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Lifetime cannabis use and childhood trauma increase risk of psychosis in carriers of *CNR1* genetic variants: findings from the STREAM study - Loureiro CM et al.

Table S1 Associations between the environmental risk factors in community-based controls and patients with first-episode psychosis

	Lifetime cannabis use, n (%)		χ^2 ; p-value ¹
	No	Yes	
Childhood trauma, n (%)			
Community-based controls (n=286)			
No	184 (64.3) ^a	34 (12.0) ^b	7.80; 0.008
Yes	47 (16.4) ^a	21 (7.3) ^b	
Total	231 (80.7)	55 (19.3)	
FEPp (n=143)			
No	34 (23.8)	35 (24.5)	0.06; 0.868
Yes	38 (26.5)	36 (25.2)	
Total	72 (50.3)	71 (49.7)	

FEPp = first-episode psychosis patients.

Bold type denotes statistically significant results.

[†] Fisher's exact test.

^{a,b} Different superscript letters denote statistically significant differences between means.

Table S2 Genotype frequencies between FEPp and controls and the risk effects of the NMDAR, D2R, and CB1R SNVs in psychosis using a dominant model

SNVs: dominant model	Variant	Controls (n=286) n (%) [†]	FEPp (n=143)	Association with psychosis	
				Unadjusted ^a	Adjusted ^b
				β (95%CI); p	
GRIN1[‡]					
rs4880213 (C>T)	CC	83 (29.0)	35 (24.5)	1.00	1.00
	CT or TT	203 (71.0)	108 (75.5)	1.3 (0.8-2.0); 0.321	1.2 (0.7-2.2); 0.455
rs11146020 (G>C)	GG	239 (83.6)	117 (81.8)	1.00	1.00
	GC or CC	47 (16.4)	26 (18.2)	1.1 (0.7-1.9); 0.650	1.1 (0.6-2.2); 0.755
GRIN2A[‡]					
rs1420040 (A>G)	AA	109 (38.1)	49 (34.3)	1.00	1.00
	AG or GG	177 (61.9)	94 (65.7)	1.2 (0.8-1.8); 0.436	1.4 (0.8-2.3); 0.220
rs11866328 (G>T)	GG	103 (36.0)	55 (38.5)	1.00	1.00
	TG or TT	183 (64.0)	88 (61.5)	0.9 (0.6-1.4); 0.620	0.9 (0.6-1.6); 0.772
GRIN2B[‡]					
rs890 (A>C)	AA	82 (28.7)	55 (38.5)	1.00	1.00
	AC or CC	204 (71.3)	88 (61.5)	0.6 (0.4-1.0); 0.041	0.6 (0.4-1.0); 0.073
rs7298664 (T>C)	TT	212 (74.1)	100 (69.9)	1.00	1.00
	TC or CC	74 (25.9)	43 (30.1)	1.2 (0.8-1.9); 0.358	1.2 (0.7-2.0); 0.564
rs2098469 (T>G)	TT	235 (82.2)	111 (77.6)	1.00	1.00
	TG or GG	51 (17.8)	32 (22.4)	1.3 (0.8-2.2); 0.262	1.4 (0.8-2.7); 0.265
DRD2[‡]					
rs1799978 (T>C)	TT	244 (85.3)	115 (80.4)	1.00	1.00
	TG or CC	42 (14.7)	28 (19.6)	1.4 (0.8-2.4); 0.197	1.9 (1.0-3.6); 0.061
rs7131056 (C>A)	CC	107 (37.4)	55 (38.5)	1.00	1.00
	AC or AA	179 (62.6)	88 (61.5)	1.0 (0.6-1.4); 0.833	0.8 (0.5-1.3); 0.355
rs6275 (G>A)	GG	117 (40.9)	48 (33.6)	1.00	1.00
	AG or AA	169 (59.1)	95 (66.4)	1.4 (0.9-2.1); 0.141	1.5 (0.9-2.4); 0.147
CNR1[‡]					
rs806380 (A>G)	AA	154 (53.8)	85 (59.4)	1.00	1.00
	AG or GG	132 (46.2)	58 (40.6)	0.8 (0.5-1.2); 0.272	0.7 (0.4-1.2); 0.169
rs806379 (A>T)	AA	92 (32.2)	44 (30.8)	1.00	1.00
	AT or TT	194 (67.8)	99 (69.2)	1.1 (0.7-1.6); 0.769	1.2 (0.7-2.0); 0.592

