

Supplementary Tables and Figures

Table S1. Demographics by Biotype

Table S2. Concomitant Medications

Table S3. PCA Loadings

Table S4. TwoStep Cluster Results

Table S5. Discriminant Function Loadings for Cognitive Control and Sensorimotor Reactivity

Table S6. Jackknife Classification Results

Table S7. Clinical Characteristics by DSM Diagnosis

Table S8. Regions of Gray Matter Volume Reduction in Probands and Relatives

Figure S1. Biotype Creation Flow Diagram

Figure S2. Gap Statistic Results

Figure S3. Biotypes versus DSM Scatter

Figure S4. Relatives by Diagnosis on Cognitive Control and Sensorimotor Reactivity

Supplementary Table 1. Demographics

	Proband by Biotype			Relatives by Proband Biotype			Healthy (n=279)
	1 (n=198)	2 (n=235)	3 (n=278)	1 (n=228)	2 (n=277)	3 (n=359)	
Age mean (SD)	37.4 (13.5)	35.8 (11.8)	35.2 (12.4)	40.1 (15.3)	41.0 (15.8)	42.0 (15.9)	36.5 (12.7)
Female %	47.5	51.9	46.8	64.0	67.9	67.4	53.8
Hispanic %	11.1	9.4	5.4	13.6	8.7	6.1	8.5
Race %							
African American	50.5	32.3	28.1	48.7	28.2	22.0	28.8
Native American	0.5	0.0	0.0	1.3	0.0	0.0	0.7
Asian	1.0	3.4	1.8	0.4	2.2	1.4	5.5
White	42.4	60.	65.1	46.1	67.5	71.6	61.7
Mixed	3.0	1.3	3.6	0.9	1.1	2.5	1.3
Other	2.5	2.1	1.4	2.6	1.1	2.5	2.0
Native Hawaiian	0.0	0.0	0.0	0.0	0.0	0.0	0.2
Marital Status %							
Never married	70.2	66.4	66.2	46.5	41.5	39.8	54.9
Ever married	29.3	33.2	33.8	51.8	56.7	59.1	40.5
Unknown	0.5	0.4	0.0	1.8	1.8	1.1	4.6
Education years mean (SD)	12.3 (2.1)	13.0 (2.3)	14.0 (2.7)	13.5 (2.7)	13.8 (2.5)	14.6 (2.7)	14.8 (2.5)
Hollingshead % (Family)							
Class I	4.0	5.1	6.1	3.1	2.9	7.0	6.5
Class II	15.2	23.0	31.7	11.0	20.2	25.6	21.1
Class III	26.8	28.1	29.1	31.1	30.3	29.5	34.0
Class IV	24.2	20.4	19.1	27.6	25.3	23.1	20.5
Class V	13.1	11.1	5.4	11.8	10.1	5.6	5.2
Unknown	16.7	12.3	8.6	15.4	11.2	9.2	12.6
Handedness							
Left	14.7	11.1	12.6	13.2	10.1	8.6	9.6
Right	81.3	86.4	84.2	83.3	86.3	89.1	82.6
Both	2.5	1.3	2.2	1.8	1.8	0.8	1.3
Unknown	1.5	1.3	1.1	1.8	1.8	1.4	6.5

Supplementary Table 2. Concomitant Medications

Medication status, n (%)	Proband by Biotype			Relatives by Proband Biotype		
	1 (n=194)	2 (n=235)	3 (n=275)	1 (n=218)	2 (n=273)	3 (n=348)
Off Any Medication	0 (0.0)	9 (3.8)	10 (3.6)	66 (30.3)	82 (30.0)	95 (27.3)
Off Psychotropic Medications	2 (1.0)	15 (6.4)	22 (8.0)	153 (70.2)	193 (70.7)	245 (70.4)
On >1 Psychotropic Medication	165 (85.1)	182 (77.5)	199 (72.4)	39 (17.9)	42 (15.4)	44 (12.6)
Antipsychotics (Any)	181 (93.3)	203 (86.4)	217 (78.9)	28 (12.8)	25 (9.2)	26 (7.5)
First Generation	30 (15.5)	17 (7.2)	23 (8.4)	3 (1.4)	4 (1.5)	1 (0.3)
Second Generation	151 (77.8)	185 (78.7)	194 (70.6)	25 (11.5)	21 (7.7)	25 (7.2)
Mood Stabilizers (Any)	84 (43.3)	104 (44.3)	131 (47.6)	20 (9.2)	21 (7.7)	22 (6.3)
Lithium	19 (9.8)	31 (13.2)	41 (14.9)	3 (1.4)	7 (2.6)	6 (1.7)
Anticonvulsants	65 (33.5)	73 (31.1)	90 (32.7)	17 (7.8)	14 (5.1)	16 (4.6)
Antidepressants (Any)	85 (43.8)	108 (46.0)	125 (45.5)	37 (17.0)	56 (20.5)	69 (19.8)
SSRIs, SNRIs	53 (27.3)	65 (27.7)	71 (25.8)	29 (13.3)	41 (15.0)	49 (14.1)
Tricyclic	1 (0.5)	8 (3.4)	3 (1.1)	2 (0.9)	2 (0.7)	2 (0.6)
MAO Inhibitors	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Miscellaneous	31 (16.0)	35 (14.9)	51 (18.6)	6 (2.8)	13 (4.8)	18 (5.2)
Anxiolytics/Sedatives/Hypnotics	57 (29.4)	66 (28.1)	67 (24.4)	17 (7.8)	23 (8.4)	38 (10.9)
Anticholinergic/Antiparkinsonian	46 (23.7)	23 (9.8)	33 (12.0)	4 (1.8)	3 (1.1)	2 (0.6)
Stimulants	12 (6.2)	10 (4.3)	25 (9.1)	9 (4.1)	7 (2.6)	7 (2.0)
Miscellaneous Psychotropic/Centrally Active	2 (1.0)	8 (3.4)	7 (2.6)	3 (1.4)	5 (1.8)	3 (0.9)

Concomitant medication data are presented based on subjects' reports and available clinical information. Missing concomitant medication data, (n) %: Proband: Biotype 1, 4 (2.0); Biotype 3, 3 (1.1); Relatives: Biotype 1, 10 (4.4); Biotype 2, 4 (1.4); Biotype 3, 11 (3.1)

