Supplementary Tables and Figures

Supplementary Table 1. Demographics

	Proband by Biotype			Relatives by Proband Biotype			
	1 (n=198)	**2 (n=235)**	**3 (n=278)**	**1 (n=228)**	**2 (n=277)**	**3 (n-359)**	**Healthy (n=279)**
Age mean (SD)	37.4	35.8	35.2	40.1	41.0	42.0	36.5
	(13.5)	(11.8)	(12.4)	(15.3)	(15.8)	(15.9)	(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	13.0	14.0	13.5	13.8	14.6	14.8
	(2.1)	(2.3)	(2.7)	(2.7)	(2.5)	(2.7)	(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

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

Concomitant medication data are presented based on subjects' reports and available clinical information. Missing concomitant medication data, (n) %: Probands: 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)

	DSM Diagnosis			Statistics		
Clinical Characteristics	**SZ**	**SZAff**	**BDP**	**(df)**	**Value**	**p**
Probands Biotype, (%)						
1	58.6	21.2	20.2	χ^2 (2)	25.95	<.001[a]
2	46.0	26.8	27.2	χ^2 (2)	3.50	.17
3	31.7	24.5	43.9	χ^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	χ^2 (2)	4.73	.09
Axis II: Cluster A and/or B Personality Disorders	9.9	11.7	10.0	χ^2 (2)	0.62	.73
Psychosis-Related Diagnoses (Axis I Psychosis + Axis II/Cluster A,B, combined)*	21.1	25.7	18.3	χ^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.

[a]Yates Corrected pair-wise chi square: SZ>SZAff, χ^2 (1)=7.86, p=.005; SZ>BDP, χ^2 (1)=23.22, p<.001
[b]Yates Corrected pair-wise chi square: BDP>SZ, χ^2 (1)=35.52, p<.001; BDP >SZAff, χ^2 (1)=7.88, p=.005; SZ>SZAff, χ^2 (1)=5.79, p=.02
[c]Tukey HSD: SZ>SZAff (p<.001) and BDP (p<.001); SZAff>BDP (p<.001)
[d] Tukey HSD: BDP<SZ (p<.001) and SZAff (p<.001); SZAff>SZ (p=.04)
[e] Tukey HSD: BDP<SZ (p<.001) and SZAff (p<.001)
[f] Tukey HSD: SZAff>SZ (p<.001) and BDP (p<.001); BDP > SZ (p=.03)
[g] Tukey HSD: SZAff>SZ (p=.02)
[h] Tukey HSD: SZ<BDP (p<.001) and Healthy (p<.001); SZAff<BDP (p<.001) and Healthy (p<.001); BDP<Healthy (p<.001)
[i] Tukey 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	Brodmann Area	Gray Matter Volume (Voxels) Left / Right	Maximum *t* (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	***Frontal***				
	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
	Cingulate				
	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
	Insula	13, 22, 40, 41, 47	3615 / 3437	9.1 (-33, 20, 2) / 9.5 (36, 22, 2)	0.94 / 0.98
	Temporal				
	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
Claustrum	*	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
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
	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
Occipital				
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
Basal Ganglia				
Claustrum	*	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
Thalamus	*	859 / 1096	6.1 (-3, -10, 2) / 6.1 (3, -10, 1)	0.59 / 0.59
Cerebellum				
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	***Frontal***				
	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
	Cingulate				
	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
	Insula	13, 22, 47	1926 / 2193	4.7 (-33, 22, 2) / 6.3 (42, 3, 4)	0.43 / 0.58
	Temporal				
	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
	Parietal				
	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

