Resting Electroencephalogram Oscillatory Abnormalities in Schizophrenia, Psychotic Bipolar Patients and their Relatives from the B-SNIP Study

Supplemental Information

Supplemental Methods & Materials

Participant Recruitment

The multi-site Bipolar & Schizophrenia Network on Intermediate Phenotypes (B-SNIP) (1) consortium was formed to primarily study intermediate phenotypes of the psychosis dimension to gain insight into common and distinct aspects of psychosis pathophysiology in schizophrenia (SZ) and psychotic bipolar disorder (PBP). Probands were recruited from inpatient and outpatient units at the five centers (Baltimore, Boston/Detroit, Chicago, Dallas and Hartford) comprising the collaborative B-SNIP study via advertisements, online postings and referral by word of mouth. Clinical and demographic characterization of the participants in the study is described elsewhere (1). Exclusions included presence of neurological illness, substance abuse (within 6 months) or dependence within 2 years or any prior extensive history of drug dependence (DSM-IV). Groups were not matched on age, sex or ethnicity. All subjects were assessed by experienced clinical raters including masters-level clinicians, doctoral-level clinical psychologists or psychiatrists to document diagnostic information using clinical data and structured interviews.

Electroencephalography (EEG) Data Collection and Processing

EEG recordings were collected independently at each site by trained research staff with identical equipment calibrated across sites to the same specifications using Neuroscan

(Compumedics, Charlotte, NC) system. EEG was collected with subjects seated comfortably in a straight-backed chair, with eyes open and fixed attention to a fixation cross at eye level on a monitor. All electrodes (see Figure S1) were adjusted for impedance ≤ 5 kΩ. Electrooculography (EOG) was used to monitor eye movement horizontally with electrodes next to both eyes, and vertically with electrodes above and below the right eye. Digitized EEG specifications included a 1000 Hz sampling rate and band pass filter down 3 dB between 0.5-100 Hz.

EEGLAB (2) and in-house custom MATLAB scripts (Mathworks, Natick, MA) were used to preprocess EEG data. EEG data were subsampled to 250 Hz, following which drift and high frequency artifacts were removed by filtering between 0.5-50 Hz. Bad electrode recordings were detected by visual inspection and fixed using spline interpolation (no ≥ 8% for any subject). Blink artifact correction was performed using independent component analysis (ICA) in conjunction with reference EOG electrodes. The initial 10 s of recordings were excluded from processing to minimize movement artifacts. Individual EEG trials/epochs were generated by segmenting the continuous data into 50% overlapping packets of 2.048 s, followed by baseline correction to the mean value of the entire trial. Trials containing extreme outliers (exceeding 150 uV threshold), improbable distribution (≥3.25 standard deviation from mean), or kurtotic behavior (3.75 standard deviation from mean) were discarded. Further pruning was done by frequency-transforming data using a Hamming window and subsequently rejecting epochs that were (+/-) 4 standard deviations from the mean spectral amplitude at all frequency points between 0.5-50 Hz. Finally, the data of accepted epochs were visually inspected by trained research personnel to reject unwanted electrical activity, while retaining valid brain EEG patterns.

EEG Frequency Analysis

Frequency transformation was applied to each clean epoch using fast Fourier transform with a Hamming window to compute frequency-power of EEG data between 1.5-50 Hz. Frequency amplitude was obtained by taking the square root of frequency-power to form the instantaneous amplitude profile of each trial. Spectral data below 1.5 Hz were excluded from further analysis to safeguard from slow lateral eye movements.

