventral tegmental area plays a crucial role in emotional learning and processing^[16] and has been implicated in schizophrenia.
- b. Additionally, we also examined the cortical-subcortical-cerebellar circuit that has been implicated in cognitive dysmetria. We hypothesized that there would be no significant differences in these interregional metabolic relationships among individuals with cannabis dependence and schizophrenia.

MATERIALS AND METHODS

Design, setting and participants

The study was conducted by the De-addiction Center (Psychiatry Department) of a Tertiary Care Hospital in collaboration with the Radiation Medicine Center, Bhabha Atomic Research Center, during January 2004 to December 2005. Approval for the study was obtained from the Institutional Review Boards of both institutions.

Three groups of participants were selected. A) 16 male patients with a DSM-IV diagnosis of cannabis dependence^[17] and ongoing cannabis consumption (confirmed by thin layer chromatography) were invited to participate in the study (Group I). Co-morbid Axis I diagnosis, other substance use (except nicotine dependence), benzodiazepine intake in the last six months, past or current history of any neurological or medical illness were ruled out. Study participants continued their ongoing pattern of consumption, their last consumption varying from 8 to 12 hours prior to the scan. B) The second group (Group II) comprised of 17 males with a DSM-IV diagnosis of schizophrenia and active psychotic symptoms, i.e. Positive and Negative Symptom Scale^[18] scores above 70 participated in the study. Patients with other comorbid Axis I diagnoses, substance abuse or dependence except nicotine dependence, mental retardation on clinical evaluation, past or current history of neurological illness, or other medical illness were excluded. None of the patients had any extrapyramidal symptoms or any abnormal movements on physical examination. C) The third group (Group III) comprised of 16 right-handed normal male volunteers with no history of past or present substance use (except nicotine dependence). Only males were invited to participate in the study to avoid all possible gender confound. Consenting participants

in Group I completed a semi-structured questionnaire detailing duration and amount of cannabis consumption. Cannabis consumption was further confirmed by urine thin layer chromatography, prior to participation in the study. No quantitative assessment was, however, carried out. All the participants smoked cannabis in cigarettes. None of the participants had any past or present history of other substance dependence except nicotine. Exclusion of other substance dependence including opiates and alcohol was confirmed by urine drug screening. Further, as the participants were not in a controlled environment prior to the scan, the urine toxicology screens were repeated prior to the scan.

Study participants continued their ongoing pattern of consumption, their last consumption varying from 10 to 12 hours prior to the scan. At the time of the scan, none of the participants reported any symptoms of cannabis intoxication or withdrawal. Subjects were also requested to refrain from nicotine and caffeine for at least 8 hours prior to the scan.

The standard FDG PET protocol was followed. F18-FDG^[19] is produced in a 16.5 MeV Medical Cyclotron Facility located in the center that hosts the scanner (RMC). Participants were fasting for at least 8 hours prior to the scan and had a blood glucose level of <150 mgdl⁻¹. An average dose of 200 MBq (160–230) of F-18, 2-fluoro, 2-deoxy-glucose (F18-FDG) was injected. Acquisition was carried out 30 minutes after the injection. Positioning was achieved with the help of LASER align lights and head was secured with restraints to minimize artifacts due to movement. The pattern of cerebral glucose metabolism was examined using F-18, 2-fluoro, 2-deoxy-glucose (F18-FDG) with a GE Advance PET System scanner NXI (General Electric Medical Systems, Milwaukee, WI). The scanner has a transaxial resolution of 4.8 to 6.2 mm FWHM (full width half maximum) depending upon the distance from the center and an axial resolution of 4.0 to 6.6 mm FWHM. Emission scans of 70 slices were obtained parallel to the cantho-meatal line from vertex to the neck. Transmission scans were obtained for the same region using Ge-68 rod sources to carry out measured attenuation correction. The images were reconstructed using the ordered subsets extraction maximization (OSEM) algorithm. These images were reformatted and converted into 35 trans-axial slices of 4.25 mm thickness.