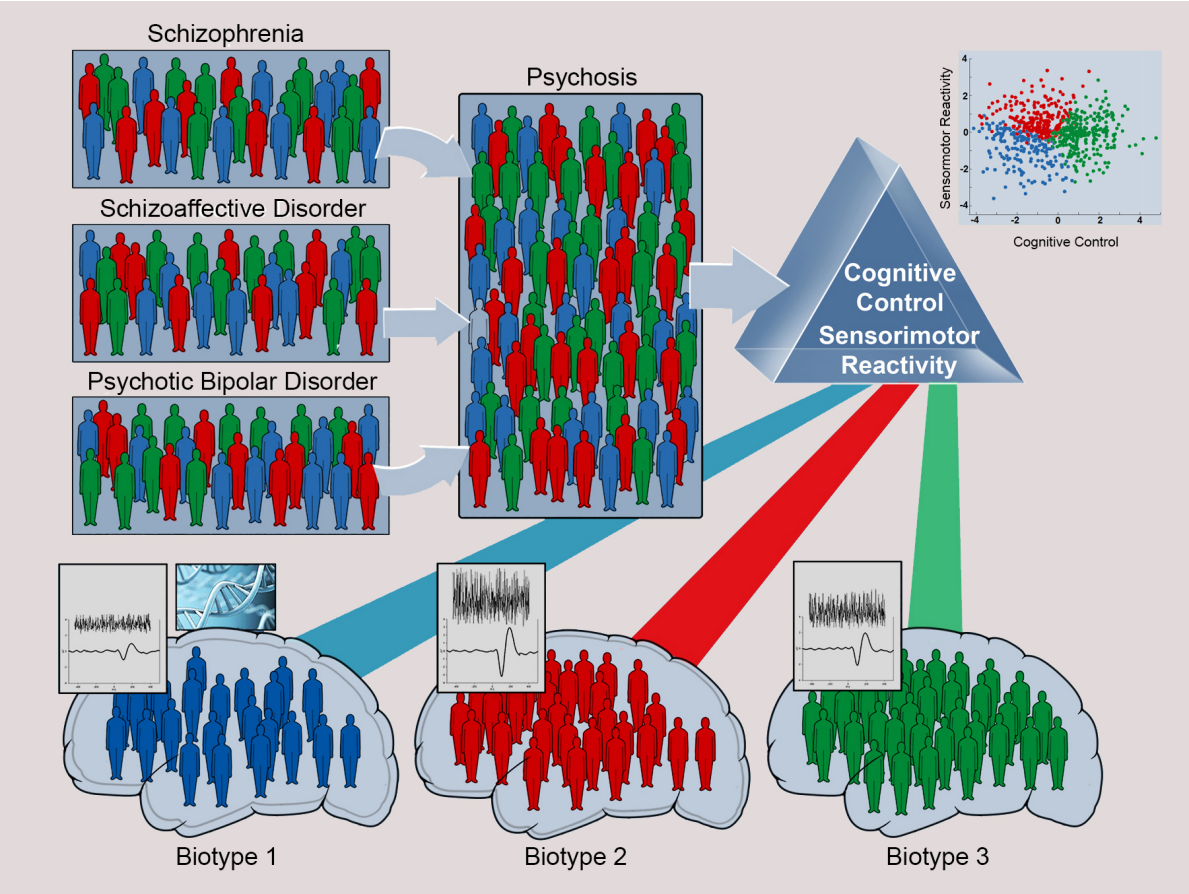
	Occipital				
	Lingual Gyrus	17, 18, 19, 30	237 / 859	3.5 (-3, -81, 3) / 4.8 (13, -51, 4)	0.32 / 0.44
	Cuneus	17, 18, 23, 30	593 / 622	3.8 (-13, -69, 16) / 4.7 (13, -59, 8)	0.35 / 0.43
	Basal Ganglia				
	Claustrum	*	178 / 89	4.0 (-33, 6, 4) / 3.7 (30, 17, -1)	0.37 / 0.34
	Caudate	*	30 / 30	3.6 (-33, -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
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 / -
	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 / -
	Parietal				
	Precuneus	31	30 / 30	3.1 (-10, -65, 18) / 3.5 (6, -73, 22)	0.31 / 0.36
	Occipital				
	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
	Basal Ganglia				
	Claustrum	*	30 / 0	3.3 (-30, 3, 11) / -	0.33 / -
	Cerebellum				
	Culmen	*	30 / 119	3.2 (-19, -33, -12) / 3.5 (27, -32, -19)	0.32 / 0.36
Healthy – Biotype2 Relatives	***Cingulate***				
	Posterior Cingulate	23, 29, 30, 31	0 / 770	- / 4.2 (10, -58, 10)	- / 0.40
	Temporal				
	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
	Parietal				
	Precuneus	*	0 / 30	- / 3.2 (6, -62, 18)	- / 0.30
	Occipital				
	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
	Cerebellum				
	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

