Supplementary Text

Clinical Assessment

The clinical profile sheet was specially devised for the purpose of study and was used to record age of initiation, frequency, duration and type of cannabis use. Edinburgh handedness inventory (EHI) is a self-rated questionnaire with dichotomous responses to an inventory of 10 items of everyday habit which allow for distinction in laterality. Mini International Neuropsychiatric Interview (M.I.N.I.) is a brief structured interview for diagnosis of psychiatric disorders in both DSM-IV and ICD-10 classifications. Psychiatric Research Interview for Substance and Mental Disorders (PRISM) is a semi-structured interview schedule for assessing psychiatric disorders that are commonly co-occurring with substance use disorders. It has a specific purpose of differentiating between expected effects of intoxication and withdrawal, substance-induced disorders and independent or primary disorders in patients using substances. It follows the DSM-IV criteria to assess for present and lifetime diagnosis. For the purpose of our study, we used PRISM section 8 (a,b,c) specific to psychotic disorders for differentiating between cannabis induced psychosis and schizophrenia with cannabis use. PANSS is a scale for rating of positive and negative symptoms based on severity and global psychopathology in schizophrenia. The Positive and Negative Syndrome scale (PANSS) evaluation for the current study was specific to assessing remission and included the 8 items recommended by the Working Group for study of Remission in Schizophrenia. When presenting with a severity score of mild or less i.e., ≤3 for a period of 6 months or more signify remission.

Image acquisition-

Images were acquired using a body coil for transmission and a standard quadrature coil for reception. In addition to the diffusion data, T2 axial, T2 Flair axial, 3D T1 magnetization prepared rapid gradient-echo/ spoiled gradient recalled echo (MPRAGE/SPGR) and susceptibility weighted sequences (SWI/SWAN) images were acquired and used for clinical

evaluation of gross brain abnormalities in each subject. A comfortable padding for holding the head was used to prevent motion and reduce noise during imaging.

Diffusion imaging-Full brain DKI sequences were acquired with a diffusion sensitized dual spin echo prepared echo-planar imaging (SE-EPI) sequence. To increase the image registration fidelity, facilitate white–grey matter classification, and enhance the specificity of region-of-interest analysis T2-weighted images were acquired from the same location as DKI. Diffusion kurtosis images were acquired using the following diffusion sequence: “TE=77 ms, TR=5800 ms, matrix = 128 × 128, field of view = 256 × 256 mm, in-plane resolution = 2 × 2 mm, slice thickness= 3 mm without gap, 48 axial slices, 25 encoding diffusion directions with two values of b (b = 1000 and 2000 s/mm2) for each direction and 10 non-diffusion weighted images (b = 0 s/mm2)”. Anatomical T1w data was acquired using a MPRAGE sequence. DTI sequences were also acquired using the same scanner with appropriate pre-set sequences.

MRI data processing-

The segmentation process began with automated stripping of the skull from the images, in-homogeneity filtering of the spin-echo images, and co-registration of the spin-echo data set to the T1-weighted images. In the next step, the software chose specific samples of grey matter, white matter, and CSF and assigns all of the voxels in the brain to these three tissue categories. Volumetric and, DKI and DTI data set post-processing was done offline i.e., at our computer system and online i.e. by sending images to laboratory at University of Miami using diffusion kurtosis estimator (DKE) software version 2.6. The steps of data post-processing included inhomogeneity filtering, motion correction, de-noising, and co-registration with Johns Hopkins University- Montreal Neurological Institute Maps (JHU-MNI) i.e.,JHU-T1w-MNI and JHU-DTI-MNI. The software processed the images to give voxel wise distribution of the whole brain. The pre-defined ROIs were automatically identified through co-registration with the JHU-MNI maps. The numbers of voxels assigned to the ROIs were used to calculate the volumes of those ROIs as well as to assess the diffusion metrics in each voxel.

