

Sex and Diagnosis Specific Associations Between DNA Methylation of the Oxytocin Receptor Gene with Emotion Processing and Temporal-Limbic and Prefrontal Brain Volumes in Psychotic Disorders

Supplemental Information

Table S1. OXTR DNA methylation levels in individuals with psychotic disorders as a function of antipsychotics and anticonvulsant/mood stabilizers

	OXTR DNA Methylation				<i>p</i> -Value
	Yes		No		
	<i>n</i>	M (SD)	<i>n</i>	M (SD)	
Antipsychotics	134	47.57 (6.64)	33	49.71 (7.57)	0.10
First generation	20	46.81 (7.66)	147	48.15 (6.76)	0.41
Second generation	120	47.58 (6.58)	47	49.04 (7.51)	0.22
Aripiprazole	33	49.37 (6.11)	134	47.65 (7.01)	0.20
Clozapine	2	52.65 (0.99)	165	47.94 (6.88)	0.33
Olanzapine	11	45.33 (5.61)	156	48.18 (6.92)	0.18
Quetiapine	20	45.72 (5.65)	147	48.30 (6.97)	0.11
Risperidone	18	48.11 (8.15)	149	47.98 (6.72)	0.94
Ziprasidone	10	46.29 (6.77)	157	48.10 (6.87)	0.42
Anticonvulsant/mood stabilizer	86	46.80 (7.63)	81	49.26 (5.72)	0.02
Lithium	24	45.44 (6.66)	143	48.42 (6.82)	0.04
Valproic acid	26	45.85 (7.67)	141	48.39 (6.66)	0.08

Table S2. Regional brain volumes (mm³) in *a priori* regions of interest based on their relation to social cognition in women and men with and without psychotic disorders

Regions	Sex								<i>p</i> -Value		
	Women				Men						
	Controls	Scz	SczA	BP	Controls	Scz	SczA	BP	Group	Sex	Group x Sex
	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)			
Left Hemisphere											
<i>Temporal and Limbic Regions</i>											
Hippocampus	4201 (62)	3837 (87)	4152 (96)	3987 (56)	4169 (64)	4064 (80)	3917 (96)	4199 (92)	0.008	0.54	0.02
Parahippocampal gyrus	2369 (59)	2234 (83)	2151 (92)	2309 (54)	2322 (62)	2182 (77)	2233 (92)	2148 (88)	0.07	0.51	0.53
Fusiform gyrus	10386 (214)	10256 (300)	10009 (332)	10552 (195)	10576 (223)	10512 (276)	9918 (333)	11153 (318)	0.03	0.33	0.68
Middle temporal gyrus	11114 (226)	11084 (317)	10738 (351)	10830 (206)	11178 (235)	11286 (291)	9686 (351)	11214 (336)	0.009	0.70	0.12
Amygdala	1579 (34)	1469 (48)	1543 (53)	1527 (31)	1587 (36)	1649 (44)	1621 (53)	1573 (51)	0.79	0.04	0.17
Insula	6369 (104)	6170 (146)	6351 (162)	6278 (95)	6522 (108)	6428 (134)	6429 (162)	6627 (155)	0.59	0.08	0.76
<i>Prefrontal Cortex</i>											
Superior frontal gyrus	22908 (352)	21378 (492)	21039 (545)	22406 (320)	22343 (365)	21743 (453)	21461 (546)	23004 (522)	0.001	0.61	0.39
Middle frontal gyrus	22890 (437)	22051 (612)	20731 (677)	22309 (398)	23355 (454)	22763 (563)	21118 (678)	23383 (648)	0.001	0.19	0.92
Inferior frontal gyrus	10925 (210)	10169 (295)	10520 (326)	10624 (191)	10797 (219)	10638 (271)	10188 (327)	11096 (312)	0.09	0.62	0.32
Orbital frontal cortex	13413 (184)	12976 (258)	12571 (285)	12982 (168)	13330 (191)	13133 (237)	13297 (286)	13587 (273)	0.20	0.09	0.20