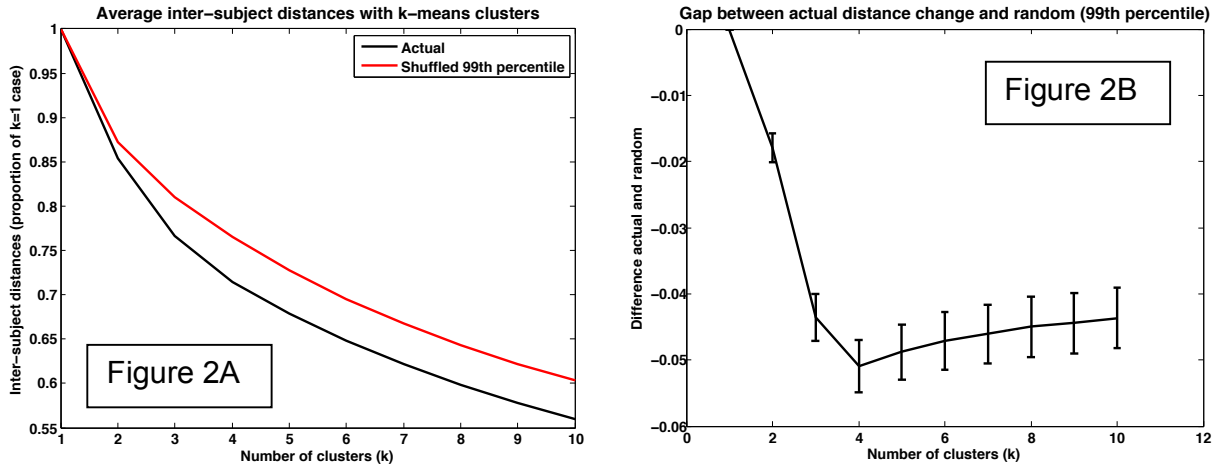
	Pyramis	*	444 / 652	4.1 (-24, -74, -28) / 3.9 (25, -70, -27)	0.39 / 0.37
	Uvula	*	296 / 652	3.9 (-22, -77, -25) / 4.2 (25, -73, -24)	0.37 / 0.40
	Inferior Semi-Lunar	*	30 / 652	3.1 (-39, -63, -36) / 3.7 (31, -64, -35)	0.30 / 0.35
	Tuber	*	356 / 504	4.0 (-27, -77, -28) / 3.9 (31, -80, -28)	0.38 / 0.37
	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