rs1049353 (C>T)	CC	186 (65.0)	95 (66.4)	1.00	1.00
	CT or TT	100 (35.0)	48 (33.6)	0.9 (0.6-1.4); 0.774	1.1 (0.6-1.8); 0.815
rs6454674 (T>G)	TT	144 (50.3)	72 (50.3)	1.00	1.00
	GT or GG	142 (49.7)	71 (49.7)	1.0 (0.7-1.5); 1.000	0.8 (0.5-1.2); 0.268
rs1535255 (T>G)	TT	194 (67.8)	85 (59.4)	1.00	1.00
	GT or GG	92 (32.2)	58 (40.6)	1.4 (0.9-2.2); 0.086	2.0 (1.2-3.4); 0.008
rs2023239 (T>C)	TT	194 (67.8)	86 (60.1)	1.00	1.00
	CT or CC	92 (32.2)	57 (39.9)	1.4 (0.9-2.1); 0.155	2.0 (1.2-3.4); 0.009
rs12720071 (T>C)	TT	242 (84.6)	117 (81.8)	1.00	1.00
	TC or CC	44 (15.4)	26 (18.2)	0.8 (0.5-1.4); 0.460	1.5 (0.8-3.0); 0.248
rs6928499 (G>C)	GG	194 (67.8)	86 (60.1)	1.00	1.00
	GC or CC	92 (32.2)	57 (39.9)	1.4 (0.9-2.1); 0.115	2.0 (1.2-3.4); 0.009
rs806374 (T>C)	TT	113 (39.5)	45 (31.5)	1.00	1.00
	CT or CC	173 (60.5)	98 (68.5)	1.4 (0.9-2.2); 0.104	1.7 (1.0-3.0); 0.042
rs7766029 (T>C)	TT	89 (31.1)	49 (34.3)	1.00	1.00
	TC or CC	197 (68.9)	94 (65.7)	0.9 (0.6-1.3); 0.511	0.8 (0.5-1.4); 0.533
rs806378 (C>T)	CC	173 (60.5)	94 (65.7)	1.00	1.00
	CT or TT	113 (39.5)	49 (34.3)	0.8 (0.5-1.2); 0.291	0.7 (0.4-1.2); 0.180
rs10485170 (T>C)	TT	221 (77.3)	102 (71.3)	1.00	1.00
	CT or CC	65 (22.7)	41 (28.7)	1.4 (0.9-2.2); 0.179	2.1 (1.2-3.7); 0.012
rs9450898 (T>C)	TT	195 (68.2)	88 (61.5)	1.00	1.00
	CT or CC	91 (31.8)	55 (38.5)	1.3 (0.9-2.0); 0.172	1.8 (1.1-3.1); 0.024

SNVs = single nucleotide variants; FEPP = first-episode psychosis patients; 1.00 = reference category; β = beta coefficient.

† Genotype frequency difference assessed by chi-square test.

‡ Genotype frequencies analyzed under dominant model (homozygous ancestral versus heterozygous + minor allele homozygous).

^a Unadjusted: binary logistic regression model including a binary outcome (community-based controls and FEPP). If $\alpha \leq 0.20$, to univariate model as significant.

^b Adjusted: binary logistic regression model including a binary outcome (community-based controls and FEPP). β adjusted by covariates sex, age, first 10 PCs, years of education, and tobacco smoking. For multiple test errors, Bonferroni's test was used, and an adjusted p-value < 0.002 (0.05/23 SNVs) was considered statistically significant.