Supplementary Table 3. PCA Loadings

ERP Variables Pattern Matrix					
	Component				
	N100	P300	Paired S2	Intrinsic	P200
Paired Stimuli - S1 (N100 ERP)	-.819	.186	.247	.033	.015
Oddball - Targets2 (N100 ERP)	-.801	-.174	-.154	.122	.258
Oddball - Standards (N100 ERP)	-.779	-.200	-.086	.080	.293
Paired Stimuli – S1 (low early latency)	.717	-.148	-.179	.135	.243
Oddball - Targets1 (low 20-100ms)	.669	.253	.070	.078	-.131
Oddball - Standards (beta 20-100ms)	.530	.170	.054	.336	-.002
Oddball - Standards (low 30-480ms)	.449	.430	.053	.118	.169
Oddball - Targets2 (low 140-280ms)	-.016	.838	-.014	-.076	.085
Oddball - Targets2 (low 280-400ms)	.029	.784	-.077	-.098	.071
Oddball - Targets1 (P3a ERP)	.000	-.679	.063	.030	.042
Oddball - Targets1 (low 190-440ms)	.166	.652	.040	-.024	.037
Oddball - Targets2 (beta 180-240ms)	-.021	.544	-.048	.324	-.003
Oddball - Targets1 (beta 140-230ms)	.070	.488	-.001	.338	.054
Paired Stimuli - S2 (late ERP)	.058	-.019	.831	-.053	.132
Paired Stimuli - preS2	-.113	-.083	.723	.104	-.199
Paired Stimuli - S2 (P50 ERP)	-.157	-.076	.698	.294	-.062
Paired Stimuli - S2 (P200 ERP)	.101	-.047	.687	-.144	.375
Paired Stimuli - S2 (N100 ERP)	-.073	-.036	.653	.116	.426
Paired Stimuli - S1 (N200 ERP)	.027	.064	.576	-.099	-.014
Oddball - Standards (gamma 480-520ms)	-.086	.007	.121	.666	-.147
Paired Stimuli – S2 (beta late)	-.021	.011	-.010	.615	-.001
Paired Stimuli - preS1 (gamma)	-.069	-.127	.055	.566	-.169
Oddball – Targets2 (gamma 20-70ms)	.129	.071	-.025	.515	.035
Oddball – Standards (beta 30-70ms)	.211	.100	.061	.497	.065
Oddball – Standards (beta 230-270ms)	.077	.324	-.065	.454	.105
Paired Stimuli – S1 (beta early)	.424	-.111	-.110	.450	.174
Oddball – Standards (P200 ERP)	.013	.118	.176	-.026	.754
Oddball – Targets2 (P200 ERP)	-.445	-.094	-.013	.103	.685
Paired Stimuli - S1 (P200 ERP)	.410	-.075	.248	-.245	.597
Oddball Targets2 (N200 ERP)	-.357	.416	-.060	-.115	.575
Paired Stimuli – S1 (low midlatency)	.376	-.020	-.257	.077	.433

Stop Signal Task Pattern Matrix	
	Stop Signal Task
Proportion Errors	-.860
Go RT Difference	.860

Saccade Tasks Pattern Matrix		
	Component	
	Saccade Latency	Antisaccade Errors
Antisaccade Error Rate	-.076	.969
Antisaccade Error Latency	.663	-.423
Prosaccade No Gap Latency	.894	-.035
Prosaccade Gap Latency	.880	-.062
Prosaccade Overlap Latency	.856	-.147

Supplementary Table 4: TwoStep Cluster Results for Determining Number of Clusters. Red shows the solution with the lowest Schwarz's Bayesian Information Criterion (BIC) and the greatest separation between clusters (3 cluster row).

Number of Clusters	(BIC)	BIC Change ^a	Ratio of BIC Changes ^b	Ratio of Distance Measures ^c
1	2303.222			
2	2230.353	-72.868	1.000	1.286
3	2197.199	-33.155	.455	1.533
4	2212.269	15.071	-.207	1.373
5	2251.915	39.646	-.544	1.062
6	2295.391	43.476	-.597	1.507
7	2359.771	64.379	-.883	1.018
8	2424.884	65.114	-.894	1.062
9	2492.359	67.474	-.926	1.007
10	2560.107	67.748	-.930	1.117

- a. Changes are from the previous number of clusters.
- b. Ratios of changes are relative to the two-cluster solution.
- c. Ratios of distance measures are based on the current number of clusters against the previous number of clusters.

Biomarker Composite Loadings on Discriminant Functions					
	Component		Three SZ Cases by Biotype		
Biomarker Composites	Cognitive Control	Sensorimotor Reactivity	Biotype-1	Biotype-2	Biotype-3
BACS	.82	.05	-3.3	-2.8	-1.0
Stop Signal Task	.33	.03	-2.0	0.1	0.6
Antisaccade Errors	-.24	.09	3.8	3.0	0.8
EEG Intrinsic Activity	-.01	.69	-0.8	0.3	-1.3
ERP N100 Response	.12	.58	-1.8	-0.8	-0.2
ERP Paired S2 Response	.02	-.48	1.2	-1.4	0.3
ERP P300 Response	.14	.47	-2.1	-0.5	-0.1
ERP P200 Response	-.14	.32	-0.7	-0.6	-0.9
Saccade Latency	-.18	-.20	2.0	-1.2	0.4
Cognitive Control			-3.6	-2.0	1.2
Sensorimotor Reactivity			-2.2	0.8	-1.1

Supplementary Table 5. Discriminant Function Loadings. The loadings of the nine biomarker composite variables on the two discriminant functions are shown under the ‘Component’ column. Also displayed are three examples of schizophrenia (SZ) cases that fell into different Biotypes. The effect size differentiation on each of the biomarker composites for each case is shown. The bottom two rows show the ‘Cognitive Control’ and ‘Sensorimotor Reactivity’ values (in standard score units) for the three cases. These values can be translated to the bivariate scatter plots in Supplementary Figure 3. Brief Assessment of Cognition in Schizophrenia (BACS); Electroencephalography (EEG); Event-Related Potential (ERP).

Predicted Biotype Membership

Original Biotype Membership	1	2	3	Total Cases
1	170 (86%)	23 (12%)	5 (2%)	198 (100%)
2	10 (4%)	213 (91%)	12 (5%)	235 (100%)
3	3 (1%)	11 (4%)	264 (95%)	278 (100%)

Predicted DSM Diagnosis Membership

Original DSM Dx Membership	SZ	SZAff	BDP	Total Cases
SZ	162 (52%)	79 (25%)	71 (23%)	312 (100%)
SZAff	72 (41%)	46 (27%)	55 (32%)	173 (100%)
BDP	54 (24%)	61 (27%)	111 (49%)	226 (100%)

Supplementary Table 6. Jackknife Results. Schizophrenia (SZ); Schizoaffective (SZAff); Bipolar Disorder with Psychosis (BDP).

Supplementary Table 7. Clinical Characteristics by DSM. Schizophrenia (SZ); Schizoaffective (SZAff); Bipolar Disorder with Psychosis (BDP)

Clinical Characteristics	DSM Diagnosis			Statistics		
	SZ	SZAff	BDP	(df)	Value	p
Probands Biotype, (%)						
1	58.6	21.2	20.2	$\chi^2(2)$	25.95	<.001 ^a
2	46.0	26.8	27.2	$\chi^2(2)$	3.50	.17
3	31.7	24.5	43.9	$\chi^2(2)$	36.46	<.001 ^b
Schizo-Bipolar Scale, mean (SD)	7.9 (1.2)	5.1 (1.5)	1.1 (1.1)	F(2,687)	1943.63	p<.001 ^c
Probands Clinical Symptom Ratings, mean (SD)						
PANSS Positive Subscale	16.7 (5.8)	17.9 (5.2)	12.9 (3.9)	F(2,692)	51.71	<.001 ^d
PANSS Negative Subscale	16.7 (6.0)	15.8 (5.0)	12.0 (3.9)	F(2,692)	56.92	<.001 ^e
MADRS	8.2 (7.9)	14.7 (10.3)	10.2 (9.3)	F(2,687)	28.70	<.001 ^f
Young Mania Rating Scale	5.5 (5.8)	7.1 (6.5)	5.8 (6.7)	F(2,688)	3.60	.03 ^g
Birchwood Social Functioning Scale, mean (SD) (Healthy, Mean = 154.8; SD=17.8)						
Probands	120.8 (24.4)	118.4 (25.1)	134.3 (22.6)	F(3,885)	120.30	<.001 ^h
Relatives	147.0 (21.4)	141.8 (23.4)	150.3 (21.6)	F(3,979)	17.31	<.001 ⁱ
Relatives Diagnoses, (%)						
Axis I Psychosis	11.5	14.8	8.6	$\chi^2(2)$	4.73	.09
Axis II: Cluster A and/or B Personality Disorders	9.9	11.7	10.0	$\chi^2(2)$	0.62	.73
Psychosis-Related Diagnoses (Axis I Psychosis + Axis II/Cluster A,B, combined)*	21.1	25.7	18.3	$\chi^2(2)$ ^h	4.10	.13

*Axis I Psychosis and % Axis II/Cluster A, B combined % do not exactly sum to % Psychosis and Psychosis-Related illnesses because some relatives have both Axis I Psychosis and Axis II/Cluster A, B. In such cases they are counted once.