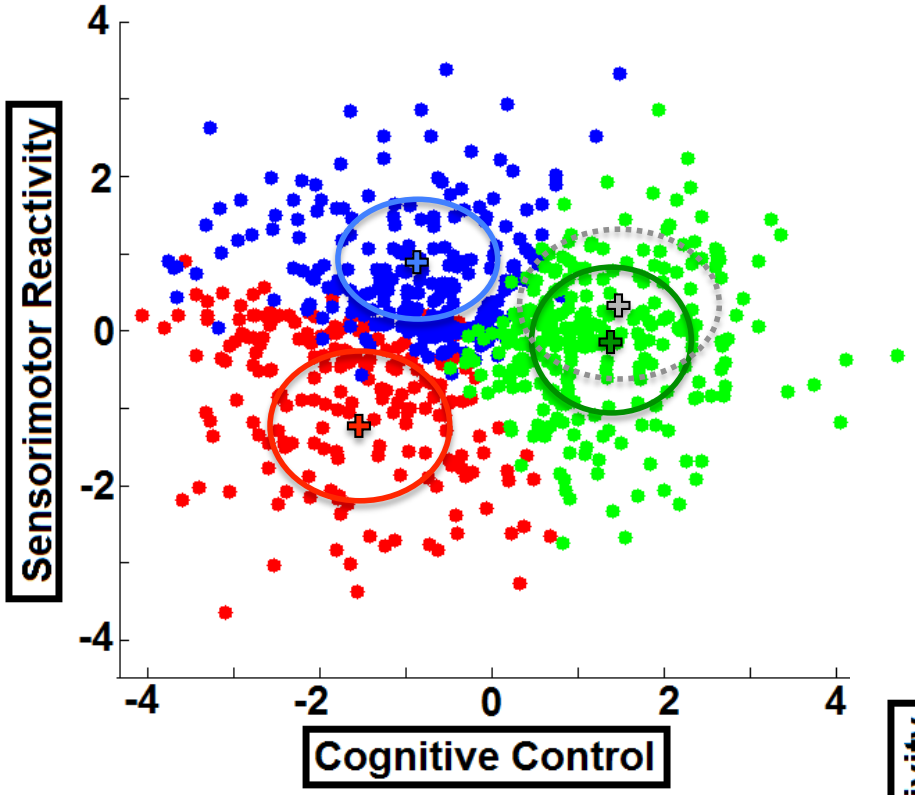
* Coordinates for peak *t* values are reported based of Group ICA for fMRI Toolbox, GIFT1.3i. All outcomes are reported at $p = .05$, using FWE cluster-level correction, based on an initial voxel threshold set to $p = .001$, uncorrected. † Effect size: Cohen's *d* derived from *t* distribution statistics = $t \cdot \{ (n_1 + n_2) / \sqrt{n_1 + n_2 - df}\sqrt{n_1 n_2} \}$ where t = t statistic; n1 and n2 = sample sizes; df = degree of freedom; 0.2 = small, 0.5 = medium, 0.8 = large



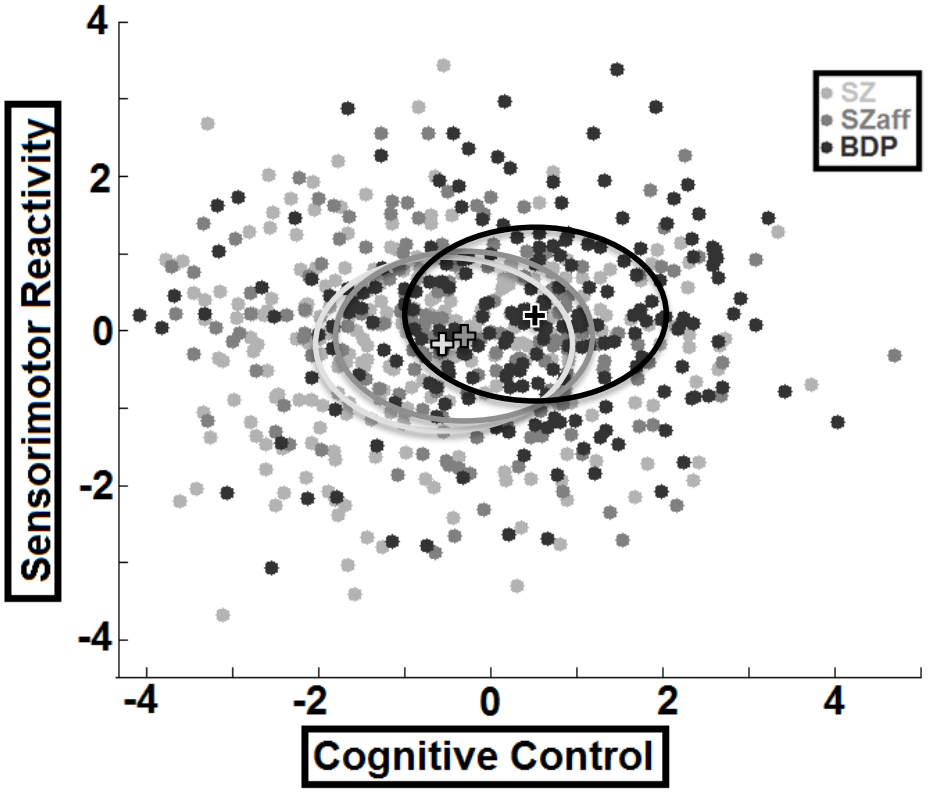
Supplementary Figure 1: Creating Neurobiologically Distinct Psychosis Biotypes. Psychosis is a defining characteristic of Schizophrenia, Schizoaffective Disorder, and Psychotic Bipolar Disorder, all pathophysiologically complex syndromes. These clinical syndromes were not distinguishable by our extensive 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.