Table S3 Genotype frequencies between FEPp and controls and the risk effects of the NMDAR, D2R, and CB1R SNVs in psychosis using an additive model

SNVs: additive model	Variant	Controls (n=286)	FEPp (n=143)	Association with psychosis	
				Unadjusted ^a	Adjusted ^b
		n (%) [†]		β (95%CI); p	
GRIN1[‡]					
rs4880213 (C>T)	CC	83 (29.0)	35 (24.5)	1.00	1.00
	CT	147 (51.4)	79 (55.2)	1.3 (0.8-2.1); 0.322	1.2 (0.7-2.2); 0.463
	TT	56 (19.6)	29 (20.3)	1.2 (0.7-2.2); 0.500	1.2 (0.6-2.5); 0.600
rs11146020 (G>C)	GG	239 (83.6)	117 (81.8)	1.00	1.00
	GC	45 (15.7)	25 (17.5)	1.1 (0.7-1.9); 0.644	1.1 (0.6-2.2); 0.749
	CC	2 (0.7)	1 (0.7)	1.0 (1.0-11.4); 0.986	1.0 (0.1-14.5); 0.992
GRIN2A[‡]					
rs1420040 (A>G)	AA	109 (38.1)	49 (34.3)	1.00	1.00
	AG	125 (43.7)	70 (49.0)	1.2 (0.8-2.0); 0.335	1.5 (0.8-2.5); 0.169
	GG	52 (18.2)	24 (16.8)	1.0 (0.6-1.9); 0.930	1.2 (0.6-2.4); 0.678
rs11866328 (G>T)	GG	103 (36.0)	55 (38.5)	1.00	1.00
	TG	147 (51.4)	66 (46.2)	0.8 (0.5-1.3); 0.437	0.8 (0.5-1.4); 0.419
	TT	36 (8.4)	22 (15.4)	1.1 (0.6-2.1); 0.671	1.7 (0.8-3.7); 0.205
GRIN2B[‡]					
rs890 (A>C)	AA	82 (28.7)	55 (38.5)	1.00	1.00
	AC	146 (51.0)	62 (43.4)	0.6 (0.4-1.0); 0.048	0.6 (0.3-1.0); 0.049
	CC	58 (20.3)	26 (18.2)	0.7 (0.4-1.2); 0.170	0.8 (0.4-1.5); 0.446
rs7298664 (T>C)	TT	212 (74.1)	100 (69.9)	1.00	1.00
	TC	68 (23.8)	37 (8.6)	1.2 (0.7-1.8); 0.548	1.1 (0.6-1.9); 0.851
	CC	6 (2.1)	6 (4.2)	2.1 (0.7-6.7); 0.203	4.8 (0.8-30.9); 0.095
rs2098469 (T>G)	TT	235 (82.2)	111 (77.6)	1.00	1.00
	TG	48 (16.8)	30 (21.0)	1.3 (0.8-2.2); 0.281	1.5 (0.8-2.9); 0.197
	GG	3 (1.0)	2 (1.4)	1.4 (0.2-8.6); 0.708	0.5 (0.1-5.4); 0.530
DRD2[‡]					
rs1799978 (T>C)	TT	244 (85.3)	115 (80.4)	1.00	1.00
	TG	41 (14.3)	26 (18.2)	1.3 (0.8-2.3); 0.281	1.8 (0.9-3.5); 0.083
	CC	1 (0.3)	2 (1.4)	4.2 (0.4-47.3); 0.240	8.5 (0.1-0.1); 0.999
rs7131056 (C>A)	CC	107 (37.4)	55 (38.5)	1.00	1.00
	AC	138 (48.3)	60 (42.0)	0.8 (0.5-1.3); 0.460	0.7 (0.4-1.3); 0.264
	AA	41 (14.3)	28 (19.6)	1.3 (0.7-2.4); 0.337	1.0 (0.5-2.0); 0.937