Statistical analyses

Regional glucose metabolism was examined in 14 pre-determined Regions of Interest (ROI) – elliptical ROIs for cortical and sub-cortical structures and circular ROI for cerebellar hemispheres. For the purpose of selection of ROIs, the slice of the brain through the basal ganglia was taken as reference slice. One slice above and below was checked for maximum uptake values (mUVs) for each region of interest (ROI). For the cerebellum, mid-cerebellar slice

was selected. Regions of interest considered included the following:

1. Prefrontal regions (right and left)
2. Temporal (right, left, medial and lateral)
3. Parietal (right and left)
4. Occipital (right and left)
5. Basal ganglia (right and left)
6. Thalamus (right and left)
7. Cerebellum (right and left)

The regional activity in a given ROI was measured as the mUVs in that ROI (KBq/cc).

During qualitative assessment, it was observed that in majority of the patients, the occipital lobes showed maximum FDG uptake. Additionally, most studies examining influence of cannabis on CBF have failed to report any changes in the occipital lobe in cannabis users. Hence, the average of the occipital lobe activity uptake values was taken as the normalizing factor. Results related to the occipital regions were not reported. The glucose uptakes in the other ROIs were expressed as relative uptake values (rUVs) – ratio of uptake value for ROI to average uptake value for the occipital lobes. Analysis was carried out using these rUVs in the various ROIs.

Data were analyzed using STATA/SE 9.2 (Stata Corporation; College Station, TX, USA). MANOVA (Multivariate analyses of variance) was used to compare the glucose uptakes of the various ROIs among the three groups. Age was entered as a covariate in these analyses. Finally, post-hoc analysis was carried out using the Bonferroni correction. In order to understand differences in the interregional correlations of the rUVs, we used linear regressions combined with Chow Tests to test if the correlation between two regions were different among the three groups. As an example, when examining the efferent relationship from frontal to medial temporal ROIs, we fitted two linear regressions, one for each group, with frontal rUVs as the independent variable and medial temporal rUVs as the dependent variable with an age correction (the age correction was used to avoid any confounding influences of age on interregional metabolic relationships). The Chow Test is a Chi-square test that tests whether the slope coefficients in these two regressions are statistically different. In the above example then, a positive test indicates that the efferent relationship from the frontal ROI to the medial temporal ROI is statistically different between the two groups. These relationships have also been illustrated using graphs in Figures 1a–c (for emotion processing) and 2a–c (for cognitive dysmetria).

RESULTS

The mean age of participants in Group I or individuals with cannabis dependence was 25.3 years. Their mean age at onset of cannabis consumption was 16.2 years (SD-3.6