Group Independent Component Analysis (GICA)

Instantaneous amplitude spectral profiles at 64 electrodes from all subjects were processed by the GICA algorithm (GIFT v1.3c; http://icatb.sourceforge.net) (3) to identify spatial maps associated with independent spectral networks representing various neural substrates. Each subject's data was organized by concatenating the amplitude spectral profile (see Figure S2) for all spatial leads across the epoch dimension. Missing epochs were imputed with the mean spectral data across valid epochs. A simple data reduction procedure using principal component analysis at the subject level was employed to reduce the spatial dimension, followed by spatial compounding of spectral data from all subjects (n = 1271) from the 5 groups (SZ, PBP, SZ relatives (SZR), PBP relatives (PBPR) and healthy controls (HC)). A second data reduction step was applied to compress the spatially and spectrally concatenated data. The number of independent components for the spectral data was derived using Akaike information and minimum description length criteria (4) for each subject. Average of the median estimates from both criteria was used as an initial estimate. To combat overfitting, a consistency check tool (ICASSO (5) within GIFT) was employed to select the final number of components, as those that yielded consistent spectral components between each run of ICA. Following the above

procedure, the compressed data were decomposed into 8 (>95% reliability) mutually independent components, estimated using infomax ICA algorithm (6). GICA extracted a spectral series and a spatial map (representing brain regions or electrodes comprising each frequency network) for each component, based on the overall group characteristics. The EEG spectral series and spatial maps were then back-reconstructed for each subject producing a series of spatial maps and component spectral profile capturing individual differences in the ICA components derived from the variations common to all subjects. The spatial map of each frequency component is the weights or loadings (dimensionless) of the individual leads, reflecting the contribution of each lead to the connection or association with that frequency component. As a final quality check, the spatial weights aggregated by 6 regions (see Figure S1) for each frequency component were examined for extreme outliers by excluding subjects if aggregated spatial weights at any of the 6 regions for any frequency component exceeded (+/-) 3.5 interquartile ranges from the respective group medians. The outlier detection procedure eliminated 34, 34, 38, 30 and 44 subjects from SZ, PBP, SZR, PBPR and HC groups respectively. Spatial topographic coefficients from GICA for each spectral component served as dependent measure to probe for group differences.

Statistical Analysis

All statistical tests were two-tailed with alpha set at 0.05. The topographic weights were normally distributed. Since both SZ and PBP share psychosis, probands were treated as a single group. Similarly, SZR and PBPR were clustered as a second group and HC treated as a comparison group. Analysis of covariance was carried out with 4 between subjects-factors (group: probands (SZ and PBP), relatives (SZR and PBPR) and HC; sex: (male/female); site: (6 levels) and race: (6 categories)). Age and number of epochs were included as covariates in all

analyses. For each frequency component, significance values were adjusted for $p = 0.05/64$ to correct for multiple comparison across all leads. Significant findings were further examined with post-hoc *t*-tests to assess scalp topographic simple effects by evaluating spatial differences between paired groups of interest; in the current study the test was limited to SZ vs HC, SZR vs HC, SZ vs PBP and similar comparisons were carried out in PBP and PBPR. *P*-values for post-hoc tests were adjusted for $p = 0.05/5$ to account for the 5 pairwise comparisons. Relative risk estimates for the spectral activity was evaluated by defining varying order of affectedness in relatives of probands. Relative risk (7-9) is computed as the ratio of percentage of relatives classified as affected based on thresholds equal to 1 or 1.5 or 2 standard deviation above the control mean to the percentage of HC designated as affected. Heritability for those spectral components that differed between probands and controls, as well between relatives and controls in the direction of probands, was estimated by computing the proportion of the variance attributed to additive genetic effects (genetic contribution to the phenotype), using variance components analysis implemented in sequential oligogenic linkage analysis routines (SOLAR) (10). For relative risk ratio and heritability estimates, the scalp weights of the leads at which both probands and relatives differed from controls served as a dependent measure. Statistical analyses were conducted using Statistical Package for the Social Sciences (GLM, ANCOVA: SPSS Inc., Chicago, Il).