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rs6275 (G>A)	GG	117 (40.9)	48 (33.6)	1.00	1.00
	AG	132 (46.2)	66 (46.2)	1.2 (0.8-1.9); 0.386	1.3 (0.7-2.2); 0.411
	AA	37 (12.9)	29 (20.3)	1.9 (1.1-4.5); 0.032	2.2 (1.1-4.4); 0.036
CNR1[†]					
rs806380 (A>G)	AA	154 (53.8)	85 (59.4)	1.00	1.00
	AG	117 (40.9)	50 (35.0)	0.8 (0.5-1.2); 0.237	0.7 (0.4-1.1); 0.121
	GG	15 (5.2)	8 (5.6)	1.0 (0.4-2.4); 0.940	1.2 (0.4-4.0); 0.781
rs806379 (A>T)	AA	92 (32.2)	44 (30.8)	1.00	1.00
	AT	148 (51.7)	69 (48.3)	1.0 (0.6-1.5); 0.913	0.9 (0.5-1.6); 0.786
	TT	46 (16.1)	30 (21.0)	1.4 (0.8-2.4); 0.298	2.3 (1.1-4.8); 0.029
rs1049353 (C>T)	CC	186 (65.0)	95 (66.4)	1.00	1.00
	CT	90 (31.5)	45 (31.5)	1.0 (0.6-1.5); 0.924	1.1 (0.6-1.8); 0.822
	TT	10 (3.5)	3 (2.1)	0.6 (0.2-2.2); 0.427	1.1 (0.2-5.2); 0.927
rs6454674 (T>G)	TT	144 (50.3)	72 (50.3)	1.00	1.00
	GT	110 (38.5)	57 (39.9)	1.0 (0.7-1.6); 0.870	0.7 (0.4-1.3); 0.275
	GG	32 (11.2)	14 (9.8)	0.9 (0.4-1.7); 0.704	0.8 (0.3-1.8); 0.585
rs1535255 (T>G)	TT	194 (67.8)	85 (59.4)	1.00	1.00
	GT	83 (29.0)	49 (34.3)	1.3 (0.9-2.1); 0.180	1.9 (1.1-3.2); 0.025
	GG	9 (3.1)	9 (6.3)	2.3 (0.9-6.0); 0.092	4.8 (1.1-20.4); 0.034
rs2023239 (T>C)	TT	194 (67.8)	86 (60.1)	1.00	1.00
	CT	83 (29.0)	49 (34.3)	1.3 (0.9-2.1); 0.197	1.8 (1.1-3.2); 0.027
	CC	9 (3.1)	8 (5.6)	2.0 (0.7-5.4); 0.167	4.6 (1.1-19.6); 0.042
rs12720071 (T>C)	TT	242 (84.6)	117 (81.8)	1.00	1.00
	TC	41 (14.3)	25 (17.5)	1.3 (0.7-2.2); 0.403	1.6 (0.8-3.3); 0.176
	CC	3 (1.0)	1 (0.7)	0.7 (0.1-6.7); 0.749	0.5 (0.1-6.2); 0.563
rs6928499 (G>C)	GG	194 (67.8)	86 (60.1)	1.00	1.00
	GC	84 (29.4)	49 (34.3)	1.3 (0.9-2.0); 0.215	1.8 (1.0-3.1); 0.037
	CC	8 (2.8)	8 (5.6)	2.3 (0.8-6.2); 0.115	7.9 (1.5-41.9); 0.016
rs806374 (T>C)	TT	113 (39.5)	45 (31.5)	1.00	1.00
	CT	126 (44.1)	72 (50.3)	1.4 (0.9-2.3); 0.116	1.7 (1.0-3.0); 0.049
	CC	47 (16.4)	26 (18.2)	1.4 (0.8-2.5); 0.275	1.7 (0.8-3.6); 0.561
rs7766029 (T>C)	TT	89 (31.1)	49 (34.3)	1.00	1.00
	TC	145 (50.7)	63 (44.1)	0.8 (0.5-1.2); 0.310	0.7 (0.4-1.2); 0.219
	CC	52 (18.2)	31 (21.7)	1.1 (0.6-1.9); 0.783	1.3 (0.7-2.7); 0.427