^aYates Corrected pair-wise chi square: SZ>SZAff, $\chi^2(1)=7.86$, p=.005; SZ>BDP, $\chi^2(1)=23.22$, p<.001

^bYates Corrected pair-wise chi square: BDP>SZ, $\chi^2(1)=35.52$, p<.001; BDP >SZAff, $\chi^2(1)=7.88$, p=.005; SZ>SZAff, $\chi^2(1)=5.79$, p=.02

^cTukey HSD: SZ>SZAff (p<.001) and BDP (p<.001); SZAff>BDP (p<.001)

^dTukey HSD: BDP<SZ (p<.001) and SZAff (p<.001); SZAff>SZ (p=.04)

^eTukey HSD: BDP<SZ (p<.001) and SZAff (p<.001)

^fTukey HSD: SZAff>SZ (p<.001) and BDP (p<.001); BDP > SZ (p=.03)

^gTukey HSD: SZAff>SZ (p=.02)

^hTukey HSD: SZ<BDP (p<.001) and Healthy (p<.001); SZAff<BDP (p<.001) and Healthy (p<.001); BDP<Healthy (p<.001)

ⁱTukey HSD: SZ<Healthy (p<.001); SZAff<BDP (p<.001) and Healthy (p<.001); BDP<Healthy (p=0.01)

Supplementary Table 8. Regions of gray matter volume reduction in probands and relatives categorized by Biotype contrasted with healthy subjects

Group Comparison	Brain Region	Brodman Area	Gray Matter Volume (Voxels) Left / Right	Maximum <i>t</i> (Talairach coordinates: x, y, z) Left / Right *	Effect size Left / Right †	
Gray matter volume reductions in Biotype proband groups vs. healthy subjects						
Healthy – Biotype1 Probands	<i>Frontal</i>					
	Inferior Frontal Gyrus	9, 10, 11, 13, 44,	6667 / 7081	9.1 (-39, 25, -1) / 10.3 (42, 22, -4)	0.94 / 1.06	
	Middle Frontal Gyrus	6, 8, 9, 10, 11, 46,	4830 / 6904	9.4 (-30, 37, -13) / 10.0 (33, 33, -16)	0.97 / 1.03	
	Medial Frontal Gyrus	6, 8, 9, 10, 11, 25,	6193 / 6133	10.8 (-1, 33, -14) / 11.0 (1, 36, -13)	1.11 / 1.13	
	Superior Frontal Gyrus	6, 8, 9, 10, 11	5511 / 6015	8.6 (-30, 42, -15) / 8.2 (12, 55, -9)	0.89 / 0.85	
	Precentral Gyrus	6, 9, 13, 43, 44	4593 / 4770	7.8 (-42, 3, 7) / 8.3 (45, 5, 9)	0.81 / 0.86	
	Paracentral Lobule	4, 5, 6, 31	593 / 800	6.6 (-3, -11, 46) / 8.4 (6, -15, 44)	0.68 / 0.87	
	Rectal Gyrus	11	237 / 148	9.3 (-1, 33, -19) / 9.2 (3, 34, -21)	0.96 / 0.95	
	Orbital Gyrus	11, 47	148 / 89	8.9 (-3, 40, -20) / 8.6 (4, 44, -19)	0.92 / 0.89	
	<i>Cingulate</i>					
	Cingulate Gyrus	23, 24, 31, 32	4800 / 4533	8.9 (-3, 22, 28) / 9.8 (9, 8, 40)	0.92 / 1.01	
	Anterior Cingulate	10, 24, 25, 32, 33	2459 / 2578	10.1 (-4, 39, -10) / 9.7 (3, 45, -6)	1.04 / 1.00	
	Posterior Cingulate	23, 29, 30, 31	1659 / 1244	8.7 (-1, -60, 14) / 8.9 (4, -56, 17)	0.90 / 0.92	
	<i>Insula</i>					
			13, 22, 40, 41, 47	3615 / 3437	9.1 (-33, 20, 2) / 9.5 (36, 22, 2)	0.94 / 0.98
	<i>Temporal</i>					
	Superior Temporal Gyrus	13, 21, 22, 38, 39,	6756 / 6281	8.7 (-33, 4, -13) / 8.3 (31, 7, -15)	0.90 / 0.86	
	Middle Temporal Gyrus	19, 20, 21, 22, 37,	5096 / 5570	7.9 (-42, 5, -37) / 8.2 (58, 2, -18)	0.82 / 0.85	
	Parahippocampal Gyrus	19, 27, 28, 30, 34,	3378 / 3289	9.5 (-27, -14, -21) / 8.9 (28, -16, -21)	0.98 / 0.92	
	Fusiform Gyrus	18, 19, 20, 36, 37	2163 / 2163	7.1 (-25, -56, -9) / 7.1 (27, -50, -8)	0.73 / 0.73	
Inferior Temporal Gyrus	19, 20, 21, 37	1659 / 1689	7.2 (-42, 0, -37) / 6.4 (42, 0, -35)	0.74 / 0.66		
Uncus	20, 28, 34, 36, 38	1037 / 1007	8.3 (-28, 2, -20) / 8.5 (33, 2, -19)	0.86 / 0.88		
Transverse Temporal	41, 42	444 / 267	8.0 (-48, -26, 12) / 8.5 (58, -20, 13)	0.83 / 0.88		

Parietal

Precuneus	7, 18, 19, 23, 31	3822 / 4652	8.3 (-1, -59, 20) / 8.7 (4, -59, 20)	0.86 / 0.90
Inferior Parietal Lobule	7, 39, 40	1126 / 2696	6.7 (-59, -38, 24) / 7.4 (55, -27, 22)	0.69 / 0.77
Postcentral Gyrus	1, 2, 3, 5, 7, 40, 43	1333 / 1570	6.7 (-50, -25, 15) / 8.2 (58, -22, 16)	0.69 / 0.85
Supramarginal Gyrus	40	89 / 978	4.4 (-53, -39, 30) / 5.6 (43, -46, 37)	0.46 / 0.58
Superior Parietal Lobule	5, 7	296 / 385	4.7 (-16, -61, 60) / 4.5 (24, -52, 58)	0.49 / 0.47
Angular Gyrus	39	0 / 296	- / 5.5 (48, -55, 36)	- / 0.57

Occipital

Cuneus	7, 17, 18, 19, 23,	3911 / 4119	7.5 (-9, -62, 7) / 8.0 (13, -62, 7)	0.76 / 0.83
Lingual Gyrus	17, 18, 19	2815 / 2726	6.7 (-4, -79, 3) / 7.4 (16, -61, 4)	0.69 / 0.77
Middle Occipital Gyrus	18, 19, 37	2370 / 2667	5.9 (-34, -84, 14) / 6.9 (24, -92, 20)	0.61 / 0.71
Inferior Occipital Gyrus	17, 18, 19	504 / 652	5.3 (-28, -94, -8) / 6.1 (27, -86, -7)	0.55 / 0.63
Superior Occipital Gyrus	19, 39	30 / 178	4.5 (-30, -88, 22) / 5.3 (33, -86, 24)	0.47 / 0.55

