Reduced Brain Cannabinoid Receptor Availability in Schizophrenia

Supplemental Information

Screening Procedures

A Structured Clinical Interview for DSM-IV-TR was conducted to verify a diagnosis of schizophrenia and to confirm the absence of any DSM-IV Axis I or II disorder in the healthy controls. Screening tests included electrocardiogram, hematology, chemistry, thyroid function tests, PT/PTT, and urinalysis and an Allen's test. Spot urine drug test, breathalyzer and urine toxicology for drugs were done at screening to confirm abstinence from illicit drug use. Detailed history of lifetime exposure to cannabis, other drugs and alcohol was assessed. A Time Line Follow Back approach for 6 months prior to screening was done to quantify drug and alcohol exposure (including) cannabis use. Subjects' status as nonsmokers (tobacco) was ascertained by self-report, the Fagerstrom Test for Nicotine Dependence, and breath carbon monoxide levels.

Magnetic Resonance Imaging Methodology

MRI scans were conducted before the PET scans to 1) exclude individuals with anatomical abnormalities, and 2) to co-register PET and MRI for image analysis. MR imaging was performed on a 3T Trio (Siemens Medical Solutions, Erlangen, Germany) with a circularly polarized head coil. MR acquisition was a Sag 3D magnetization-prepared rapid gradient-echo sequence.

Table S1. Postmortem Findings of CB1R in Schizophrenia

Author	Method	Finding	Region
Dean *et al.*, 2001 (1)	Autoradiography: [^{3}H]CP-55940 (CB1R agonist)	Increased	DLPFC
		No change	CP, temporal lobe
Zavitsanou *et al.*, 2004 (2)	Autoradiography:[^{3}H]SR141716A (CB1R antagonist)	Increased	ACC
Newell *et al.*, 2006 (3)	Autoradiography: [^{3}H]CP-55940 (CB1R agonist)	Increased	PCC
Deng *et al.*, 2007 (4)	Autoradiography: [^{3}H]CP-55940 (CB1R agonist) and [^{3}H]SR141716A (CB1R antagonist)	No change	STG
Koethe *et al.*, 2007 (5)	Immunohistochemistry	No change	ACC, DLPFC
Eggan *et al.*, 2008 (6)	In situ hybridization	Decreased	DLPFC
	Immunocytochemistry	Decreased	
Uriguen *et al.*, 2009 (7)	Immunocytochemistry	Decreased	PFC (*in un-medicated patients)
		No change*	
Eggan *et al.*, 2010 (8)	Immunohistochemistry	Decreased	DLPFC
Dalton *et al.*, 2011(9)	Autoradiography: [^{3}H]CP-55940 (CB1R agonist)	Increased	DLPFC
	Immunocytochemistry	No change	
Jenko *et al.*, 2012 (10)	Autoradiography: [^{3}H]MePPEP (CB1R inverse agonist)	Increased	DLPFC
Volk *et al.*, 2014 (11)	Autoradiography: [^{3}H]-OMAR (CB1R inverse agonist)	Increased	DLPFC
	In situ hybridization (CB1R mRNA)	Decreased	
	Immunohistochemistry (CB1R protein)	Decreased	

ACC, anterior cingulate cortex; CP, caudate-putamen; DLPFC, dorsolateral prefrontal cortex; PCC, posterior cingulate cortex; PFC, prefrontal cortex; STG, superior temporal gyrus.

Table S2. Statistical Results for OMAR V_T Data Across All Subject Groups

	Composite Score	Amygdala	Caudate	Cerebellum	Cingulum_Ant	Cingulum_Post	Frontal	Hippocampus	Hypothalamus	Insula	Occipital	Pallidum	Parietal	Putamen	Temporal	Thalamus
Free Fraction Unadjusted Results																
SCZ vs. HC	0.02*	0.03*	0.00*	ns	0.06	0.00*	ns	0.03*	0.02*	0.03*	ns	ns	0.09	0.08	ns	0.06
SCZ_Unmed vs. HC	0.03*	0.03*	0.03*	ns	ns	0.03*	ns	0.06	0.08	0.06	ns	0.02*	ns	0.06	ns	0.09
SCZ _Med vs. HC	0.07	ns	0.06	ns	ns	0.02*	ns	ns	0.06	ns	ns	ns	ns	ns	ns	ns
SCZ_Unmed vs. SCZ_Med	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	0.06	ns	ns	ns	ns
SCZ-Nonsmokers vs. HC	0.01*	0.04*	0.03*	0.09	0.06	0.01*	0.05*	0.05*	0.04*	0.04*	0.05*	0.05*	0.03*	0.05*	0.09	ns
SCZ-Smokers vs. HC	ns	ns	0.08	ns	ns	0.08	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
SCZ-Nonsmokers vs. SCZ-Smokers	ns	ns	ns	0.09	ns	ns	0.06	ns	ns	ns	0.05*	ns	0.02*	ns	0.08	ns
Free Fraction Adjusted Results																
SCZ vs. HC	0.00*	0.03*	0.02*	0.05*	0.00*	0.01*	0.04*	0.02*	0.01*	0.02*	0.04*	0.02*	0.03*	0.03*	0.04*	0.03*
SCZ_Unmed vs. HC	0.00*	0.02*	0.02*	0.04*	0.00*	0.02*	0.03*	0.02*	0.03*	0.02*	0.03*	0.01*	0.03*	0.02*	0.03*	0.03*
SCZ_Med vs. HC	0.02*	0.09	0.07	ns	0.00*	0.04*	ns	0.08	0.04*	0.08	ns	0.07	ns	ns	ns	ns
SCZ_Unmed vs. SCZ_Med	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
SCZ-Nonsmokers vs. HC	0.00*	0.05*	0.04*	0.06	0.00*	0.02*	0.04*	0.04*	0.03*	0.04*	0.04*	0.03*	0.04*	0.04*	0.05*	0.06
SCZ-Smokers vs. HC	0.05*	ns	0.08	ns	0.00*	0.07	ns	ns	0.07	ns	ns	0.09	ns	ns	ns	ns
SCZ-Nonsmokers vs. SCZ-Smokers	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

All values represent *p*-values of post-hoc F-tests derived from linear mixed models of 1) Free fraction unadjusted OMAR V_T between HCs and SCZ groups [top half of table] and 2) Free fraction adjusted OMAR V_T between HCs and SCZ groups [bottom half of table]. (*: $p \leq 0.05$; ns: $p \geq 0.1$)

Table S3. Group Differences in ROI Volume and V_T after Gray Matter Masking

Regions of Interest	ROI Volume with GM Masking			V_T with GM Masking		
	HCs	SCZs	% Diff	HCs	SCZs	% Diff
ACC	14.00	13.51	-3.56	1.81	1.50	-21.10
PCC	3.74	3.51	-6.67	1.46	1.17	-24.54
Insula	20.97	20.49	-2.35	1.76	1.47	-19.66
Frontal Cortex	126.52	120.31	-5.17	1.71	1.48	-15.59
Parietal Cortex	32.70	30.92	-5.78	1.61	1.40	-14.74
Temporal Cortex	97.73	96.37	-1.42	1.66	1.45	-14.81
Occipital Cortex	44.81	42.52	-5.39	1.55	1.35	-15.09
Mean			-4.33			-17.93
SD			1.93			3.88

Supplementary References

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