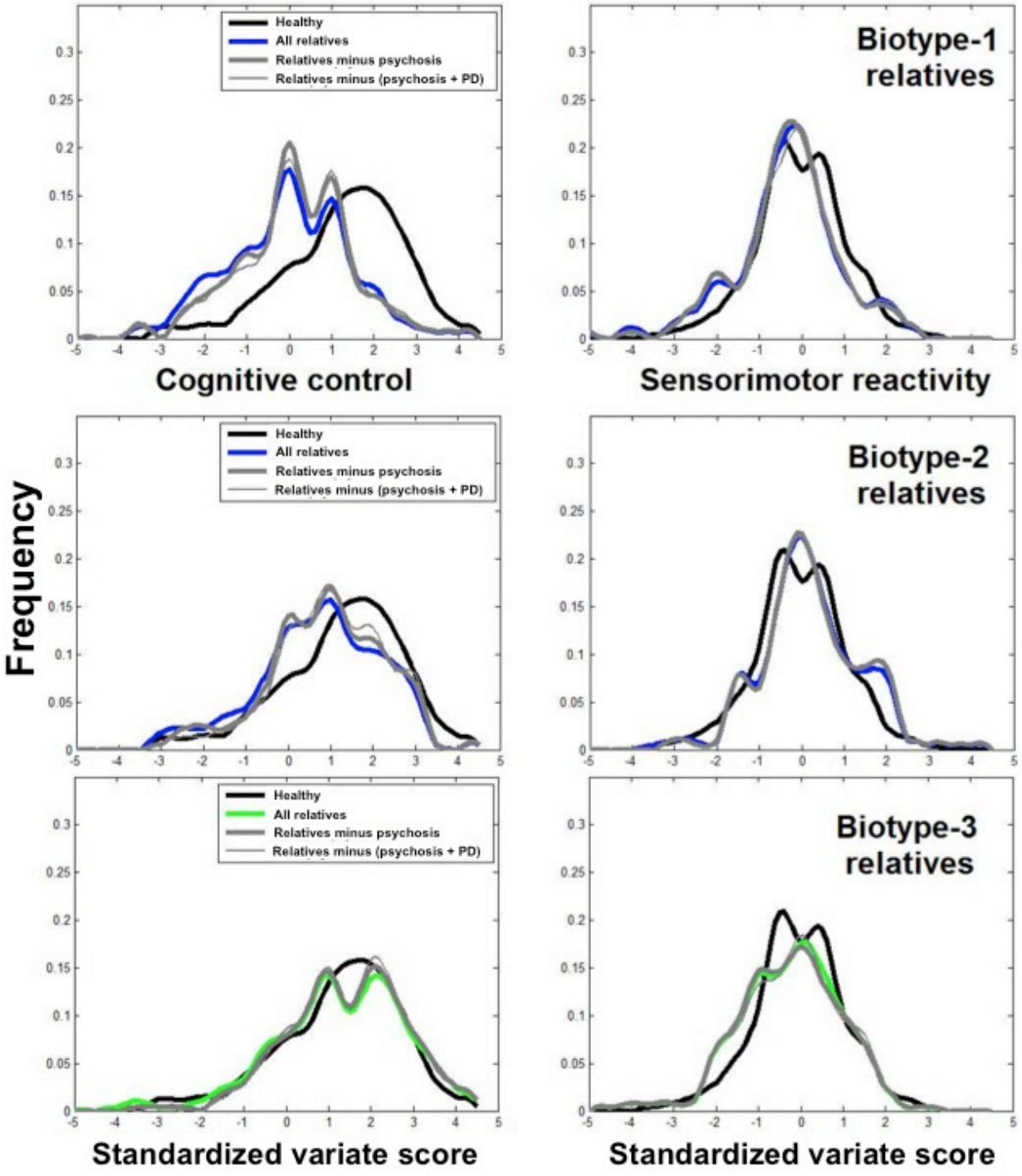


Supplementary Figure 3a: Sensorimotor Reactivity by Cognitive Control as a Function of Biotype. Each dot indicates the location of an individual in this bivariate biomarker space. (red=Biotype-1, blue=Biotype-2, green=Biotype-3). The color coded crosses and ellipsoids show the centroids and +/-1 SD for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