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rs806378 (C>T)	CC	173 (60.5)	94 (65.7)	1.00	1.00
	CT	104 (36.4)	42 (29.4)	0.7 (0.5-1.2); 0.184	0.7 (0.4-1.1); 0.104
	TT	9 (3.1)	7 (4.9)	1.4 (0.5-4.0); 0.490	1.8 (0.5-7.0); 0.399
rs10485170 (T>C)	TT	221 (77.3)	102 (71.3)	1.00	1.00
	CT	60 (21.0)	37 (25.9)	1.3 (0.8-2.1); 0.229	1.9 (1.1-3.5); 0.027
	CC	5 (1.7)	4 (2.8)	1.7 (0.5-6.6); 0.420	5.7 (0.7-47.2); 0.107
rs9450898 (T>C)	TT	195 (68.2)	88 (61.5)	1.00	1.00
	CT	82 (28.7)	49 (34.3)	1.3 (0.9-2.0); 0.205	1.7 (1.0-2.9); 0.060
	CC	9 (3.1)	6 (4.2)	1.5 (0.5-4.3); 0.472	5.5 (1.0-28.9); 0.044

SNVs = single nucleotide variants; FEPp = first-episode psychosis patients; 1.00 = reference category; β = beta coefficient.

[†] Genotype frequency difference assessed by chi-square test.

[‡] Genotype frequencies analyzed under additive model (homozygous ancestral versus heterozygous versus minor allele homozygous).

^a Unadjusted: binary logistic regression model including a binary outcome (community-based controls and FEPp). If $\alpha \leq 0.20$, to univariate model as significant.

^b Adjusted: binary logistic regression model including a binary outcome (community-based controls and FEPp). β adjusted by covariates sex, age, first 10 PCs, years of education, and tobacco smoking. For multiple test errors, Bonferroni's test was used, and an adjusted p-value < 0.002 (0.05/23 SNVs) was considered statistically significant.

Table S4 Genotype frequencies between FEPp and controls and the risk effects of the NMDAR, D2R, and CB1R SNVs in psychosis using a recessive model

SNVs: recessive model	Variant	Controls (n=286)	FEPp (n=143)	Association with psychosis	
				Unadjusted ^a	Adjusted ^b
		n (%) [†]		β (95%CI); p	
<i>GRIN1</i>[‡]					
rs4880213 (C>T)	CC or CT	230 (80.4)	114 (79.7)	1.00	1.00
	TT	56 (19.6)	29 (20.3)	1.0 (0.6-1.7); 0.864	1.0 (0.6-1.9); 0.878
rs11146020 (G>C)	GG or GC	284 (99.3)	142 (99.3)	1.00	1.00
	CC	2 (0.7)	1 (0.7)	1.0 (0.1-11.1); 1.000	1.0 (0.1-14.2); 0.996
<i>GRIN2A</i>[‡]					
rs1420040 (A>G)	AA or AG	233 (81.8)	119 (83.2)	1.00	1.00
	GG	52 (18.2)	24 (16.8)	0.9 (0.5-1.5); 0.709	1.2 (0.6-2.3); 0.604
rs11866328 (G>T)	GG or TG	250 (87.4)	121 (84.6)	1.00	1.00
	TT	36 (12.6)	22 (15.4)	1.3 (0.7-2.2); 0.425	1.9 (0.9-4.0); 0.082
<i>GRIN2B</i>[‡]					
rs890 (A>C)	AA or AC	228 (79.7)	117 (81.8)	1.00	1.00
	CC	58 (20.3)	26 (18.2)	0.9 (0.5-1.5); 0.606	1.1 (0.6-2.0); 0.840
rs7298664 (T>C)	TT or TC	280 (97.9)	137 (95.8)	1.00	1.00
	CC	6 (2.1)	6 (4.2)	2.0 (0.6-6.5); 0.223	4.8 (0.8-30.2); 0.097
rs2098469 (T>G)	TT or TG	282 (99.0)	141 (98.6)	1.00	1.00
	GG	3 (1.0)	2 (1.4)	1.3 (0.2-8.1); 0.751	0.4 (0.1-4.8); 0.469
<i>DRD2</i>[‡]					
rs1799978 (T>C)	TT or TG	285 (99.7)	141 (98.6)	1.00	1.00
	CC	1 (0.3)	2 (1.4)	4.0 (0.4-45.0); 0.256	0.7 (0.1-0.1); 0.999
rs7131056 (C>A)	CC or AC	245 (85.7)	115 (80.4)	1.00	1.00
	AA	41 (14.3)	28 (19.6)	1.5 (0.9-2.5); 0.165	1.1 (0.6-2.3); 0.701
rs6275 (G>A)	GG or AG	249 (87.1)	114 (79.7)	1.00	1.00
	AA	37 (12.9)	29 (20.3)	1.7 (1.0-2.9); 0.049	1.9 (1.0-3.7); 0.053
<i>CNR1</i>[‡]					
rs806380 (A>G)	AA or AG	271 (94.8)	135 (94.4)	1.00	1.00
	GG	15 (5.2)	8 (5.6)	1.1 (0.4-2.6); 0.880	1.4 (0.4-4.6); 0.575
rs806379 (A>T)	AA or AT	240 (83.9)	113 (79.0)	1.00	1.00
	TT	46 (16.1)	30 (21.0)	1.4 (0.8-2.3); 0.212	2.4 (1.2-4.7); 0.009