Regions	Sex								p-Value		
	Women				Men						
	Controls	Scz	SczA	BP	Controls	Scz	SczA	BP	Group	Sex	Group x Sex
M (SE)	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)				
Right Hemisphere											
Temporal and Limbic Regions											
Hippocampus	4270 (62)	3914 (88)	4199 (97)	4072 (57)	4264 (65)	4053 (81)	4055 (97)	4222 (93)	0.001	0.63	0.27
Parahippocampal gyrus	2183 (49)	2015 (69)	2123 (76)	2081 (45)	2179 (51)	2163 (63)	1989 (76)	2080 (73)	0.10	0.97	0.23
Fusiform gyrus	9771 (185)	9662 (259)	9237 (287)	9782 (168)	10224 (192)	9754 (238)	9342 (287)	10887 (274)	0.001	0.04	0.09
Middle temporal gyrus	12405 (244)	11982 (341)	12292 (378)	12239 (222)	12820 (253)	12324 (314)	11463 (378)	12804 (361)	0.07	0.65	0.17
Amygdala	1706 (39)	1637 (54)	1692 (60)	1664 (35)	1710 (40)	1721 (50)	1721 (60)	1698 (57)	0.86	0.39	0.84
Insula	6588 (114)	6445 (160)	6391 (177)	6412 (104)	6723 (119)	6763 (147)	6483 (178)	6445 (170)	0.20	0.27	0.77
Prefrontal Cortex											
Superior frontal gyrus	21706 (345)	20677 (483)	21580 (314)	20315 (534)	22047 (358)	20606 (444)	22814 (512)	20917 (535)	0.001	0.18	0.45
Middle frontal gyrus	23688 (427)	22568 (598)	21419 (662)	22820 (389)	23470 (444)	22963 (550)	21316 (663)	23496 (634)	0.001	0.70	0.77
Inferior frontal gyrus	11359 (193)	10422 (271)	10927 (299)	10956 (176)	11288 (201)	10952 (249)	10647 (300)	11670 (287)	0.007	0.31	0.13
Orbital frontal cortex	13174 (201)	13009 (282)	13010 (312)	13087 (183)	13509 (209)	12956 (259)	13162 (312)	13621 (299)	0.33	0.29	0.66

L, left; R, right; Scz, schizophrenia; SczA, schizoaffective; BP, psychotic bipolar.

All analyses adjusted for age, race, and total intracranial volume.

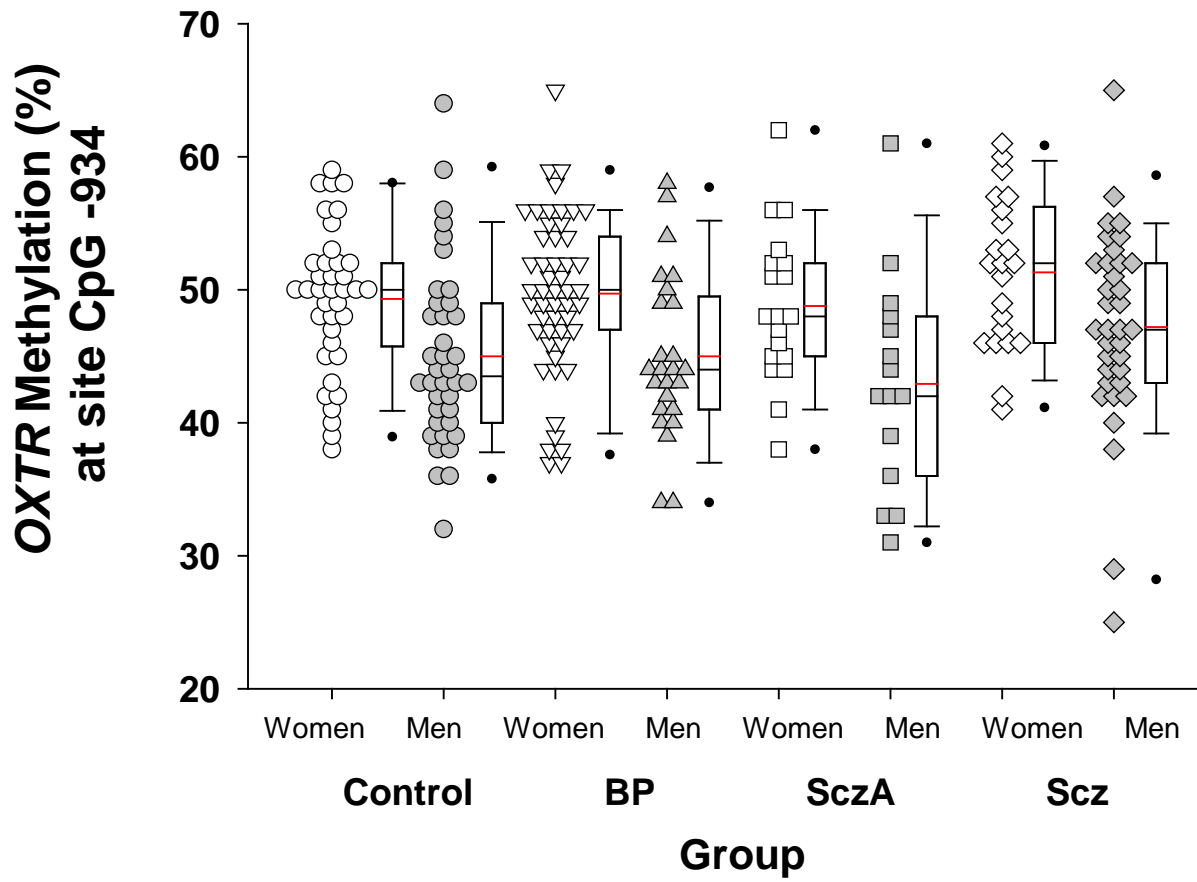


Figure S1. Raw *OXTR* DNA methylation levels as a function of group and sex. Scz, schizophrenia; SczA, schizoaffective; BP, psychotic bipolar. Red line is the mean.