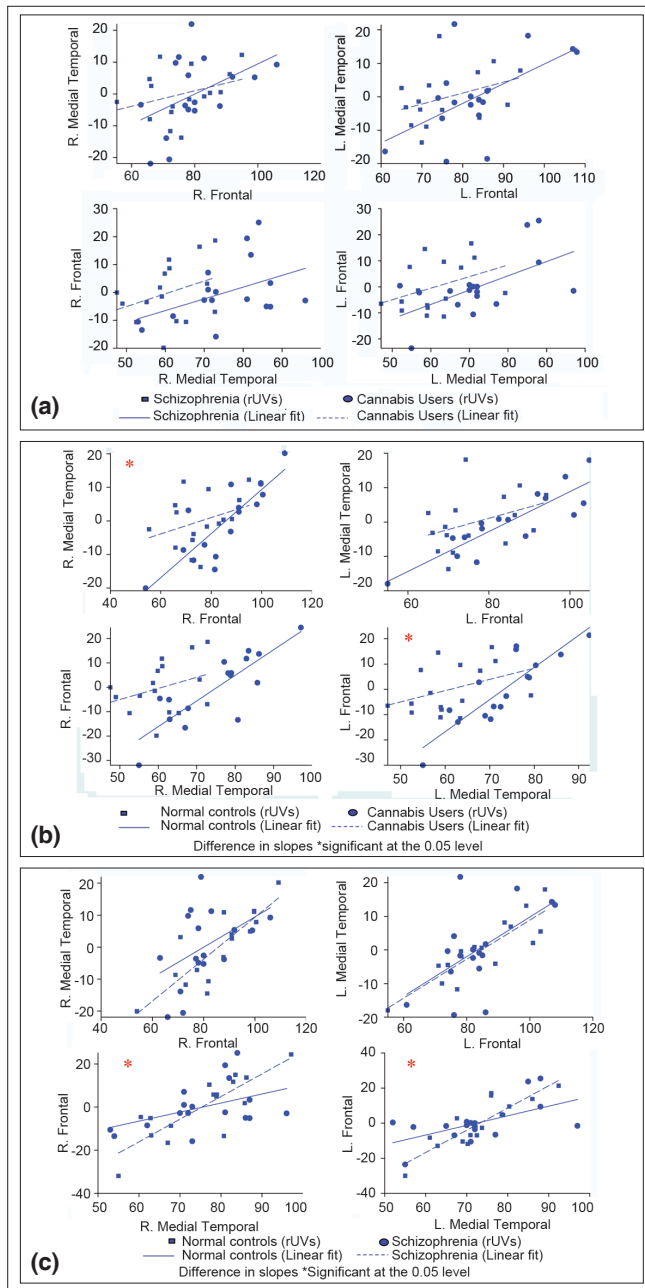


Figure 1a-c: Illustrate the afferent and efferent relationship of the frontal region with the medial temporal region (the emotion processing circuit). Each graph plots the rUVs of the afferent (dependent variable) on the Y-axis and the rUVs of the efferent (independent variable) on the X-axis. The figure also includes two linear best fits based on linear regressions, one for each group. As can be noted from the figures, the relationships in Figure 1a in all four graphs are close to parallel, indicating similar relationships. Figures 1b and 1c on the other hand, have more intersecting relationships, suggesting that there are differences in the relationships; two plots in each demonstrating statistically significant differences (marked with *). (a) Differences in interregional relationships in the temporo-frontal-circuit – cannabis dependence and Schizophrenia; (b) differences in interregional relationships in the temporo-frontal-circuit – cannabis dependence and normal controls; (c) differences in interregional relationships in the temporo-frontal-circuit – schizophrenia and normal controls