rs1049353 (C>T)	CC or CT TT	276 (96.5) 10 (3.5)	140 (98.6) 2 (1.4)	1.00 0.4 (0.1-1.8); 0.394	1.00 0.7 (0.1-4.5); 0.732
rs6454674 (T>G)	TT or GT GG	254 (88.8) 32 (11.2)	129 (90.2) 14 (9.8)	1.00 1.0 (0.4-1.7); 0.659	1.00 0.9 (0.4-2.0); 0.820
rs1535255 (T>G)	TT or GT GG	277 (96.9) 9 (3.1)	134 (93.7) 9 (6.3)	1.00 2.1 (0.8-5.3); 0.133	1.00 3.9 (0.9-16.2); 0.064
rs2023239 (T>C)	TT or CT CC	277 (96.9) 9 (3.1)	135 (94.4) 8 (5.6)	1.00 1.8 (0.7-4.8); 0.227	1.00 3.7 (0.9-15.7); 0.077
rs12720071 (T>C)	TT or TC CC	283 (99.0) 3 (1.0)	142 (99.3) 1 (0.7)	1.00 0.7 (0.1-6.4); 0.724	1.00 0.4 (0.1-5.9); 0.539
rs6928499 (G>C)	GG or GC CC	278 (97.2) 8 (2.8)	135 (94.4) 8 (5.6)	1.00 2.1 (0.8-5.6); 0.157	1.00 6.4 (1.2-33.9); 0.028
rs806374 (T>C)	TT or CT CC	239 (83.6) 47 (16.4)	117 (81.8) 26 (18.2)	1.00 1.1 (0.7-2.0); 0.650	1.00 0.8 (0.4-1.6); 0.583
rs7766029 (T>C)	TT or TC CC	234 (81.8) 52 (18.2)	112 (78.3) 31 (21.7)	1.00 1.2 (0.8-2.1); 0.388	1.00 1.6 (0.9-3.0); 0.110
rs806378 (C>T)	CC or CT TT	277 (96.9) 9 (3.1)	136 (95.1) 7 (4.9)	1.00 1.6 (0.6-4.3); 0.371	1.00 2.1 (0.6-8.1); 0.278
rs10485170 (T>C)	TT or CT CC	281 (98.3) 5 (1.7)	139 (97.2) 4 (2.8)	1.00 1.6 (0.4-6.1); 0.479	1.00 4.9 (0.6-40.0); 0.141
rs9450898 (T>C)	TT or CT CC	277 (96.9) 9 (3.1)	137 (95.8) 6 (4.2)	1.00 1.3 (0.9-2.0); 0.172	1.00 4.6 (0.9-24.0); 0.069

SNVs = single nucleotide variants; FEPP = first-episode psychosis patients; 1.00 = reference category; β = beta coefficient.