Supplementary Results

Resting State (RS)-EEG Spectral Components using GICA

The ordering of the frequency components in GICA is random but we sorted the components from low to high frequency. The 8 frequency components (Figure 1) comprised of 2 delta, 1 theta, 1 slow alpha, 2 fast alpha, 1 slow beta and 1 fast beta oscillatory networks, with a noticeable peak within the respective frequency ranges that characterize EEG spectral bands.

Scalp topography weights are emphasized or positively correlated or de-emphasized or negatively correlated (anti-correlated) with respect to the peak of mean spectral component curve. Two delta (1.5 – 4 Hz) components N6 (delta-theta mix but for simplicity we refer to as delta) and N8 with anterior and posterior maximal distribution were identified with a peak at 1.5 Hz and 4 Hz respectively. One theta component N1 with a peak between 4.15-8 Hz was noticed with a frontal to posterior and central distribution respectively. Slow alpha (N3) and fast alpha components (N2 and N5) were validated by a peak between 8.15-10 Hz and 10.15-13 Hz respectively with maximum amplitude distribution over central-parietal and parietal regions. The slow beta component (N4) had a peak within 13.15-20 Hz range with a central/parietal distribution. The fast beta component (N7) was validated by the peak at 25 Hz and having a maximal distribution localized frontally.

Relative Risk and Heritability

Relative risk ratio for delta and slow beta abnormalities in SZ were in the range of 1.5-2.9 and for fast alpha and slow beta activity in PBP were between 1.6-1.9, as summarized in Tables S2 and S3. RS-EEG frequency abnormalities shared between probands and relatives were moderately heritable, with significant h^2 values (estimated using SOLAR) ranging between 0.16

and 0.31, as listed in Table S4 for those spatial leads that differed between HC and both probands and relatives.