MRI data metrics-

Diffusion imaging metrics-

The standard diffusion metrics derived through post-processing with the DKE are: Axial diffusivity (AD), Radial diffusivity (RD), Mean diffusivity (MD), Fractional Anisotropy (FA), Axial kurtosis (AK), Radial kurtosis (RK), and Mean kurtosis (MK). As per the study protocol, MD and FA for diffusion tensors and MK and KFA for Kurtosis were included in analysis. The diffusion metrics for a specific ROI were calculated on the basis of number of voxels assigned to it and presented as the number of voxels assigned, diffusion metric according to the hemisphere of brain i.e., left or right, range i.e., minimum and maximum diffusivity among the voxels allotted to a ROI, mean diffusivity of voxels allotted to the ROI and standard deviation of diffusivity of the voxels allotted to the ROI.

Volumetric imaging metrics-

Brain structures for volumetric analysis including grey matter (GM) ROIs and lateral ventricles were selected for comparison between the study groups. In addition, whole brain volume was calculated for comparison as well to serve as a covariate in comparison of individual GM ROIs between the study groups. These brain structures were selected on the basis of a meta-analysis of over 18,000 subjects from various morphometric studies in patients of schizophrenia. Data post-processing and co-registration with JHU-MNI T1w maps was done for each subject and volumes of GM ROIs were calculated from the output.

Supplementary Table 1 Socio-demographic profile of the study groups- Cannabis induced psychosis group (*CIP*), Schizophrenia with cannabis use (SZC) and Control group (CG)

Socio-demographic variable	***CIP* (n=20)**	**SZC(n=20)**	**CG (n=20)**	**Fischer's exact**	**p value**
Marital status				**12.622**	**0.006****
Single	16	14	7		
Married	3	5	13		
Divorced	1	1	0		
Occupation				**28.259**	**<.001*****
Unemployed	5	10	0		
Clerical/shop/farm	1	2	1		
Skilled worker	4	3	4		
Semi-skilled worker	6	3	10		
Student	4	0	1		
Semi-professional	0	2	0		
Professional	0	0	4		
Monthly income				**32.358**	**<.001*****
Nil	5	10	0		
1351-3999	3	1	0		
4000-6499	2	4	0		
6500-9999	7	1	1		
10000-12999	0	3	3		
13000-26499	0	0	10		
26500 and above	3	1	6		
Religion				2.450	.360
Hindu	16	16	19		
Non-Hindu	4	4	1		
Type of family				.491	.942
Nuclear	12	13	14		
Extended/Joint	8	7	6		
Locality				**9.314**	**.011****
Urban	9	14	18		
Rural	11	6	2		

****-Significant; ***-Highly significant**

Supplementary Table 2a Comparison of grey matter volume patients with cannabis induced psychosis group (*CIP*), Schizophrenia with cannabis use (SZC) and control group (CG)

Brain structure	PRISM group N= 20 in each group	Volume (mm^3)				ANOVA F (p value) Post-Hoc Tukey	GLM F (p value) Post-Hoc Bonferroni
		Mean	Std. Dev.	Range			
				Minimum	Maximum		
Whole brain	*CIP*	1219770.2	100024.1	998189.3	1428032.6	0.440 (0.646)	----------
	SZC	1190196.3	85321.1	1046683.7	1359814.8		
	CG	1204111.2	112205.9	1035365.4	1420463.7		
Lateral ventricle Left	*CIP*	7178.5	3099.9	1687.5	13687.5	0.833 (0.440)	0.932 (0.400)
	SZC	6686.2	2444.6	3562.1	13115.8		
	CG	6099.1	2333.7	2677.1	10801.6		
Lateral ventricle Right	*CIP*	6941.0	1984.1	3688.5	10087.1	2.908 (0.063) *CIP*>CG (0.055)	3.060 (0.055) *CIP*>CG (0.05)
	SZC	5825.1	2265.0	2704.5	11351.3		
	CG	5282.6	2384.6	1594.1	10812.6		
Hippocampus Left	*CIP*	3219.6	492.2	2402.2	4221.6	1.986 (0.147)	2.268 (0.113)
	SZC	3113.5	455.2	2490.5	3897.4		
	CG	2898.8	597.6	1967.6	4221.6		
Hippocampus Right	*CIP*	3138.2	697.3	2226.2	5145.8	2.212 (0.119)	2.118 (0.130)
	SZC	2925.5	649.5	2028.3	4502.4		
	CG	2898.6	597.3	2619.2	3178.5		
Amygdala Left	*CIP*	1650.7	472.2	1082.9	2830.9	0.586 (0.560)	0.391 (0.678)
	SZC	1502.5	427.1	885.0	2578.0		
	CG	1553.4	422.6	841.1	2501.1		