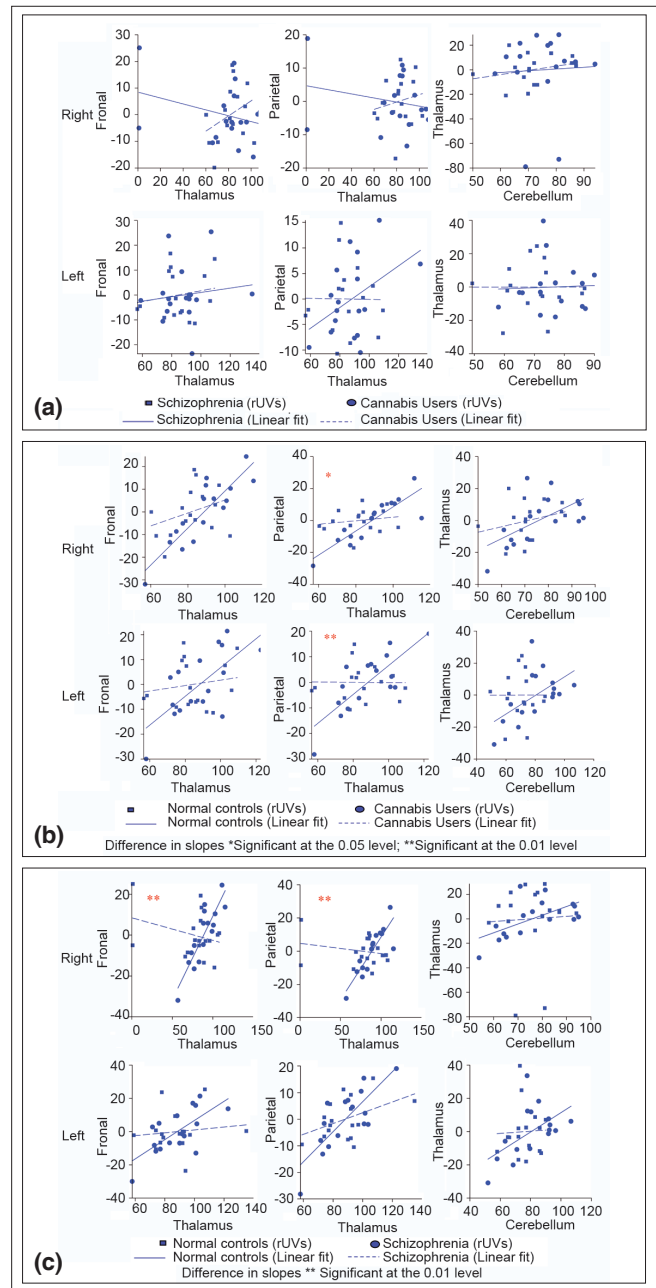


Figure 2a-c: Illustrate the differences in interregional relationships in the circuit for cognitive dysmetria – cannabis dependence, schizophrenia, and normal controls. (a) Differences in interregional relationships in the cortical-subcortical-cerebellar circuit – cannabis dependence and schizophrenia; (b) differences in interregional relationships in the cortical-subcortical-cerebellar circuit – cannabis dependence and normal controls; (c) differences in interregional relationships in the cortical-subcortical-cerebellar circuit – schizophrenia and normal controls

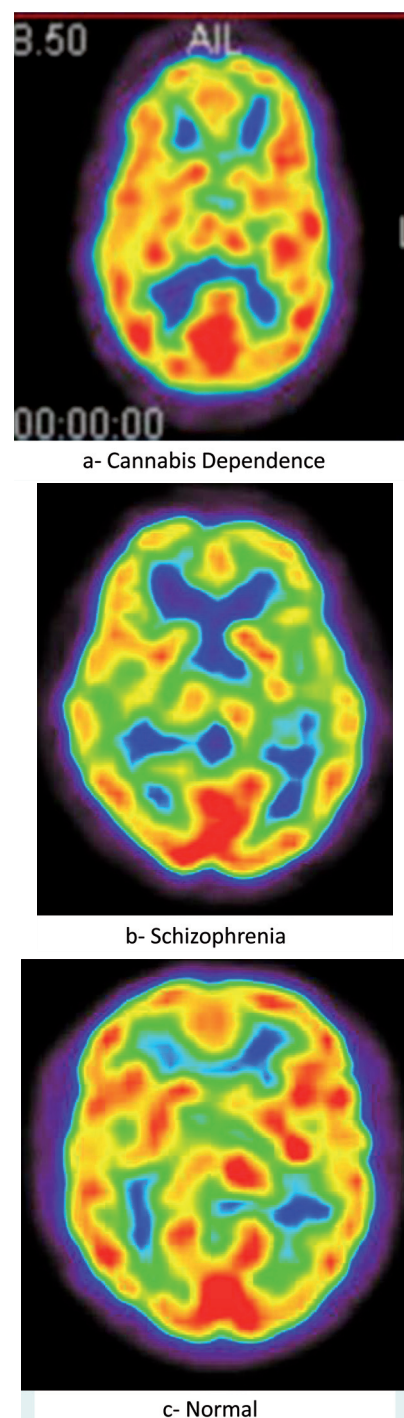
years) with duration of consumption varying from 6 months to 40 years (mean=8.6 years). The mean age in Group II or individuals with schizophrenia was 28.7 years, ranging from 19–44 years with a standard deviation of 6.61 years. Mean age at onset of schizophrenia was 22.7 years with the average duration of illness being 5.9 years. Their total PANSS

scores ranged from 78 to 119 (mean = 94.1). In Group III or normal controls, the mean age was 29.5 years (SD=8.39). The mean age in the three groups was comparable ($P>0.05$).

