

Supplemental information

Table S1. Demographic, postmortem, and clinical characteristics of individual human subjects included in the study.

Table S2. Statistical results of sum CB1R intensity and mean CB1R intensity analyses without outlier pair.

Table S3. Mean values of Ctrl/SZ subject pair sum CB1R intensity ratios for pairs with and without cannabis and medication exposure history. Values are represented as mean \pm SEM.

Table S4. Mean values and T-tests results of Ctrl/SZ subject pair mean CB1R intensity ratios for pairs with and without cannabis and medication exposure history for each terminal type. Values are represented as mean \pm SEM.

Figure S1. Mean CB1R intensity frequency histograms for inhibitory (vGAT-IR) boutons from postmortem PFC samples of subjects with schizophrenia (SZ) and unaffected comparisons (Ctrl), measured in analogue-to-digital units (ADU). The line at 712 ADU denotes the median value of mean CB1R intensity for vGAT-IR boutons in Ctrl.

Figure S2. Mean CB1R intensity in excitatory (vGlut1-IR) boutons (top), low-CB1R-expressing inhibitory (vGAT-IR) boutons (middle), and high-CB1R-expressing inhibitory (vGAT-IR) boutons (bottom) for individual subjects across cortical layers. Each individual data point represents the mean intensity averaged across all sampled sites for a single subject. Central line indicates the median, box boundaries extend from the 25th to 75th percentiles, and whiskers

extend from the minimum to maximum value. There was a main effect of subject group for excitatory and high-CB1R-expressing inhibitory boutons, $p < 0.001$. $**p < 0.001$.

Table S1.

Healthy Comparison Subjects										Subjects with Schizophrenia									
Pair	Case	Sex/ Race	Age	PMI ^a	Storage Time ^b	pH	Cause of Death	Case	DSM IV diagnosis	Sex/ Race	Age	PMI ^a	Storage Time ^b	pH	Cause of Death	History of Cannabis Use	Antipsychotic ATOD	Antidepressant ATOD	Benzodiazepine / VPA ATOD
1	681	MW	51	11.6	190	7.2	Hypertrophic cardio-myopathy	640	Chronic paranoid schizophrenia	MW	49	5.2	195	6.9	Pulmonary embolism	None	Y	Y	N
2	685	MW	56	14.5	189	6.6	Hypoplastic coronary artery	622	Chronic undifferentiated schizophrenia	MW	58	18.9	197	6.8	Right MCA infarction	None	N	N	N
3	592	M/B	41	22.1	202	6.7	ASCVD	533	Chronic undifferentiated schizophrenia	MW	40	29.1	212	6.8	Accidental Asphyxiation	None	Y	N	N
4	727	M/B	19	7.0	183	7.2	Trauma	829	Schizoaffective disorder; ADC; OAR	MW	25	5.0	164	6.8	Suicide by salticylate overdose	Abuse in remission	N	N	Y
5	700	MW	42	26.1	187	7.0	ASCVD	539	Schizoaffective disorder; ADR	MW	50	40.5	211	7.1	Suicide by combined drug overdose	None	Y	Y	Y
6	551	MW	61	16.4	209	6.6	Cardiac tamponede	625	Chronic disorganized schizophrenia; AAC	M/B	49	23.5	197	7.3	ASCVD	None	Y	Y	N
7	604	MW	39	19.3	200	7.1	Hypoplastic coronary artery	581	Chronic paranoid schizophrenia; ADC; OAC	MW	46	28.1	204	7.2	Accidental combined drug overdose	Use	Y	N	Y
8	818	FW	67	24.0	167	7.1	Anaphylactic reaction	917	Chronic undifferentiated schizophrenia	FW	71	23.8	147	6.8	ASCVD	None	Y	N	N
9	871	MW	28	16.5	155	7.1	Trauma	878	Disorganized schizophrenia; ADC	MW	33	10.8	154	6.7	Myocardial fibrosis	Use	Y	Y	Y
10	630	MW	65	21.2	196	7.0	ASCVD	566	Chronic undifferentiated schizophrenia; AAR	MW	63	18.3	207	6.8	ASCVD	None	Y	Y	Y
	Mean		46.9	17.9	187.8	6.96					48.4	20.3	188.8	6.920		3Y/7N	8Y/2N	5Y/5N	5Y/5N
	SD		15.9	5.9	16.3	0.24					13.7	11.2	24.4	0.20					

^a PMI, postmortem interval (hours); ^b Storage time (months) at -80C. Other abbreviations: ASCVD, arteriosclerotic cardiovascular disease; MCA, middle cerebral artery; ATOD, at time of death; ADC, alcohol dependence, current at time of death; ADR, alcohol dependence, in remission at time of death; AAC, alcohol abuse, current at time of death; AAR, alcohol abuse, in remission at time of death; ODC, other substance dependence, current at time of death; ODR, other substance dependence, in remission at time of death; OAC, other substance abuse, current at time of death; OAR, other substance abuse, in remission at time of death; VPA, valproic acid

Table S2.

Variable	Factor	p-value
Sum CB1R intensity		
Paired analysis	Main effect of subject group	$F_{(1,88)}=7.532, p=0.007$
	Main effect of cortical layer	$F_{(5,88)}=4.803, p<0.001$
Unpaired analysis	Main effect of subject group	$F_{(1,91)}=6.410, p=0.013$
	Main effect of cortical layer	$F_{(5,91)}=4.706, p<0.001$
Mean CB1R intensity		
Paired analysis	Main effect of terminal type	$F_{(2,280)}=1053.740, p<0.001$
	Subject group x terminal type interaction	$F_{(2,280)}=34.872, p<0.001$
	<i>Post hoc</i>	
	vGlut-IR effect	$F_{(1,280)}=8.451, p=0.004$
	high-CB1R-expressing vGAT-IR effect	$F_{(1,280)}=69.393, p<0.001$
Unpaired analysis	Main effect of terminal type	$F_{(2,283)}=1026.559, p<0.001$
	Subject group x terminal type interaction	$F_{(2,283)}=33.972, p<0.001$
	<i>Post hoc</i>	
	vGlut-IR effect	$F_{(1,283)}=8.575, p=0.004$
	high-CB1R-expressing vGAT-IR effect	$F_{(1,283)}=65.369, p<0.001$

Table S3.