Amygdala Right	*CIP*	1699.1	567.7	1055.4	3226.7	1.014 (0.369)	0.844 (0.436)
	SZC	1491.1	349.7	747.5	2253.7		
	CG	1554.1	478.3	824.5	2589.1		
Fusiform Gyrus Left	*CIP*	16481.6	1779.7	12654.0	20410.3	0.559 (0.575)	0.348 (0.707)
	SZC	15921.2	1573.1	13517.1	18425.9		
	CG	16516.5	2516.9	13115.8	23444.7		
Fusiform Gyrus Right	*CIP*	16939.2	2473.4	12252.8	22169.4	0.456 (0.636)	0.228 (0.797)
	SZC	16156.5	2434.1	12983.9	20641.2		
	CG	16865.6	3540.5	12549.6	23257.8		
Superior Temporal Gyrus Left	*CIP*	10359.1	1684.2	6750.3	13000.4	1.293 (0.296)	2.946 (0.061)
	SZC	11300.7	2369.4	8437.9	17326.5		
	CG	10693.3	1597.1	8828.1	14297.7		
Superior Temporal Gyrus Right	*CIP*	13110.3	1696.9	11329.3	17117.6	2.274 (0.112)	1.932 (0.154)
	SZC	11973.2	1924.9	9037.1	18332.5		
	CG	12091.7	1930.4	9779.1	16952.7		

PRISM- Psychiatric research interview for substance use and mental disorders; **ANOVA**- Analysis of variance; **GLM-** General linear modelling; * $p<0.05$ (after Bonferroni test)

Supplementary Table 2b Comparison of grey matter volumes among patients with cannabis induced psychosis group (*CIP*), Schizophrenia with cannabis use (SZC) and control group (CG)

Brain structure	PRISM group N= 20 in each group	Volume (mm^3)				ANOVA F (p value) Post-Hoc Tukey	GLM F (p value) Post-Hoc Bonferroni
		Mean	Std. Dev.	Range			
				Minimum	Maximum		
SFG PFC Left	*CIP*	22086.6	3698.6	15259.6	28864.7	0.181 (0.835)	0.353 (0.704)
	SZC	21797.8	4185.1	15023.3	32201.4		
	CG	21375.9	3337.8	16210.6	28584.4		
SFG PFC Right	*CIP*	21293.1	4255.4	14418.6	29562.8	0.190 (0.827)	0.148 (0.863)
	SZC	20628.0	4005.8	14286.7	30310.4		
	CG	20629.1	3505.1	14594.5	27177.1		
SFG Frontal Pole Left	*CIP*	6397.1	1415.1	4721.9	10625.7	3.346 (0.042)	3.041 (0.056)
	SZC	5592.3	1651.6	3094.8	9696.7		
	CG	5321.9	937.2	2479.1	7311.1		
SFG Frontal Pole Right	*CIP*	6755.2	1504.6	4315.1	10977.5	1.790 (0.176)	1.513 (0.229)
	SZC	6010.6	1863.4	2116.3	9322.9		
	CG	5898.2	1238.9	2649.5	8382.9		
SFG Post Segment Left	*CIP*	19633.1	3138.5	11323.8	24857.4	0.109 (0.897)	0.865 (0.427)
	SZC	20034.1	3629.4	16128.2	29573.8		
	CG	20068.7	3054.1	14616.5	24351.7		
SFG Post Segment Right	*CIP*	22225.4	3910.1	12632.1	28969.1	0.254 (0.777)	0.036 (0.965)
	SZC	21377.2	4006.6	16727.3	33707.6		
	CG	21658.4	3582.8	15930.3	26896.8		
Insula Left	*CIP*	5107.2	750.4	4089.7	7239.5	0.818 (0.447)	0.618 (0.543)
	SZC	4844.2	856.7	3836.9	6700.8		
	CG	4798.3	861.5	3254.2	6398.5		
Insula Right	*CIP*	4494.8	1077.6	2979.3	7415.4	1.039 (0.360)	0.852 (0.432)
	SZC	4155.7	959.1	3149.7	6728.3		
	CG	4086.4	822.9	2852.9	5497.1		