Factoring in age as a covariate, MANOVA (df = 2, 46, 48) was performed to explore differences in glucose uptakes of the ROIs among the three groups, i.e. cannabis dependence (Group I), schizophrenia (Group II) and normal controls (Group III) (Table 1, Figures 3a–c). The Wilks's lambda was 0.001 ($f(32, 60) = 3.717$) indicating significant differences among the three groups. Levene's test for equality of variances did not reject the hypothesis that the variances were equal across groups. These differences were primarily between the lateral and medial temporal regions ($P<0.05$, df = 3, $f: 5.023\text{--}13.449$) (as identified by the tests for between-subjects effects). This was followed by post-hoc analyses using Bonferroni correction with a single fixed factor (group). These analyses suggested that the cannabis dependence group differed significantly from the other two groups, namely schizophrenia and normal volunteers in their temporal uptakes ($P<0.05$). Additionally, the cannabis dependence group differed significantly from normal individuals in their left cerebellar uptake. Specifically, when we compared the metabolic profiles of individuals with cannabis dependence (Group I) and schizophrenia (Group II) using *t*-test (Bonferroni correction, equal variance assumed, df = 31), significant differences were noted in glucose uptakes in the medial and lateral temporal regions and the left parietal region. However when these were corrected for multiple comparisons using Bonferroni correction (0.05/16=0.0031), only the lateral temporal regions and the right medial temporal region remained statistically significant.

Finally, Chow tests were employed to examine the interregional metabolic patterns for the two circuits that have been described in the hypothesis.

- Medial Temporal - Frontal cortical region or the temporo-frontal relationship (afferent and efferent relationships between medial temporal and frontal ROIs): As can be noted from Table 2 and Figures 1a–c, there were no differences in the interregional metabolic relationship in the temporo-frontal network among Groups I and II (cannabis dependence and schizophrenia). Significant differences were noted in these relationships when the two groups were compared with Group III i.e. normal controls. This suggests that while the temporo-frontal interregional relationships were similar in Groups I and II; they differed from Group III.
- Cortical-subcortical-cerebellar circuit (Table 3 and Figures 2a–c): Similarly, we studied the unidirectional relationship between the cerebellum–thalamus–frontal and parietal cortices. No differences were noted in the cortical–subcortical–cerebellar interregional metabolic relationships between Groups I and II. Significant



Figures 3a-c: Representative images showing the metabolic uptakes in the various ROIs among the three groups

differences were noted in the cortical–subcortical relationships between Groups II and III and Groups I and III. In other words, individuals with cannabis dependence and schizophrenia differed in the cortical–subcortical relationship from normal controls. However, cortical-subcortical-cerebellar interregional metabolic relationships were similar in individuals with cannabis dependence and schizophrenia.

Table 1: Relative uptake values in ROIs in individuals with cannabis dependence (Group I), schizophrenia (Group II) and normal controls (Group III). MANOVA df - 2

	Group I		Group II		Group III		F	P-value
	Mean	SD	Mean	SD	Mean	SD		
Right frontal	75.94	10.62	80.06	11.08	85.77	14.48	1.73	0.17
Left frontal	76.64	9.58	83.41	11.65	84.75	13.82	1.54	0.22
Right parietal	78.51	7.39	81.29	8.58	85.94	13.85	1.45	0.24
Left parietal	76.13	7.19	83.76	7.75	83.30	11.71	2.38	0.08
Right M temporal	61.03	7.74	75.47	11.77	75.34	11.44	6.70	0.001*
Left M temporal	61.14	8.22	72.29	12.06	73.18	9.34	5.02	0.004*
Right L temporal	79.99	12.64	58.82	8.68	67.70	9.87	11.07	0.000*
Left L temporal	77.63	10.61	58.82	5.86	62.57	9.78	13.45	0.000*
Right occipital	99.44	3.37	99.06	3.54	100.42	4.74	1.03	0.40
Left occipital	101.18	4.16	100.18	3.56	99.66	4.74	0.61	0.61
Right cerebellum	71.41	9.61	75.71	9.76	75.93	13.01	0.69	0.56
Left cerebellum	69.86	9.73	76.12	8.60	80.37	14.99	2.73	0.06
Right thalamus	81.66	12.05	76.78	30.73	88.69	15.45	0.96	0.42
Left thalamus	84.44	14.80	88.12	16.58	88.36	16.32	1.01	0.40
Right basal ganglia	83.58	12.11	76.65	7.88	86.53	16.70	1.74	0.17
Left Basal ganglia	82.44	10.78	77.06	9.68	83.92	14.28	1.03	0.39