Basal Ganglia

Caudate	*	444 / 593	5.5 (-4, 10, -6) / 6.1 (4, 10, -4)	0.57 / 0.63
Clastrum	*	326 / 296	8.0 (-28, 19, 2) / 7.8 (30, 19, -1)	0.83 / 0.81
Lentiform Nucleus	*	89 / 119	5.7 (-22, -12, -6) / 5.7 (30, -18, 13)	0.59 / 0.59

Thalamus

	*	1333 / 1304	6.3 (-7, -13, 10) / 5.5 (9, -15, 12)	0.65 / 0.57
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Cerebellum

Culmen	*	2815 / 3437	6.9 (-19, -56, -20) / 7.0 (18, -27, -15)	0.71 / 0.72
Declive	*	1867 / 2756	6.8 (-13, -62, -18) / 6.1 (13, -59, -18)	0.70 / 0.63
Inferior Semi-Lunar	*	830 / 1274	4.9 (-3, -63, -36) / 5.7 (16, -73, -42)	0.51 / 0.59
Uvula	*	385 / 919	4.8 (-3, -66, -33) / 5.1 (33, -62, -23)	0.50 / 0.53
Tuber	*	0 / 415	- / 4.8 (31, -57, -27)	- / 0.50
Pyramis	*	119 / 385	3.7 (-27, -60, -29) / 4.5 (27, -60, -27)	0.38 / 0.47
Cerebellar Tonsil	*	119 / 385	4.0 (-3, -57, -36) / 4.4 (7, -57, -41)	0.41 / 0.45
Uvula of Vermis	*	119 / 89	5.0 (0, -69, -33) / 4.9 (3, -66, -33)	0.52 / 0.51
Declive of Vermis	*	59 / 119	4.0 (-1, -72, -15) / 4.4 (1, -69, -15)	0.41 / 0.46
Culmen of Vermis	*	89 / 89	5.7 (-3, -61, 2) / 5.9 (6, -61, 1)	0.59 / 0.61

Fastigium	*	59 / 59	5.5 (-9, -55, -19) / 5.5 (9, -56, -19)	0.57 / 0.57
Pyramis of Vermis	*	30 / 30	3.7 (0, -71, -30) / 3.1 (3, -71, -28)	0.38 / 0.32

**Healthy –
Biotype2
Probands**

Frontal

Inferior Frontal Gyrus	6, 9, 10, 11, 13, 25,	5926 / 6193	8.2 (-39, 19, -2) / 8.5 (43, 19, -5)	0.80 / 0.83
Superior Frontal Gyrus	6, 8, 9, 10, 11	5600 / 5896	7.1 (-27, 52, -4) / 7.1 (10, 57, -1)	0.69 / 0.69
Middle Frontal Gyrus	6, 8, 9, 10, 11, 46,	5096 / 5719	7.4 (-30, 36, -14) / 6.6 (33, 34, -16)	0.72 / 0.64
Medial Frontal Gyrus	6, 8, 9, 10, 11, 25,	5333 / 5570	8.2 (-12, 47, 16) / 7.5 (4, 55, 15)	0.80 / 0.73
Precentral Gyrus	6, 9, 13, 42, 43, 44	2548 / 3585	6.9 (-46, -11, 9) / 7.5 (43, 3, 8)	0.67 / 0.73
Paracentral Lobule	4, 5, 6, 31	296 / 533	4.9 (-7, -24, 43) / 6.6 (9, -18, 44)	0.48 / 0.64
Rectal Gyrus	11	237 / 148	5.8 (-4, 32, -21) / 5.5 (3, 24, -19)	0.56 / 0.53
Orbital Gyrus	11	148 / 119	7.4 (-4, 43, -21) / 5.9 (3, 51, -20)	0.72 / 0.57

Cingulate

Cingulate Gyrus	23, 24, 31, 32	4030 / 4178	6.0 (-6, 23, 28) / 7.5 (9, -24, 37)	0.58 / 0.73
Anterior Cingulate	10, 24, 25, 32, 33	2548 / 2193	7.6 (-9, 48, -2) / 7.2 (7, 45, -5)	0.74 / 0.70
Posterior Cingulate	23, 29, 30, 31	1659 / 1333	7.1 (-9, -58, 11) / 7.5 (10, -55, 8)	0.69 / 0.73

Insula

	13, 22, 41	3467 / 3763	8.4 (-36, 18, 1) / 8.3 (43, 3, 3)	0.82 / 0.81
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Temporal

Superior Temporal Gyrus	13, 21, 22, 38, 39,	6993 / 6311	8.2 (-55, -17, 9) / 8.1 (52, -1, 3)	0.80 / 0.79
Middle Temporal Gyrus	19, 20, 21, 22, 37,	5719 / 5630	7.3 (-56, -11, -10) / 6.9 (62, -35, 3)	0.71 / 0.67
Parahippocampal Gyrus	19, 27, 28, 30, 34,	3378 / 3259	6.8 (-24, -44, -10) / 6.5 (24, -48, -8)	0.67 / 0.63
Fusiform Gyrus	18, 19, 20, 37	2607 / 1985	6.9 (-27, -54, -9) / 6.8 (24, -62, -8)	0.67 / 0.66
Inferior Temporal Gyrus	19, 20, 21, 37	1807 / 1600	5.8 (-39, 0, -37) / 5.7 (39, -19, -29)	0.56 / 0.55
Uncus	20, 28, 34, 36, 38	1037 / 948	6.4 (-34, -13, -28) / 6.2 (36, -16, -28)	0.62 / 0.60
Transverse Temporal	41, 42	385 / 356	8.4 (-55, -21, 11) / 7.9 (58, -21, 13)	0.82 / 0.77

Parietal

Precuneus	7, 19, 23, 31, 39	3141 / 3407	5.9 (0, -63, 24) / 6.8 (4, -59, 18)	0.57 / 0.66
Postcentral Gyrus	2, 3, 40, 43	681 / 1393	6.3 (-61, -24, 14) / 7.1 (55, -24, 14)	0.61 / 0.69
Inferior Parietal Lobule	7, 39, 40	1244 / 1807	7.0 (-58, -40, 24) / 6.3 (59, -27, 22)	0.68 / 0.61