Post Cingulate Left	*CIP*	5685.8	924.3	4007.3	8223.5	1.714 (0.189)	0.019 (0.981)
	SZC	5575.1	996.1	4128.2	7706.5		
	CG	5685.8	1429.9	3831.5	8861.6		
Post Cingulate Right	*CIP*	7292.8	1417.2	5678.6	12159.3	0.146 (0.865)	0.517 (0.599)
	SZC	7287.5	975.5	5711.3	9795.6		
	CG	7598.5	1487.8	5255.1	9971.4		
MFG DPFC Left	*CIP*	18757.1	3348.1	9311.9	23796.5	0.523 (0.595)	1.283 (0.285)
	SZC	16939.3	2610.8	12170.3	20811.6		
	CG	17584.3	3419.9	11114.9	23829.5		
MFG DPFC Right	*CIP*	19676.5	4237.2	10829.1	29364.9	2.726 (0.074)	2.956 (0.060)
	SZC	18105.1	4389.4	7778.2	25709.4		
	CG	16760.1	3110.2	9515.3	23081.9		

SFG- Superior frontal gyrus; **MFG-** Middle frontal gyrus; **PFC-** Pre frontal cortex; **DPFC-** Dorsal pre frontal cortex; **PRISM-** Psychiatric research interview for substance use and mental disorders**; ANOVA**- Analysis of variance; **GLM-** General linear modelling; * $p<0.05$ (after Bonferroni test)

Supplementary Table 2c Comparison of grey matter volumes among patients with cannabis induced psychosis group (*CIP*), Schizophrenia with cannabis use (SZC) and control group (CG)

Brain structure	PRISM group N= 20 in each group	Volume				ANOVA F (p value) Post-Hoc Tukey	GLM F (p value) Post-Hoc Bonferroni
		Mean	Std. Dev.	Range			
				Minimum	Maximum		
MFG Post Segment Left	*CIP*	17053.6	3103.9	8108.1	21405.3	0.146 (0.865)	0.453 (0.638)
	SZC	17142.9	3510.8	12643.1	23686.5		
	CG	16624.1	3119.5	11818.5	24676.1		
MFG Post Segment Right	*CIP*	16294.2	3540.2	12126.3	27567.4	0.253 (0.595)	0.340 (0.713)
	SZC	15484.2	3668.2	10350.8	23758.1		
	CG	15281.1	2638.4	11301.8	22075.9		
IFG Pars Opercularis Left	*CIP*	5666.5	1339.9	2402.1	8064.1	0.221 (0.803)	0.421 (0.658)
	SZC	5695.9	1464.4	3204.7	8289.4		
	CG	5437.1	1232.9	2913.4	7294.5		
IFG Pars Opercularis Right	*CIP*	5698.4	1099.7	3891.8	7602.3	0.231 (0.795)	0.128 (0.880)
	SZC	5505.5	1245.9	2677.1	8982.1		
	CG	5485.1	917.7	3364.1	7272.5		

IFG Pars Orbitalis Left	*CIP*	7367.1	3014.1	5134.2	180d63.1	0.986 (0.379)	1.075 (0.348)
	SZC	7251.9	2164.9	4738.4	12747.5		
	CG	6418.8	1590.1	4221.7	9993.5		
IFG Pars Triangularis Left	*CIP*	7136.7	1635.7	3908.3	9762.6	0.891 (0.416)	1.018 (0.368)
	SZC	6975.6	1544.8	4452.5	9251.4		
	CG	6517.7	1371.4	4727.4	9130.5		

IFG- Inferior frontal gyrus; **PRISM-** Psychiatric research interview for substance use and mental disorders; **ANOVA**- Analysis of variance; **GLM-** General linear modeling; * $p<0.05$ (after Bonferroni test)

Supplementary Figure 1 Axial view of the cerebellum in the co-registered subject space mean kurtosis (MK) MR image and the John's Hopkin's University-Montreal Neurological Institute (JHU-DTI-MNI) map space [Please use colour]