

SUPPLEMENTARY INFORMATION

SUPPLEMENTARY FIGURES

Supplementary Figure S1

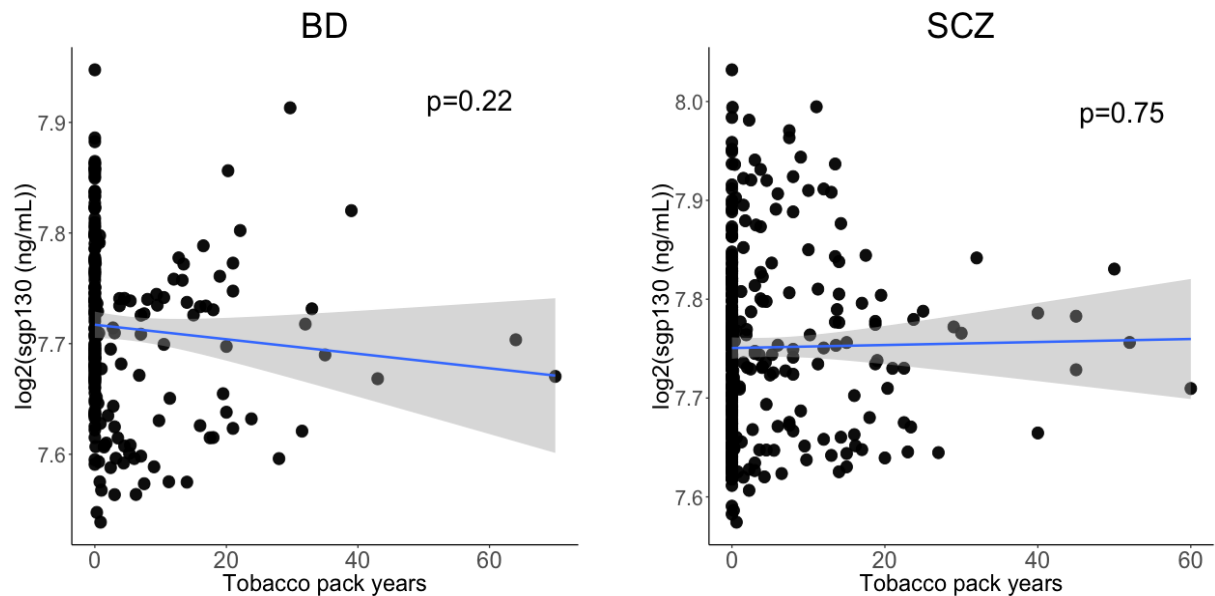


Figure S1. Relationship between sgp130 and tobacco pack-years. The figures show the relationship between plasma levels of sgp130 and tobacco pack-years in BD and SCZ patients. Tobacco pack-years is a measure of how much and for how long an individual has been smoking tobacco. Pack-years were defined as the number of cigarettes currently smoked per day multiplied by the number of years the individual has been smoking and divided by 20. No significant relationships were found between sgp130 and tobacco pack-years in BD or SCZ patients.

Supplementary Figure S2

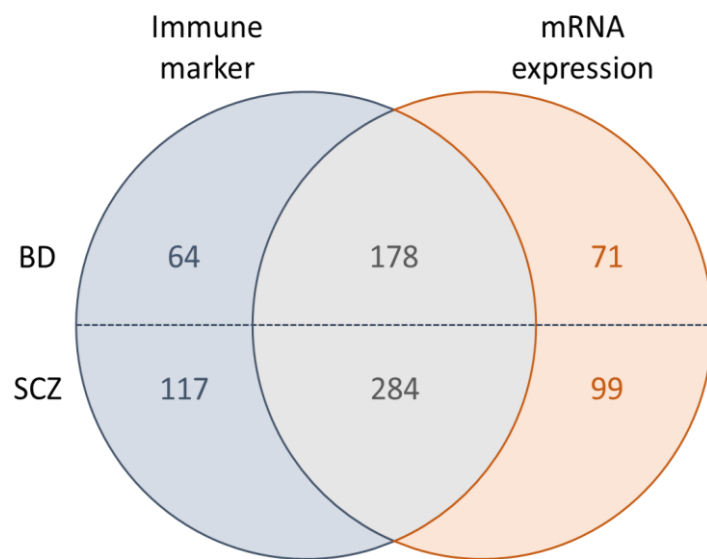


Figure S2. Partly overlapping immune marker and mRNA expression samples. To investigate whether the significantly associated serum markers were correlated with cannabis use at the gene expression level, a partly overlapping sample of 249 BD and 383 SCZ patients were used to test for associations between gene expression levels and cannabis exposure. “Immune marker” represents the study sample used to analyze inflammatory markers in serum, while “mRNA expression” represents the study sample used to analyze gene expression levels.