Supplementary Figure 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 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.



Subjects

Persons meeting a DSM-IV-TR (*1*) diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder with psychosis were rated on the Positive and Negative Syndrome (*2*), Young Mania Rating (*3*), Montgomery-Asberg Depression Rating (*4*), Schizo-Bipolar (*5*), and Birchwood Social Functioning (*6*) scales. They were also rated on the Hollingshead Index of Social Position (*7*).

Laboratory tasks

Brief Assessment of Cognition in Schizophrenia. This battery is a widely used test of global neuropsychological function. It covers multiple cognitive domains (Verbal Memory, Processing Speed, Reasoning and Problem Solving, Working Memory), although a global neuropsychological functioning composite score integrating over these domains yields the best measure of psychosis-related cognitive deviation (*8*); this measure was used in Biotype construction.

Pro- and Anti-Saccade Tasks. Eye movement recordings were analyzed using established methods (*9*). Saccade latency (time from peripheral cue onset to saccade onset) and percentage of error responses were recorded for each condition. The prosaccade task consisted of 3 blocks of 32 trials in which the timing of the central fixation crosshair was experimentally manipulated to extinguish simultaneously with (no gap condition), 200 ms before (gap condition) or 200 ms after (overlap condition) peripheral cue appearance. Subjects were instructed to make a saccade to the peripheral cue when it appeared. The antisaccade task consisted of 4 blocks of 20 overlap trials. The overlap condition was used because it is most sensitive to relatives' deficits (*10*). Subjects were instructed to not look to the peripheral cue but saccade to the mirrored location in the opposite visual field.

Stop Signal Task. Trials begin with a central fixation cross after which subjects were shown a Go cue to the left or right. On 40% of trials a Stop Signal was presented at central fixation (with delays between 50 and 282 ms after Go cue onset). Participants were to respond to the Go cue with a button press as quickly as possible unless they encountered the Stop Signal. Strategic slowing (difference between response latencies on baseline Go trials, a block of trials not interspersed with Stop Signal trials, and Go trials during Stop Signal performance) and proportion of Stop Signal errors were used in Biotype construction (see (*11*) for complete task and analysis details). All trials began with the presentation of a white central fixation crosshair for a random interval of 750-1500ms followed by a green circle (the Go cue) to the right or left of center for 650ms. On 40% of trials, a Stop Signal (red stop sign) was presented at the location of the central fixation crosshair at delays varying between 50-282ms after the Go stimulus was shown. The ordering of Stop Signal delays and occurrences of Stop trials varied pseudorandomly. Participants were instructed to respond as quickly and accurately as possible with a button press. The task was administered over four blocks of 63 trials each (38 Go; 25 Stop). A baseline task consisting of 50 consecutive Go trials, evenly and randomly distributed to cues on the left and right side of the screen, was administered to assess baseline reaction time to Go cues.

Auditory Paired-Stimuli and Oddball Evoked Brain Responses. For the paired stimuli task, subjects listened to 150 binaural broadband auditory click pairs (500-ms interclick interval) occurring an average of every 9.5s. For the oddball task, subjects listened to 567 standard (1000Hz) and 100 target (1500Hz) tones presented in pseudorandom order (1300ms inter-trial interval). Subjects were asked to press a button when a target was detected.