*Significant at the 0.001 level (2-tailed)

Table 2: Differences in inter-regional metabolic relationships in the temporo-frontal-circuit (Chow Test with Bonferroni corrections)

Afferent	Efferent	P-value		
			Cannabis dependence vs schizophrenia	
			Group I	Group II
Medial temporal	Frontal			
Right		1.13	0.24	0.48
Left		0.39	0.33	0.61
Frontal	Medial temporal			
Right		3.64	0.46	0.42
Left		3.01	0.45	0.56
			Cannabis dependence vs normal	
			Group I	Group III
Medial temporal	Frontal			
Right		0.02*	0.24	0.66
Left		0.50	0.33	0.59
Frontal	Medial temporal			
Right		0.28	0.46	1.09
Left		0.01*	0.45	1.31
			Schizophrenia vs normal	
			Group II	Group III
Medial temporal	Frontal			
Right		1.33	0.48	0.66
Left		3.37	0.61	0.59
Frontal	Medial temporal			
Right		0.03*	0.42	1.09
Left		0.04*	0.56	1.31

*Significant at the 0.05 level (2- tailed)

DISCUSSION

Glucose uptake patterns are reflective of neuronal functioning. Studies^[20,21] have established that individuals with schizophrenia demonstrate specific patterns that can vary with symptoms profiles and chronicity of illness, in other words, the phenomenology of the illness affects glucose uptake. Similarly, studies have observed changes in the orbitofrontal cortex, putamen, and precuneus^[22] and cerebellum^[23] in chronic cannabis users. Our study noted that individuals with schizophrenia and cannabis dependence had similar glucose uptake values in most regions of interest. However, contrary to our first hypothesis, the two groups did differ significantly in the temporal (medial and lateral) regions. The medial temporal regions have been identified as a nidus for psychosis.^[20,24] This could probably explain the difference as none of the participants in the cannabis dependence group had any active psychotic symptoms. The explanation for differences in the lateral temporal uptakes is a matter of speculation. Chronic cannabis use has been associated with changes in the auditory, speech and association areas of the temporal region, which can potentially explain the differences in the lateral temporal region.

Our second hypothesis assumed that interregional metabolic relationships in important circuits, involved in emotional and cognitive processing, would be similar in individuals with schizophrenia and cannabis dependence. Neuronal integrity is important for a number of cognitive and emotional tasks. A number of pathways involving the mesiotemporal, frontal, parietal and cerebellar structures (limbic, neocortical and cortical-subcortical-cerebellar

Table 3: Differences in inter-regional metabolic relationships in the cortical-subcortical- cerebellar circuit (Chow Test with Bonferroni corrections)

Afferent	Efferent	P-value	Cannabis dependence vs schizophrenia	
			Group I	Group II
Thalamus	Cerebellum			
Right		4.94	0.54	0.15
Left		7.33	0.003	0.07
Frontal	Thalamus			
Right		0.83	0.29	-0.11
Left		7.97	0.11	0.11
Parietal	Thalamus			
Right		2.11	0.11	-0.06
Left		0.31	-0.005	0.25
Cannabis dependence vs normal				
			Group I	Group III
Thalamus	Cerebellum			
Right		4.67	0.54	0.74
Left		2.58	0.003	0.58
Frontal	Thalamus			
Right		0.21	0.29	0.82
Left		0.12	0.11	0.61
Parietal	Thalamus			
Right		0.01*	0.11	0.76
Left		0.00**	-0.005	0.60
Schizophrenia vs normal				
			Group II	Group III
Thalamus	Cerebellum			
Right		3.36	0.15	0.74
Left		1.14	0.07	0.58
Frontal	Thalamus			
Right		6.342e-09**	-0.11	0.82
Left		0.45	0.11	0.61
Parietal	Thalamus			
Right		0.00**	-0.06	0.76
Left		0.18	0.25	0.60