Supramarginal Gyrus	40	563 / 800	5.9 (-58, -41, 30) / 5.8 (58, -54, 29)	0.57 / 0.56
Angular Gyrus	39	237 / 356	3.8 (-48, -71, 33) / 5.8 (53, -61, 31)	0.37 / 0.56
Superior Parietal Lobule	7	59 / 296	3.4 (-39, -69, 45) / 5.3 (30, -68, 45)	0.33 / 0.51
<i>Occipital</i>				
Lingual Gyrus	17, 18, 19, 30	2578 / 2785	7.1 (-24, -72, -9) / 6.3 (13, -52, 3)	0.69 / 0.61
Middle Occipital Gyrus	18, 19, 37	2133 / 2607	6.0 (-46, -66, -8) / 6.6 (31, -85, 19)	0.58 / 0.64
Cuneus	7, 17, 18, 19, 23,	2193 / 2281	6.5 (-9, -61, 9) / 6.7 (12, -59, 8)	0.63 / 0.65
Inferior Occipital Gyrus	17, 18, 19	504 / 711	5.4 (-42, -77, -5) / 6.2 (28, -85, -7)	0.52 / 0.60
Superior Occipital Gyrus	19, 39	385 / 326	4.4 (-33, -76, 31) / 6.3 (34, -85, 22)	0.43 / 0.61
<i>Basal Ganglia</i>				
Clastrum	*	326 / 296	7.0 (-33, -23, 8) / 6.2 (34, 0, 8)	0.68 / 0.60
Caudate	*	59 / 89	4.4 (-36, -27, -6) / 4.4 (6, 11, -4)	0.43 / 0.43
Lentiform Nucleus	*	0 / 30	- / 3.7 (30, -20, 9)	- / 0.36
<i>Thalamus</i>				
	*	859 / 1096	6.1 (-3, -10, 2) / 6.1 (3, -10, 1)	0.59 / 0.59
<i>Cerebellum</i>				
Culmen	*	3319 / 3556	6.6 (-22, -40, -11) / 6.1 (33, -52, -19)	0.64 / 0.59
Declive	*	3200 / 3289	6.1 (-25, -65, -12) / 6.1 (27, -65, -11)	0.59 / 0.59
Inferior Semi-Lunar	*	1511 / 1215	5.0 (-22, -69, -42) / 5.2 (25, -78, -40)	0.49 / 0.50
Uvula	*	978 / 919	4.5 (-4, -64, -33) / 4.9 (6, -70, -32)	0.44 / 0.48
Pyramis	*	504 / 859	3.9 (0, -67, -24) / 4.8 (21, -75, -34)	0.38 / 0.47
Cerebellar Tonsil	*	326 / 770	4.2 (-28, -38, -33) / 5.0 (31, -40, -33)	0.41 / 0.49
Tuber	*	296 / 533	4.3 (-36, -61, -23) / 4.7 (39, -61, -23)	0.42 / 0.46
Declive of Vermis	*	89 / 119	5.6 (-1, -69, -15) / 6.0 (1, -69, -13)	0.54 / 0.58
Uvula of Vermis	*	89 / 59	4.5 (-1, -67, -33) / 4.5 (1, -64, -33)	0.44 / 0.44
Culmen of Vermis	*	30 / 89	4.7 (-1, -66, -8) / 4.9 (6, -61, -1)	0.46 / 0.48
Pyramis of Vermis	*	59 / 59	4.5 (-1, -71, -28) / 4.7 (1, -71, -30)	0.44 / 0.46
Fastigium	*	30 / 59	3.3 (-10, -61, -21) / 4.4 (7, -56, -19)	0.32 / 0.43
Nodule	*	0 / 59	- / 3.6 (1, -48, -29)	- / 0.35
Tuber of Vermis	*	30 / 30	4.4 (-3, -71, -24) / 4.7 (1, -71, -25)	0.43 / 0.46

Healthy – Biotype3 Probands					
	<i>Frontal</i>				
	Medial Frontal Gyrus	6, 8, 9, 10, 11, 25,	2578 / 3615	5.5 (-3, 49, -4) / 6.3 (3, 37, -13)	0.51 / 0.58
	Inferior Frontal Gyrus	9, 10, 13, 44, 45,	1600 / 3141	5.2 (-39, 22, -4) / 6.0 (43, 19, -3)	0.48 / 0.55
	Middle Frontal Gyrus	9, 10, 11, 46	1689 / 2015	4.9 (-30, 34, -14) / 4.8 (43, 13, 27)	0.45 / 0.44
	Superior Frontal Gyrus	9, 10, 11	1156 / 1007	5.1 (-27, 52, -4) / 4.7 (13, 55, -8)	0.47 / 0.43
	Precentral Gyrus	6, 9, 13, 43, 44	267 / 859	4.1 (-55, -10, 10) / 6.3 (50, -8, 6)	0.38 / 0.58
	Paracentral Lobule	31	148 / 237	4.1 (-6, -17, 44) / 5.3 (7, -15, 44)	0.38 / 0.49
	Orbital Gyrus	11	59 / 89	4.6 (-3, 41, -21) / 5.0 (3, 41, -20)	0.42 / 0.46
	Rectal Gyrus	11	30 / 89	3.9 (-4, 35, -21) / 5.3 (3, 35, -19)	0.36 / 0.49
	<i>Cingulate</i>				
	Cingulate Gyrus	23, 24, 31, 32	2489 / 3022	5.0 (-9, 18, 34) / 6.2 (10, -14, 41)	0.46 / 0.57
	Anterior Cingulate	10, 24, 25, 32	1719 / 1333	5.3 (-4, 52, -1) / 5.8 (3, 47, 0)	0.49 / 0.53
	Posterior Cingulate	23, 29, 30, 31	563 / 1037	4.6 (-1, -60, 17) / 5.2 (3, -60, 17)	0.42 / 0.48
	<i>Insula</i>				
		13, 22, 47	1926 / 2193	4.7 (-33, 22, 2) / 6.3 (42, 3, 4)	0.43 / 0.58
	<i>Temporal</i>				
	Superior Temporal Gyrus	13, 21, 22, 38, 41,	1926 / 4148	4.9 (-55, -8, 6) / 6.5 (50, -6, 3)	0.45 / 0.60
	Parahippocampal Gyrus	19, 28, 30, 34, 35,	1422 / 1778	4.9 (-28, 4, -17) / 5.1 (25, 5, -17)	0.45 / 0.47
	Middle Temporal Gyrus	21, 22, 38	30 / 1541	3.2 (-50, 6, -23) / 5.1 (49, 0, -26)	0.30 / 0.47
	Uncus	20, 28, 34, 36	267 / 741	4.5 (-28, 1, -19) / 5.8 (28, 5, -19)	0.42 / 0.53
	Transverse Temporal	41, 42	326 / 148	4.5 (-50, -24, 11) / 5.0 (56, -18, 12)	0.42 / 0.46
	Inferior Temporal Gyrus	20, 21	0 / 207	- / 4.1 (49, -3, -29)	- / 0.38
	Fusiform Gyrus	20	0 / 89	- / 4.4 (49, -3, -24)	- / 0.41
	<i>Parietal</i>				
	Precuneus	23, 31	444 / 681	4.5 (0, -64, 24) / 5.0 (1, -63, 20)	0.42 / 0.46
	Inferior Parietal Lobule	40	444 / 178	4.3 (-52, -43, 23) / 3.8 (53, -27, 23)	0.40 / 0.35
	Postcentral Gyrus	40, 43	89 / 178	3.9 (-53, -9, 16) / 4.2 (56, -24, 14)	0.36 / 0.39
	Supramarginal Gyrus	40	30 / 30	3.4 (-55, -45, 23) / 3.9 (55, -46, 22)	0.31 / 0.36

Occipital

Lingual Gyrus	17, 18, 19, 30	237 / 859	3.5 (-3, -81, 3) / 4.8 (13, -51, 4)	0.32 / 0.44
Cuneus	17, 18, 23, 30	593 / 622	3.8 (-13, -69, 16) / 4.7 (13, -59, 8)	0.35 / 0.43

Basal Ganglia

Clastrum	*	178 / 89	4.0 (-33, 6, 4) / 3.7 (30, 17, -1)	0.37 / 0.34
Caudate	*	30 / 30	3.6 (-33, -25, -6) / 3.4 (34, -25, -3)	0.33 / 0.31
Lentiform Nucleus	*	0 / 30	- / 3.6 (21, -9, -6)	- / 0.33