Table S3. Partial correlations between OXTR DNA methylation and peripheral oxytocin levels in women and men with and without psychotic disorders

Group	Sex	
	Women <i>r</i>	Men <i>r</i>
Controls	-0.17	-0.35 ^T
Patients	0.23*	-0.24*
Schizophrenia	0.37	-0.27
Schizoaffective	-0.09	-0.50 ^T
Bipolar	0.26 ^T	-0.14

** $p < 0.01$; * $p < 0.05$; ^T $p > 0.05$ and $p < 0.10$.

Adjusted for age and race.

Table S4. Partial correlations (r) between peripheral oxytocin and regional brain volumes in women and men with and without psychotic disorders for *a priori* regions of interest based on their relation to social cognition

Region	OT Levels							
	Women				Men			
	Controls ($n = 35$)	Scz ($n = 17$)	SczA ($n = 13$)	BP ($n = 41$)	Controls ($n = 33$)	Scz ($n = 22$)	SczA ($n = 13$)	BP ($n = 16$)
Left Hemisphere								
<i>Temporal and Limbic Regions</i>								
Hippocampus	0.40*	-0.02	0.33	0.38*	-0.14	-0.31	-0.50	-0.10
Parahippocampal gyrus	-0.04	0.04	-0.32	0.21	-0.44*	0.32	-0.44	0.11
Fusiform gyrus	-0.24	0.39	0.40	-0.04	-0.07	0.09	-0.16	-0.36
Middle temporal gyrus	-0.28	0.32	-0.28	-0.17	-0.13	-0.14	-0.36	0.47
Amygdala	0.17	0.11	0.11	0.05	-0.08	-0.12	0.31	0.20
Insula	-0.21	0.19	0.25	-0.07	-0.11	-0.17	-0.68*	-0.19
<i>Prefrontal Cortex</i>								
Superior frontal gyrus	-0.04	0.16	0.49	-0.14	0.14	-0.07	0.05	0.42
Middle frontal gyrus	-0.18	0.35	-0.03	-0.22	-0.26	-0.08	0.35	0.23
Inferior frontal gyrus	0.06	-0.07	0.55	-0.14	-0.18	-0.08	-0.31	0.38
Orbital frontal cortex	0.16	0.21	-0.09	-0.07	-0.16	0.19	-0.39	0.39
Right Hemisphere								
<i>Temporal and Limbic Regions</i>								
Hippocampus	0.19	0.07	0.25	0.40*	0.07	-0.17	-0.43	-0.49
Parahippocampal gyrus	0.04	-0.34	0.13	0.21	-0.44*	0.31	0.32	0.11
Fusiform gyrus	-0.51*	0.57*	0.73*	-0.28 ^T	-0.12	-0.12	0.18	0.03

Region	OT Levels							
	Women				Men			
	Controls (n = 35)	Scz (n = 17)	SczA (n = 13)	BP (n = 41)	Controls (n = 33)	Scz (n = 22)	SczA (n = 13)	BP (n = 16)
Middle temporal gyrus	-0.17	0.36	0.04	-0.01	-0.13	0.02	-0.70*	0.01
Amygdala	-0.12	0.12	-0.06	0.09	0.11	-0.21	0.13	-0.33
Insula	-0.01	0.37	0.67*	-0.11	-0.05	-0.17	-0.47	0.09
<i>Prefrontal Cortex</i>								
Superior frontal gyrus	0.04	0.18	0.02	-0.11	-0.20	-0.04	-0.04	0.49
Middle frontal gyrus	0.01	0.30	0.77*	-0.22	-0.13	-0.18	0.05	0.12
Inferior frontal gyrus	-0.02	0.26	0.22	-0.22	-0.01	0.01	0.04	0.41
Orbital frontal cortex	0.13	0.11	0.06	-0.28 ^T	-0.19	0.12	-0.49	0.29

** $p < 0.01$; * $p < 0.05$; ^T $p > 0.05$ and $p \leq 0.09$.

Scz, schizophrenia; SczA, schizoaffective; BP, psychotic bipolar.

Adjusted for age, race, and total intracranial volume. In multivariable regression analyses, in women, the association between peripheral OT levels and brain regions differed by group, with significant peripheral OT level x group interactions in some brain regions. Specifically, an OT level x group interaction was observed in the right fusiform gyrus ($p = 0.004$). This interaction was driven by effects in all patient groups, with the exception of females with schizophrenia. Higher peripheral levels of OT were associated with smaller volumes in the right fusiform gyrus in healthy controls ($\beta = -0.36$, $p = 0.004$) and females with schizoaffective ($\beta = 0.66$, $p = 0.01$) and psychotic bipolar disorder [trend, $\beta = -0.23$, $p = 0.06$]. In men, an OT levels x group interaction was significant in the right parahippocampal gyrus ($p = 0.01$) with a similar trend in the left parahippocampal gyrus ($p = 0.06$). These associations were driven primarily by the male controls in whom higher levels of OT were associated with smaller volumes in the right ($\beta = -0.51$, $p = 0.004$) and left parahippocampal gyri ($\beta = -0.54$, $p = 0.002$).