Electroencephalography data pre-processing was completed using previously published protocols (*12,13*). To maximize use of available spatial, temporal, and oscillatory information in the evoked auditory response, a frequency-wise principal component analysis of evoked power was first conducted across all subjects to define frequency bands for analysis: (a) LOW, 4–16 Hz; (b) BETA, 17–33 Hz; and (c) GAMMA, 34–55 Hz. Spatial principal component analysis (*12,13*) was completed on the broadband grand-averaged event-related potential waveforms (for traditional event-related potential analyses) and then once for each frequency band to define specific neural oscillatory activities. “Virtual sensors” were constructed based on the principal component analysis outcomes for the broadband event-related potentials and each frequency band (*12,13*). These analyses were performed separately for the paired-stimuli and oddball paradigms. Data from principal components capturing the majority of response variance were then analyzed. Data were analyzed over time (not just at voltage peaks) for both voltage amplitudes and powers in the empirically defined frequency bands. For each condition and subject, the individual principal component waveforms were analyzed in 10ms bins after adjusting for age effects (*12,13,14*). For each time bin, for each principal component, a one-way analysis of variance was conducted comparing DSM-diagnosed proband groups and healthy individuals, adjusting for multiple comparisons (*12,13*). The outcome was 31 electroencephalography variables in both time-voltage and time-frequency space that differentiated psychosis probands and healthy persons (see Table 2), and these variables were used in Biotype construction.

MRI acquisition and Voxel-Based Morphometry. T1-weighted Magnetization Prepared RApid Gradient Echo (MPRAGE) images using he Alzheimer's Disease Neuroimaging Initiative (ADNI) protocol (http://www.loni.ucla.edu/ADNI/Research/Cores/),

with sequence parameters standardized across sites. Images were processed in MATLAB2013a/SPM8/VBM8/DARTEL following standard steps. Modulated grey matter segments were smoothed with 8mm isotropic Gaussian kernel before group-level statistics (see (*15)* for complete details). Voxel-wise grey matter volume between-group differences were examined using full factorial design in SPM8 (analysis of covariance followed by pairwise *t*-contrasts), adjusted for site, age, sex, and handedness; correction for individual brain size was done during DARTEL segmentation/normalization step. To control for multiple testing, a cluster-level correction was employed with p = .05 FWE-R [Family Wise Error based on random field theory (*23*)], using an initial cluster-defining threshold of p = .001, uncorrected. Regional volume reduction analyses were based on Group ICA for fMRI Toolbox, GIFT1.3i, www.sourceforge.net) (*24*). Effect sizes for regional between-group grey matter volume differences were calculated using Cohen's *d* derived from *t* distribution statistics, similar to (*25*).

Medication and clinical effects on biomarkers

Most probands (>90%) and some relatives, were medicated, some with more than one agent, including mood stabilizers, antipsychotic, antidepressants and other psychotropic drugs (see Supplementary Table 2). Antipsychotic dose was estimated by chlorpromazine equivalents (*16*), benztropine (anti-cholinergic) dose, and the presence (vs. absence) of current antipsychotics, mood stabilizers, and antidepressants. For all subjects, medication status, prior history of substance abuse/dependence, and clinical symptom ratings were minimally related to biomarker variables (r^2's <0.04 (*8,9,11-13,15,17-19*)).

Kinship

Strong claims of traditional genetic heritability in the current sample are problematic given the absence of either monozygotic twin pairs or second-degree relatives (*20*), so the more conservative term “kinship” was chosen to refer to the degree to which biomarker measures are predicted by family membership. Kinship was assessed in proband-relative pedigrees via h^2r estimates calculated using SOLAR (Sequential Oligogenic Linkage Analysis Routines (*21*)). Total phenotypic variance was partitioned into additive polygenic and random environmental components. We assessed effects of age and sex on each phenotype and, when significant, adjusted for their effects in kinship analyses.

Imputation

The requirement for inclusion in this project was available data on a majority of the biomarker variables. Estimates of missing values were generated via a regression-based multiple imputation method (*22*) as implemented in SAS PROC MI using all available information from other biomarker variables. Multiple estimates from 1000 iterations were combined to provide final estimates of the missing values. Analyses for integrating data across measures and for generating Biotypes resulted in highly similar results when using imputed data versus when eliminating all cases with missing data.

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