Cerebellum

Culmen	*	30 / 237	3.4 (-19, -28, -15) / 3.9 (18, -40, -7)	0.31 / 0.36
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Gray matter volume reductions in Biotype relative groups vs. healthy subjects**Healthy –
Biotype1
Relatives*****Frontal***

Medial Frontal Gyrus	10, 11, 25	1185 / 444	4.4 (-3, 26, -13) / 4.4 (3, 31, -13)	0.45 / 0.45
Inferior Frontal Gyrus	11, 13, 47	89 / 1067	3.9 (-28, 8, -18) / 4.4 (25, 18, -16)	0.40 / 0.45
Superior Frontal Gyrus	10	237 / 0	3.7 (-9, 59, -7) / -	0.38 / -
Middle Frontal Gyrus	11	30 / 30	3.2 (-42, 22, 22) / 3.5 (25, 24, -16)	0.30 / 0.32

Cingulate

Anterior Cingulate	10, 24, 25, 32	1511 / 356	4.7 (-3, 29, -10) / 4.1 (1, 19, -7)	0.43 / 0.38
Posterior Cingulate	18, 23, 29, 30, 31	919 / 770	4.2 (-19, -59, 11) / 4.5 (9, -56, 10)	0.39 / 0.42
Cingulate Gyrus	24, 31, 32	919 / 296	4.8 (-13, -10, 42) / 4.0 (9, -6, 35)	0.44 / 0.37

Insula

13	444 / 0	3.7 (-34, 8, 7) / -	0.34 / -
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Temporal

Parahippocampal Gyrus	28, 30, 34, 35, 36,	1600 / 1837	5.9 (-30, -13, -22) / 5.1 (31, -13, -22)	0.54 / 0.47
Middle Temporal Gyrus	20, 21, 38	978 / 30	5.1 (-42, 2, -23) / 3.2 (49, -11, -11)	0.47 / 0.30
Uncus	20, 28, 36	593 / 385	4.6 (-30, -1, -21) / 3.8 (22, -7, -22)	0.42 / 0.35
Superior Temporal Gyrus	38	593 / 148	4.8 (-45, 5, -22) / 3.9 (33, 4, -17)	0.44 / 0.36
Fusiform Gyrus	20, 37	30 / 178	4.4 (-42, -3, -23) / 4.1 (27, -34, -15)	0.41 / 0.38

	Inferior Temporal Gyrus	*	59 / 0	3.7 (-33, -1, -42) / -	0.38 / -	
	<i>Parietal</i>					
	Precuneus	31	30 / 30	3.1 (-10, -65, 18) / 3.5 (6, -73, 22)	0.31 / 0.36	
	<i>Occipital</i>					
	Cuneus	18, 30	504 / 504	4.3 (-16, -71, 16) / 4.8 (15, -62, 6)	0.44 / 0.49	
	Lingual Gyrus	18, 19	178 / 415	3.6 (-13, -52, 5) / 4.4 (15, -58, 4)	0.37 / 0.45	
	<i>Basal Ganglia</i>					
	Clastrum	*	30 / 0	3.3 (-30, 3, 11) / -	0.33 / -	
	<i>Cerebellum</i>					
	Culmen	*	30 / 119	3.2 (-19, -33, -12) / 3.5 (27, -32, -19)	0.32 / 0.36	
Healthy – Biotype2 Relatives	<i>Cingulate</i>					
		Posterior Cingulate	23, 29, 30, 31	0 / 770	- / 4.2 (10, -58, 10)	- / 0.40
		<i>Temporal</i>				
		Parahippocampal Gyrus	19, 30, 35, 36, 37	59 / 652	3.6 (-24, -36, -13) / 4.7 (21, -56, -6)	0.34 / 0.45
		Fusiform Gyrus	19, 20, 37	504 / 415	4.2 (-43, -56, -17) / 4.5 (24, -63, -7)	0.40 / 0.43
		Uncus	20	0 / 59	- / 3.6 (34, -19, -27)	- / 0.34
		<i>Parietal</i>				
		Precuneus	*	0 / 30	- / 3.2 (6, -62, 18)	- / 0.30
		<i>Occipital</i>				
		Lingual Gyrus	18, 19	267 / 711	4.2 (-9, -78, -9) / 4.6 (21, -60, -6)	0.40 / 0.44
		Cuneus	18, 30	0 / 119	- / 4.1 (13, -59, 7)	- / 0.39
		<i>Cerebellum</i>				
		Declive	*	2222 / 2607	4.4 (-9, -58, -17) / 4.4 (9, -65, -13)	0.42 / 0.42
		Culmen	*	1096 / 2281	4.4 (-9, -53, -18) / 4.8 (25, -36, -16)	0.42 / 0.46

Pyramis	*	444 / 652	4.1 (-24, -74, -28) / 3.9 (25, -70, -27)	0.39 / 0.37
Uvula	*	296 / 652	3.9 (-22, -77, -25) / 4.2 (25, -73, -24)	0.37 / 0.40
Inferior Semi-Lunar	*	30 / 652	3.1 (-39, -63, -36) / 3.7 (31, -64, -35)	0.30 / 0.35
Tuber	*	356 / 504	4.0 (-27, -77, -28) / 3.9 (31, -80, -28)	0.38 / 0.37
Cerebellar Tonsil	*	385 / 356	3.5 (-43, -56, -35) / 3.6 (27, -66, -33)	0.33 / 0.34
Declive of Vermis	*	89 / 30	3.9 (-1, -69, -17) / 3.5 (1, -72, -18)	0.37 / 0.33
Culmen of Vermis	*	59 / 30	3.9 (-3, -66, -8) / 3.9 (3, -66, -8)	0.37 / 0.37
Fastigium	*	30 / 30	3.7 (-7, -61, -20) / 3.5 (10, -49, -20)	0.35 / 0.33
Uvula of Vermis	*	0 / 30	- / 3.3 (3, -69, -33)	- / 0.31

**Healthy –
Biotype3
Relatives**

Frontal				
Inferior Frontal Gyrus	*	0 / 30	- / 3.6 (28, 7, -15)	- / 0.32
Temporal				
Parahippocampal Gyrus	28, 34	652 / 504	4.2 (-28, 2, -18) / 4.4 (28, 3, -18)	0.37 / 0.40
Uncus	28, 34	178 / 237	3.7 (-27, -1, -20) / 3.9 (28, 0, -20)	0.33 / 0.35
Superior Temporal Gyrus	38	30 / 30	3.5 (-31, 5, -18) / 4.0 (31, 6, -18)	0.32 / 0.36

Gray matter volume reductions in Biotype relative groups after removing relatives with psychosis-related diagnoses vs. healthy subjects

**Healthy –
Biotype1
Relatives
(All-Psychosis)**

Temporal				
Parahippocampal Gyrus	28, 34, 35	1007 / 0	4.5 (-19, -18, -17) / -	0.46 / -
Uncus	*	119 / 0	3.7 (-30, 0, -20) / -	0.38 / -
Superior Temporal Gyrus	38	89 / 0	3.4 (-30, 7, -15) / -	0.35 / -