[†] Genotype frequency difference assessed by chi-square test.

[‡] Genotype frequencies analyzed under recessive model (homozygous ancestral + heterozygous versus minor allele homozygous).

^a Unadjusted: binary logistic regression model including a binary outcome (community-based controls and FEPP). If $\alpha \leq 0.20$, to univariate model as significant.

^b Adjusted: binary logistic regression model including a binary outcome (community-based controls and FEPP). β adjusted by covariates sex, age, first 10 PCs, years of education and tobacco smoking. For multiple test errors, Bonferroni's test was used, and an adjusted p-value < 0.002 (0.05/23 SNVs) was considered statistically significant.

Table S5 Multifactor dimensionality reduction analysis of gene-environment interactions

Models of gene-environment interactions in psychosis	Adj. bal. acc CV training	Adj. bal. acc CV testing	CV consistency	p-value for testing bal. acc
Lifetime cannabis use (Figure 2A)				
Lifetime cannabis use	0.6521	0.6521	10/10	0.0010-0.0020
<i>CNR1</i> rs12720071, Lifetime cannabis use	0.6757	0.6641	10/10	0.0000-0.0010
<i>CNR1</i> rs12720071, <i>GRIN1</i> rs4880213, Lifetime cannabis use	0.692	0.64	5/10	0.0010-0.0020
<i>CNR1</i> rs806379, <i>CNR1</i> rs7766029, <i>GRIN2B</i> rs890, Lifetime cannabis use	0.7179	0.5818	5/10	0.0770-0.0780
<i>DRD2</i> rs7131056, <i>DRD2</i> rs6275, <i>CNR1</i> rs806374, <i>CNR1</i> rs7766029, Lifetime cannabis use	0.7306	0.5599	2/10	0.2250-0.2260
Childhood trauma (Figure 2B)				
Childhood trauma	0.6399	0.6399	10/10	0.0010-0.0020
<i>CNR1</i> rs12720071, Childhood trauma	0.6549	0.6206	6/10	0.0040-0.0050
<i>CNR1</i> rs7766029, <i>GRIN2A</i> rs11866328, Childhood trauma	0.6956	0.6171	6/10	0.0060-0.0070
<i>CNR1</i> rs7766029, <i>CNR1</i> rs806378, <i>GRIN2A</i> rs1420040 Childhood trauma	0.7157	0.5819	2/10	0.0780-0.0790
<i>CNR1</i> rs806374, <i>CNR1</i> rs7766029, <i>GRIN2A</i> rs11866328, <i>GRIN2A</i> rs1420040, Childhood trauma	0.7275	0.5494	2/10	0.3110
Lifetime cannabis use and childhood trauma (Figure 2C)				
Lifetime cannabis use	0.6544	0.6066	8/10	0.0170
Childhood trauma, Lifetime cannabis use	0.7028	0.7028	10/10	0.000-0.0010
<i>CNR1</i> rs7766029, Childhood trauma, Lifetime cannabis use	0.7249	0.6929	8/10	0.0000-0.0010
<i>DRD2</i> rs7131056, <i>CNR1</i> rs7766029, Childhood trauma, Lifetime cannabis use	0.7432	0.6826	7/10	0.0000-0.0010
<i>DRD2</i> rs7131056, <i>CNR1</i> rs6454674, <i>GRIN2B</i> rs890, Childhood trauma, Lifetime cannabis use	0.7502	0.589	2/10	0.0490-0.0500

Bal. acc = balance-accuracy; CV = cross-validation.

Multifactor dimensionality reduction analysis for each factor summarizing the average cross-validation consistency, adjusted testing balance accuracy, and the empirical p-value derived from permutation testing (p-values based on 1000 permutations) at the 0.05 significance level.

Best model of gene-environment interaction per analysis that shows a) the minimal prediction error; b) the cross-validation consistency upper of 9 or 10-fold cross validation; c) a significant p-value (less than 0.05); and d) close values of the training and testing balance accuracy (TBA=0.55-0.69) (in bold) as described by Moore (2006).

Results demonstrated as mean p-value.