Supplementary Figure S3

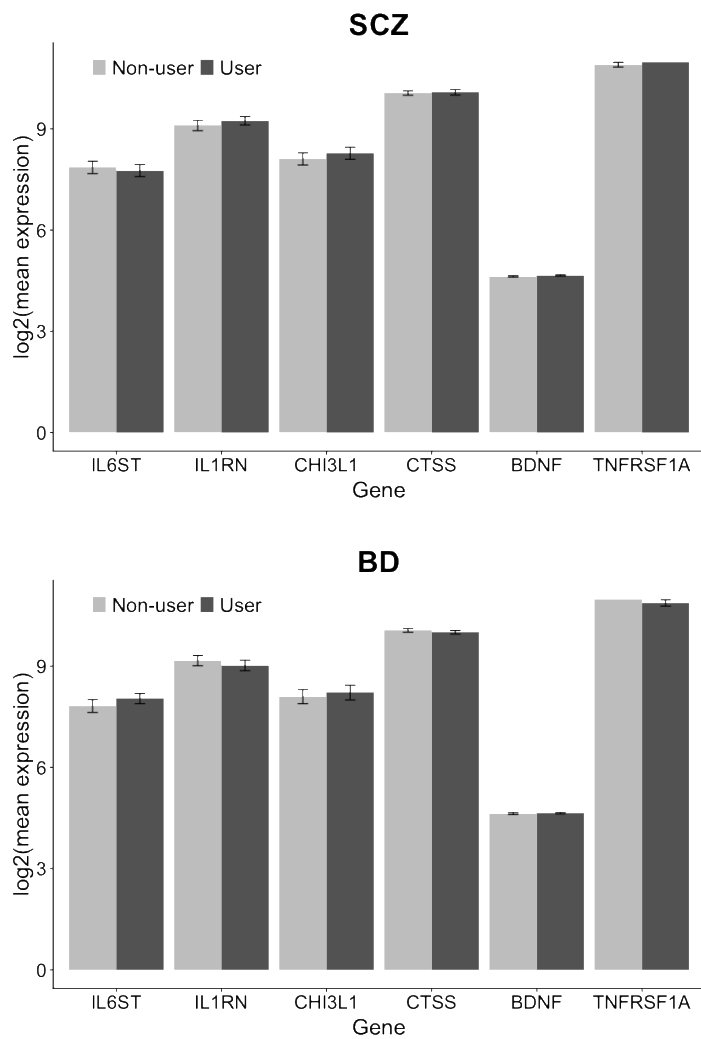


Figure S3. Effect of cannabis use on gene expression levels of inflammatory markers.

Expression levels of the genes encoding the cannabis-related inflammatory immune markers were tested for associations with cannabis exposure. No significant association was found for any of the six genes in BD or SCZ patients. This finding suggests that the observed effects of cannabis on inflammatory markers do not involve peripheral immune cell modulation, but rather reflect the involvement of other tissues and cell types. The correspondence between gene symbol and immune marker is as follows: *IL6ST* – sgp130, *IL1RN* – IL-1RA, *CHI3L1* – YKL40, *CTS* – CatS, *BDNF* – BDNF, *TNFRSF1A* – sTNFR1.

Supplementary Table S1. Demographic and clinical characteristics of schizophrenia (SCZ) and bipolar disorder (BD) patients in the mRNA expression sample grouped according to recent cannabis use (User) or no recent cannabis use (Non-user).