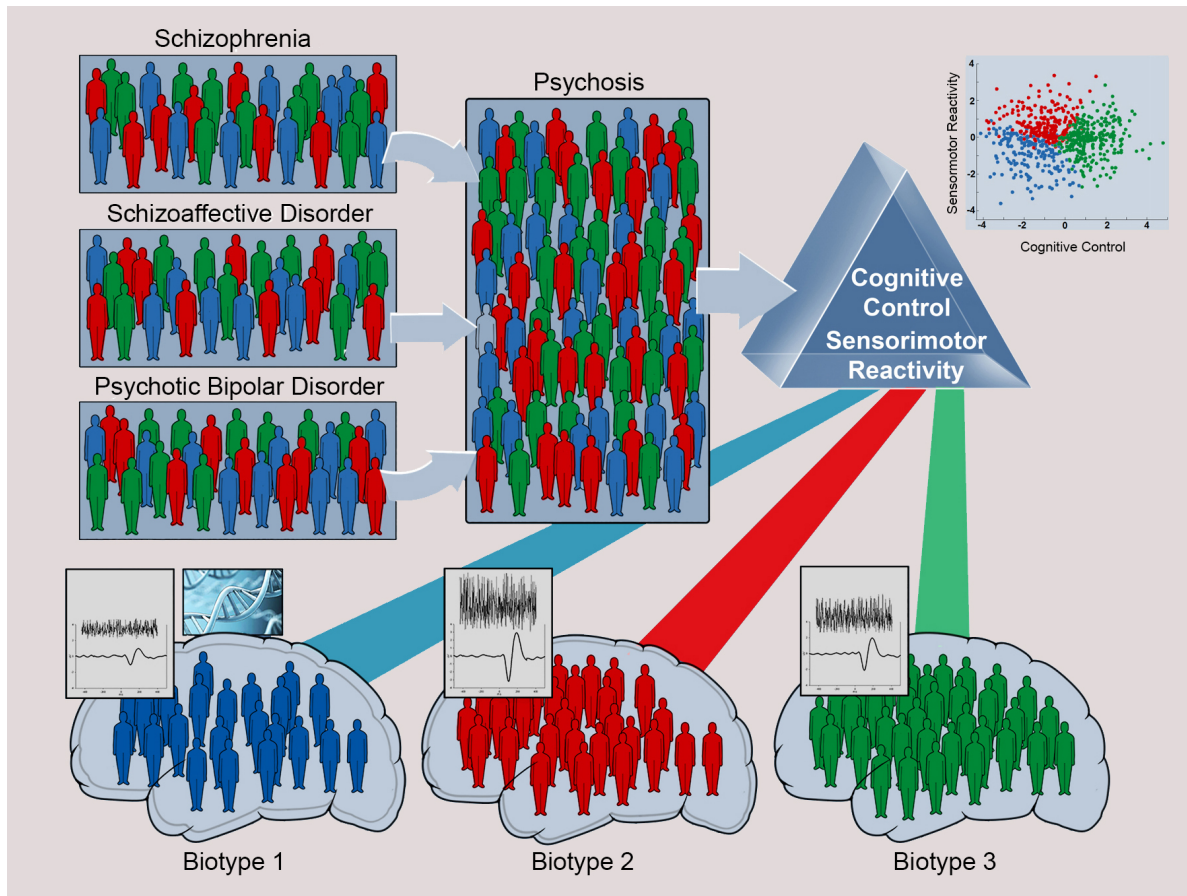
**Healthy –
Biotype2
Relatives
(All-Psychosis)**

Temporal				
Parahippocampal Gyrus	19, 36	0 / 119	- / 3.6 (19, -56, -6)	- / 0.34
Fusiform Gyrus	37	0 / 59	- / 3.3 (28, -36, -15)	- / 0.31
Occipital				
Lingual Gyrus	18, 19	0 / 148	- / 3.5 (13, -58, 0)	- / 0.33

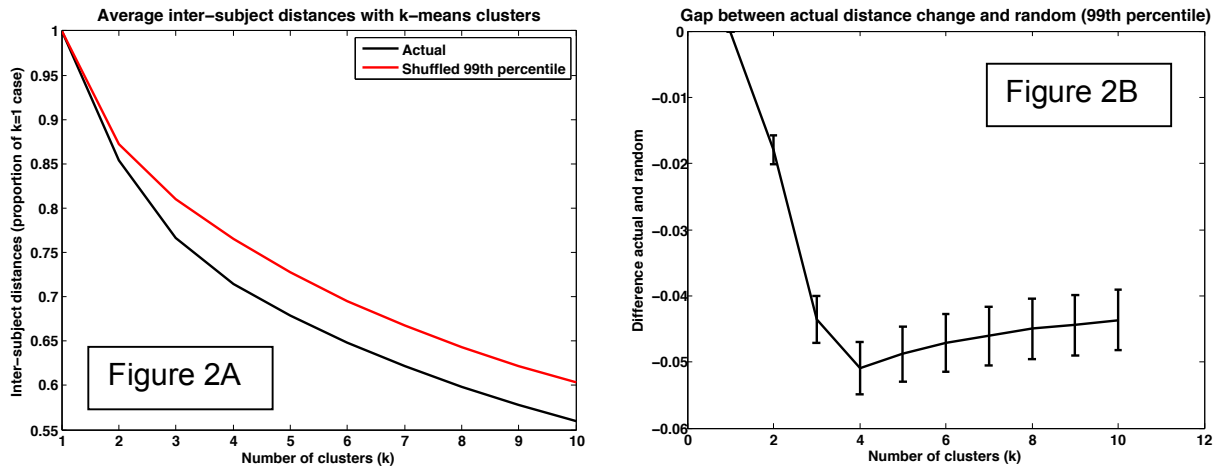
Cerebellum

	Culmen	*	0 / 741	- / 4.2 (24, -37, -15)	- / 0.40
	Declive	*	0 / 119	- / 3.3 (18, -55, -12)	- / 0.31
Healthy – Biotype3 Relatives (All-Psychosis)	Frontal				
	Inferior Frontal Gyrus	*	0 / 30	- / 4.1 (28, 7, -15)	- / 0.37
	Temporal				
	Parahippocampal Gyrus	28, 34, 38	770 / 741	4.8 (-27, 2, -18) / 5.1 (28, 3, -18)	0.43 / 0.46
	Uncus	28, 34	207 / 356	4.3 (-18, 1, -19) / 4.8 (16, 1, -19)	0.39 / 0.43
	Superior Temporal Gyrus	38	30 / 59	3.7 (-33, 2, -18) / 4.6 (31, 6, -18)	0.33 / 0.41