Substance/ medication	Use history in SZ (n)	Mean of Ctrl/SZ sum CB1R intensity ratio (mean \pm SEM)	<i>p</i>-value
Cannabis	Yes (3)	95.832 \pm 9.026	t(8)=0.403
	No (7)	86.170 \pm 4.726	<i>p</i> =0.697
Antipsychotics	Yes (8)	91.541 \pm 4.783	t(8)=0.452
	No (2)	79.181 \pm 9.326	<i>p</i> =0.664
Antidepressants	Yes (5)	95.131 \pm 5.866	t(8)=0.557
	No (5)	83.006 \pm 6.105	<i>p</i> =0.593
Benzodiazepines/ valproic acid	Yes (5)	105.216 \pm 5.977	t(8)=1.699
	No (5)	72.910 \pm 4.528	<i>p</i> =0.128

Abbreviations: Ctrl = unaffected comparison, SZ = schizophrenia, SEM = standard error of mean

Table S4.

Terminal type	Substance/ medication	Use history in SZ	Mean of Ctrl/SZ mean CB1R intensity ratio (mean \pm SEM)	p -value	
Excitatory (vGlut1-IR)	Cannabis	Yes	86.269 \pm 20.197	t(8)=0.267	
		No	80.159 \pm 12.307	p =0.796	
	Antipsychotics	Yes	81.696 \pm 11.097	t(8)=-0.056	
		No	83.174 \pm 31.533	p =0.957	
	Antidepressants	Yes	88.234 \pm 14.661	t(8)=0.606	
		No	75.750 \pm 14.490	p =0.562	
	BZD/VPA	Yes	97.432 \pm 13.173	t(8)=1.712	
		No	66.551 \pm 12.315	p =0.125	
	High-CB1R- expressing Inhibitory (vGAT-IR)	Cannabis	Yes	140.101 \pm 23.453	t(8)=1.104
			No	115.563 \pm 10.910	p =0.302
Antipsychotics		Yes	130.094 \pm 10.448	t(8)=1.480	
		No	92.246 \pm 26.412	p =0.177	
Antidepressants		Yes	128.398 \pm 15.658	t(8)=0.509	
		No	117.451 \pm 14.767	p =0.625	
BZD/VPA		Yes	126.176 \pm 15.424	t(8)=0.299	
		No	119.673 \pm 15.330	p =0.773	
Low-CB1R- expressing Inhibitory (vGAT-IR)		Cannabis	Yes	92.728 \pm 7.645	t(8)=-0.456
			No	95.609 \pm 2.757	p =0.660
	Antipsychotics	Yes	93.710 \pm 3.391	t(8)=-0.730	
		No	98.887 \pm 0.375	p =0.486	
	Antidepressants	Yes	95.181 \pm 4.466	t(8)=0.149	
		No	94.309 \pm 3.784	p =0.885	
	BZD/VPA	Yes	95.865 \pm 4.620	t(8)=0.386	
		No	93.625 \pm 3.519	p =0.710	

Abbreviations: BZD = benzodiazepine, Ctrl = unaffected comparison, SZ = schizophrenia, SEM = standard error of mean, VPA = valproic acid

Figure S1.

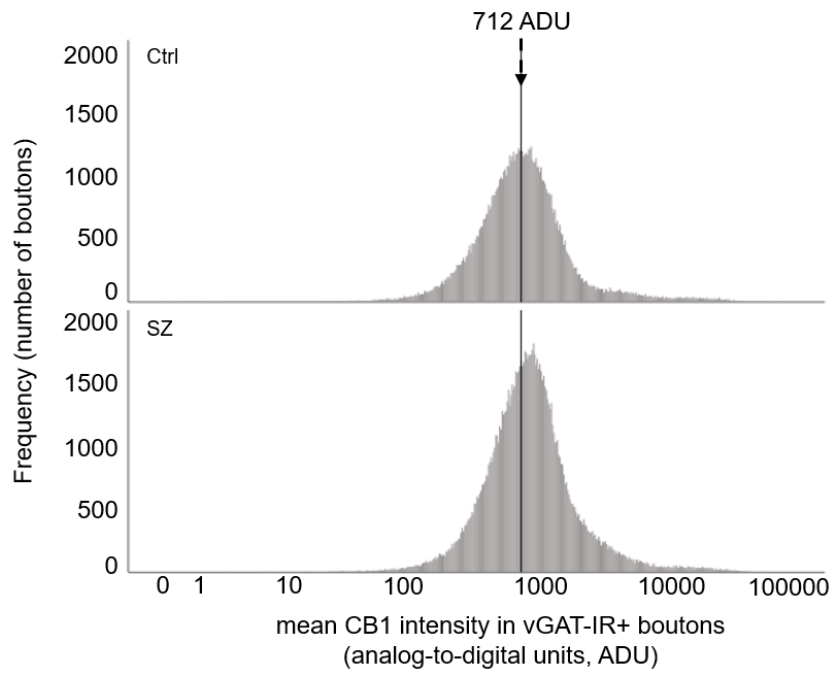


Figure S2.