**Significant at the 0.01 level (2- tailed); *Significant at the 0.05 level (2- tailed)

networks)^[25,26] have been implicated in various symptoms of schizophrenia. The connection between the medial temporal and the frontal cortex is a dopaminergic circuit that has been implicated in emotional processing,^[16] while cortical-subcortical-cerebellar circuit has been associated with cognitive dysmetria. Individuals with cannabis dependence had similar intermetabolic relationships in both these circuits as individuals with schizophrenia; both the schizophrenia and the cannabis dependence groups differed in this from normal individuals. Cannabis dependence is associated with changes in the frontal-medial temporal (amygdala) - thalamic circuit.^[27] Thus while the state-of-being substance dependent can contribute to changes in the temporo-frontal relationship that we

studied (medial temporal – frontal), it should not lead to changes in the cortical-subcortical-cerebellar circuit. This further suggests that individuals with cannabis dependence have the potential to developing emotional and cognitive deficits, two important components of schizophrenia.

Like in any functional imaging study, confounding factors affecting the glucose uptake is a definite possibility. The altered mood states noted during cannabis intoxication and withdrawal can affect glucose metabolism. Indeed, acute cannabis intoxication has been associated with changes in the medial temporal region and right hemisphere, consistent with the affective symptoms of cannabis intoxication.^[28,29] However, none of the participants with cannabis dependence reported any symptoms suggestive of either intoxication or withdrawal. It is also generally accepted that cannabis intoxication wears off in 4 hours. Thus, in our group of individuals with cannabis dependence, it is highly unlikely that the changes in the neural circuits measured as the interregional metabolic relationships were influenced by either cannabis intoxication or withdrawal. It has also been suggested that the effects of cannabis on glucose metabolism can last for up to 28 days.^[30] In other words, based on our cross-sectional findings at a maximum duration of 12 hours abstinence, it would be imprudent to state with utmost certainty that cannabis use leads to changes similar to schizophrenia.

Our study is also technically limited by the application of the manual method of analysis instead of statistical parametric mapping. In order to avoid the operator-based errors of this method, we ensured that the same blinded neuro-diagnostician reported all the scans. Furthermore, we were unable to provide finer definition of the anatomical regions such as the amygdala and prefrontal cortex. Our study is also limited, in that details regarding cannabis consumption, including amount of cannabis consumption and duration of last consumption were based on participant self report.^[31] As discussed above, in order to ascertain that the changes that we noted are long term, and not reversible, it would be essential to examine the participants over a longer period of at least a month's abstinence. Nevertheless, our study does establish, beyond any reasonable doubt that cannabis use can lead to changes in important psychosis circuits.

Summarizing, while our study did not note any similarities in glucose uptake in the “nidus of psychosis” – medial temporal regions of individuals with cannabis dependence and schizophrenia, we did observe that cannabis dependence can alter important neuronal relationships. The neuronal circuits that we explored play important roles in normal emotional processing and mental coordination; two processes that have been discussed as core disturbances in schizophrenia. Despite its limitations, the study establishes that individuals with cannabis dependence have alterations in interregional metabolic relationships that have been

attributed to the core symptoms of schizophrenia. In the current literature, there is only one more imaging study - Ashtari *et al.*, - who have explored this link between cannabis and schizophrenia in human subjects. These findings bring to fore a definite need for further longitudinal research using finer anatomical areas such as the prefrontal cortex and the amygdala before a final decision on this long-intriguing cannabis-psychosis debate.

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