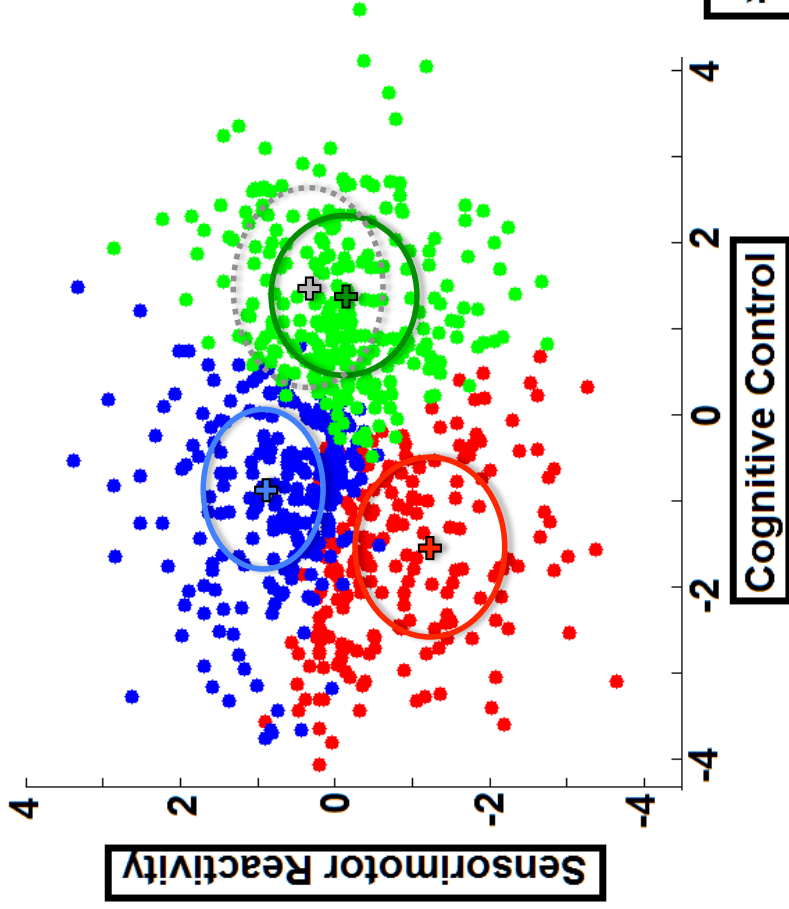
* Coordinates for peak t values are reported based of Group ICA for fMRI Toolbox, GIFT1.3i. All outcomes are reported at $p = .05$, using FWE cluster-level correction, based on an initial voxel threshold set to $p = .001$, uncorrected. † Effect size: Cohen's d derived from t distribution statistics = $t \cdot \{ (n_1 + n_2) / \sqrt{n_1 + n_2 - df} \sqrt{n_1 n_2} \}$ where t = t statistic; n_1 and n_2 = sample sizes; df = degree of freedom; 0.2 = small, 0.5 = medium, 0.8 = large



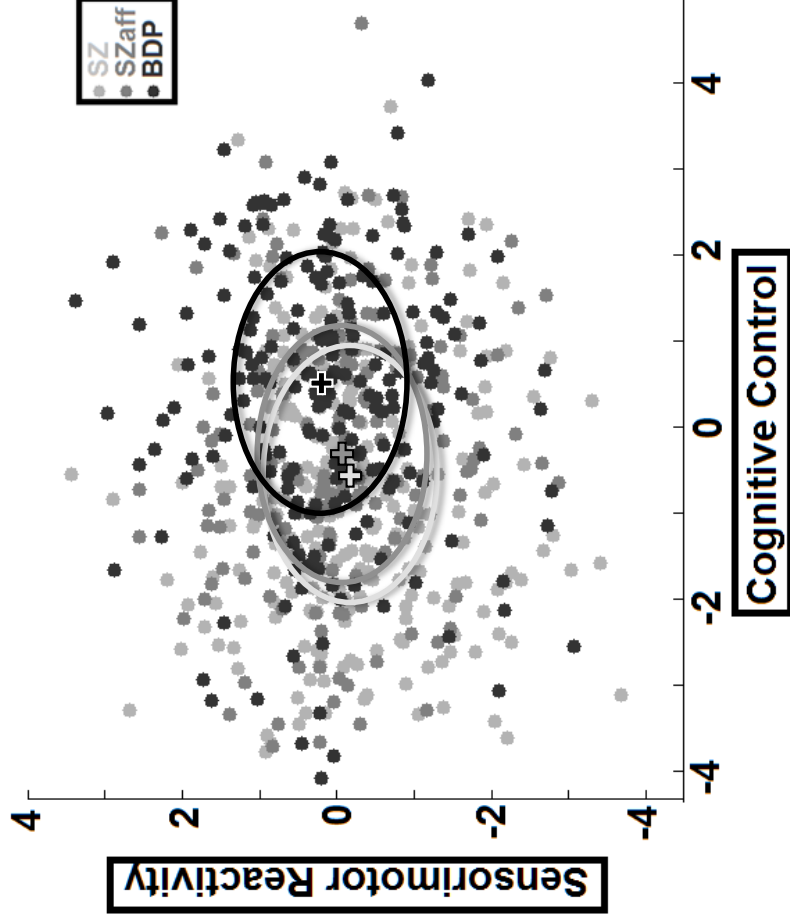
Supplementary Figure 1: Creating Neurobiologically Distinct Psychosis Biotypes. Psychosis is a defining characteristic of Schizophrenia, Schizoaffective Disorder, and Psychotic Bipolar Disorder, all pathophysiologically complex syndromes. These clinical syndromes were not distinguishable by our extensive biomarker panel. Psychosis subjects, therefore, were combined into a single group, independent of DSM diagnosis, and biomarker variables were used to define subgroups with shared neurobiological variance. Two biomarker dimensions, ‘cognitive control’ and ‘sensorimotor reactivity’, provided a means for creating biomarker-defined subgroups (called psychosis *Biotypes*). Biotype-1, -2, and -3, had distinctive neurobiological characteristics, including on variables not used in their definition (called external validators). Biotype-1 cases were fewest in number, had low grey matter volume, significant neurobiological impairment, high numbers of clinically affected relatives, and poor psychosocial functioning. Biotype-2 cases had high neural reactivity, modestly small grey matter volumes, and more modest but still significant cognitive impairment. Biotype-3 cases were most numerous, had nearly normal cognition and neural reactivity, lowest numbers of clinically affected relatives, and the best psychosocial functioning. Neural characteristics as they segregate in these groups could be the basis for distinct molecular and therapeutic targets.



Supplementary Figure 2: Gap Statistic Results. The gap statistic provided one means for estimating the number of clusters in our data prior to implementing the *k*-means algorithm. Figure 1A shows differences between the pooled within-cluster sums of squares as a function of the number of requested clusters for the actual (black line) and null (red line) distributions. Functions are plotted for each distribution as a proportion of the 1 cluster (no subgroups) case. Figure 1B shows the gap function (the difference between the actual and null distribution functions), including the standard errors of the within cluster sums of squares at each requested cluster number. Although the peak was at 4 clusters, that gap value did not significantly differ from the 3-cluster case, so the latter most parsimoniously described the number of subgroups given or data.



Supplementary Figure 3b: Sensorimotor Reactivity by Cognitive Control as a Function of DSM diagnosis. Each dot indicates the location of an individual in this bivariate biomarker space. (light gray=schizophrenia (SZ), medium gray=schizoaffective disorder (SZAff), black=bipolar disorder with psychosis (BDP)). The gray scale coded crosses and ellipsoids show the centroids and ± 1 SD for each DSM Diagnosis.



Supplementary Figure 3a: Sensorimotor Reactivity by Cognitive Control as a Function of Biotype. Each dot indicates the location of an individual in this bivariate biomarker space. (red=Biotype-1, blue=Biotype-2, green=Biotype-3). The color coded crosses and ellipsoids show the centroids and ± 1 SD for each Biotype. The gray cross and ellipse show the same values for the healthy group

Supplementary Figure 4: Relative Group Comparisons on Discriminant Functions. Comparisons between healthy persons and biological relatives as a function of their probands' Biotype on cognitive control and sensorimotor reactivity. Relatives are subdivided within Biotype according to their clinical diagnoses (all relatives, then relatives minus psychosis cases, then relatives minus psychosis and personality disorder (PD) cases). There are three important points: (i) Clinically affected relatives were more abnormal, excluding them did not eliminate relatives' differences from healthy persons; (ii) Biotype-1, and to a lesser extend Biotype-2, relatives seem to possess constitutional predisposition to cognitive control deviation; (iii) Biotype-3 relatives appear largely normal on these functions.