	SCZ patients						BD patients					
	Non-user n=321		User n=62		Test statistic	p-value	Non-user n=208		User n=41		Test statistic	p-value
	Mean	SD	Mean	SD			Mean	SD	Mean	SD		
Age	31.7	9.9	26.2	7.1	t=5.14	1.16e-6**	35.8	12.13	28.12	8.17	t=5.02	3.08e-6**
Sex, female (n, %)	142	44.2	20	32.3	$\chi^2=2.58$	0.108	128	61.5	17	41.5	$\chi^2=4.88$	0.027*
Education (years)	13.1	2.9	12.3	2.2	t=2.42	0.017*	14.6	3.1	13.7	2.5	t=1.99	0.051
BMI	26.9	5.6	25.1	4.4	t=2.76	0.007*	25.8	4.4	25.5	4.7	t=0.40	0.688
Tobacco use, yes (n, %)	155	48.3	51	82.3	$\chi^2=23.69$	1.13e-6**	109	52.4	29	70.7	$\chi^2=3.94$	0.047*
Alcohol units 6 months (MD, range)	13	0-1456	40	0-1098	W=6561.5	2.11e-4**	37.5	0-1820	143	2-2184	W=2555	1.10e-4**
Age of onset (years)	24.7	8.6	20.3	5.6	t=5.12	1.14e-6**	23.2	9.7	20.8	7.0	t=1.89	0.063
PANSS positive	15.1	5.3	16.4	5.2	t=-1.87	0.066	10.0	3.8	10.8	3.9	t=-1.21	0.230
PANSS negative	15.8	5.8	15.6	6.2	t=0.20	0.839	10.4	3.7	9.6	3.7	t=1.20	0.236
PANS general	31.8	8.5	33.7	8.3	t=-1.66	0.099	26.0	6.5	24.9	5.7	t=1.14	0.261
PANSS total	62.7	15.9	65.8	17.1	t=-1.33	0.187	46.3	11.5	45.3	10.4	t=0.59	0.559
IDS	17.2	12.3	15.1	11.8	t=0.99	0.323	16.6	12.2	15.7	12.1	t=0.38	0.703
YMRS	4.8	4.8	5.5	5.5	t=-0.84	0.406	3.7	5.2	3.6	4.6	t=0.16	0.870
GAF Symptoms	43.1	11.4	40.4	11.4	t=1.68	0.097	56.5	12.0	57.4	10.4	t=-0.49	0.625
GAF Function	43.8	11.1	41.2	9.6	t=1.91	0.059	53.4	12.9	54.0	12.0	t=-0.27	0.787
Antipsychotics (DDD)	1.57	3.21	1.84	2.80	t=-0.68	0.500	0.69	1.56	0.50	0.83	t=1.09	0.277
Anticonvulsants (DDD)	0.088	0.27	0.056	0.21	t=1.04	0.303	0.32	0.50	0.26	0.40	t=0.83	0.411
Antidepressants (DDD)	0.45	0.87	0.38	0.65	t=0.74	0.462	0.57	0.94	0.34	0.77	t=1.63	0.109
Lithium (DDD)	0.026	0.17	0.048	0.28	t=-0.62	0.540	0.21	0.46	0.21	0.47	t=-0.03	0.973

**p<0.001, *p<0.05. BMI: Body Mass Index, PANSS: Positive and Negative Syndrome Scale, IDS: Inventory of Depression Scale, YMRS: Young Mania Rating Scale, GAF: Global Assessment of Functioning, MD: Median, DDD: Defined Daily Dose.

Supplementary Table S2. Associations between mRNA expression levels of significant serum markers and cannabis use in schizophrenia and bipolar disorder patients.

Gene	Immune marker	SCZ patients						BD patients					
		p-value Nominal	p-value Bonferroni	Non-user		User		p-value Nominal	p-value Bonferroni	Non-user		User	
				Mean	SD	Mean	SD			Mean	SD	Mean	SD
<i>IL6ST</i>	gp130	0.198	1.000	7.858	0.182	7.764	0.181	0.208	1.000	7.816	0.189	8.038	0.152
<i>IL1RN</i>	IL-1RA	0.091	0.546	9.103	0.156	9.240	0.123	0.781	1.000	9.163	0.153	9.021	0.158
<i>CHI3L1</i>	YKL40	0.419	1.000	8.110	0.182	8.278	0.180	0.494	1.000	8.097	0.212	8.217	0.220
<i>CTSS</i>	CatS	0.721	1.000	10.063	0.066	10.085	0.082	0.711	1.000	10.060	0.057	10.004	0.055
<i>BDNF</i>	BDNF	0.168	1.000	4.629	0.022	4.659	0.025	0.476	1.000	4.632	0.032	4.643	0.023
<i>TNFRSF1A</i>	sTNFR1	0.161	0.966	10.902	0.070	10.975	0.066	0.379	1.000	10.973	0.101	10.871	0.092

The means and standard deviations (SD) shown are for the fitted values from the full regression model.