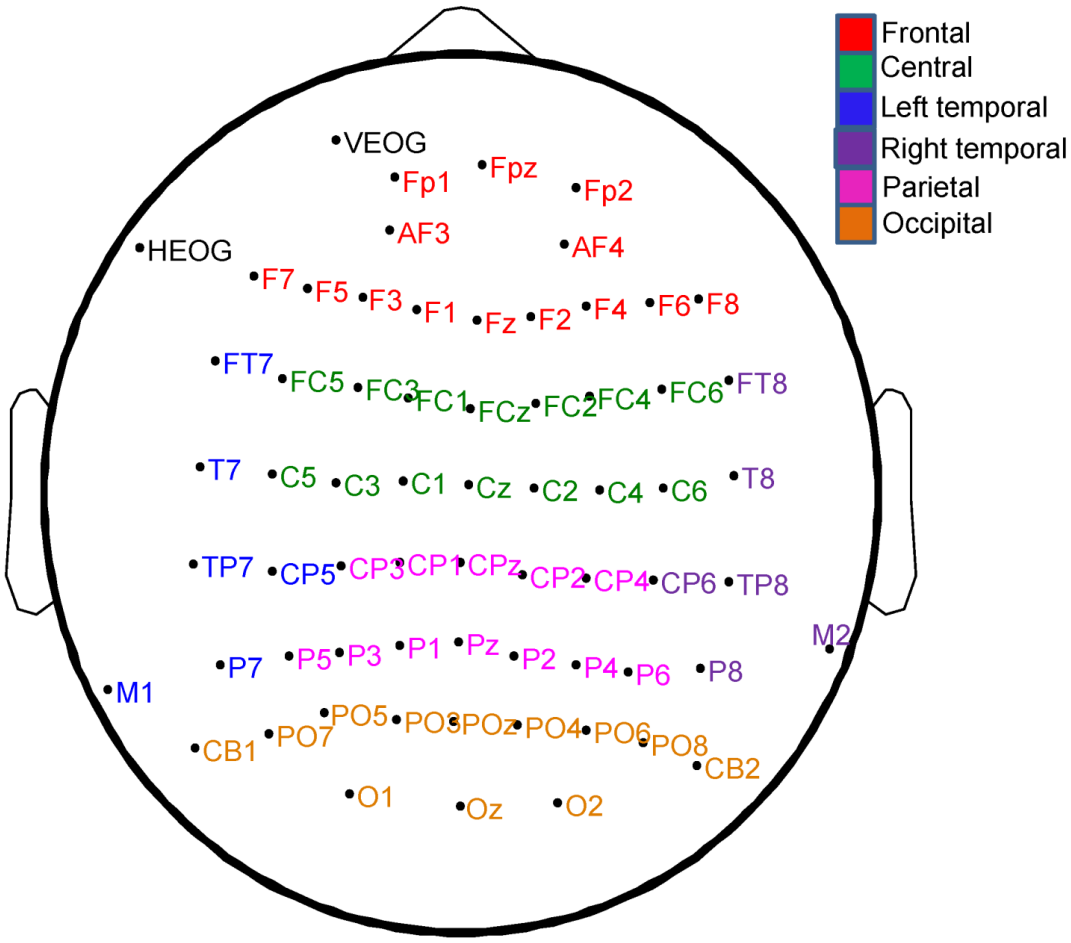

Figure S1. Recording electrodes (*n* = 66) montage for analyses. Six regional clusters shown in color for outlier elimination.

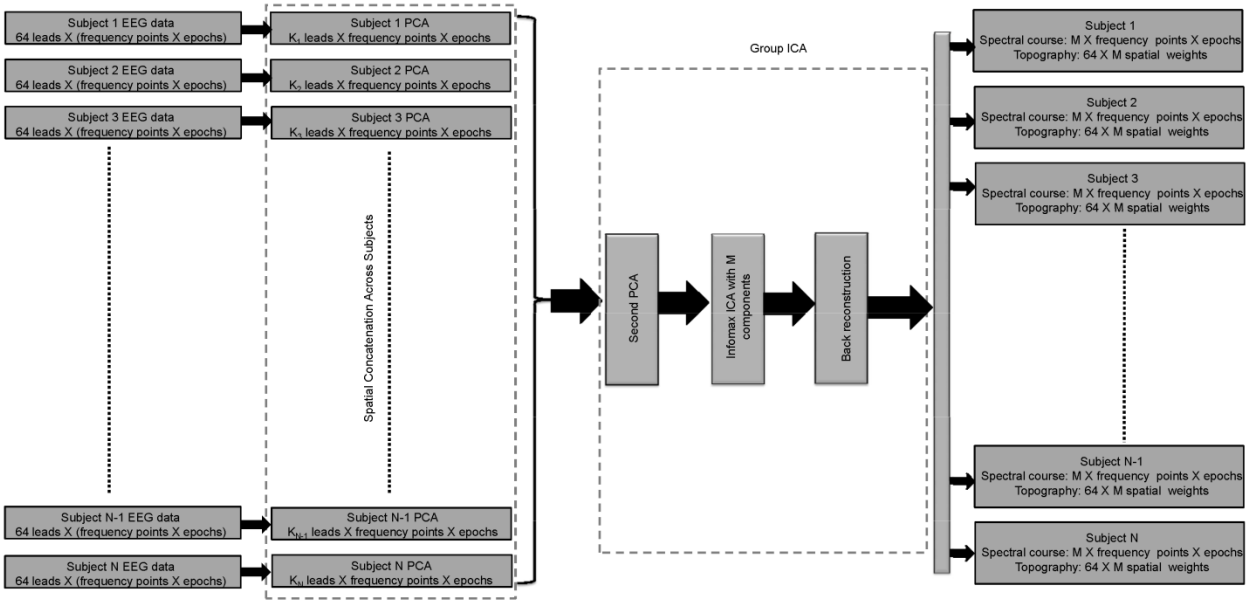

Figure S2. Schematic depicting the data organization for estimating independent frequency components using group independent component analysis (ICA) approach. EEG, electroencephalogram; PCA, principal component analysis.

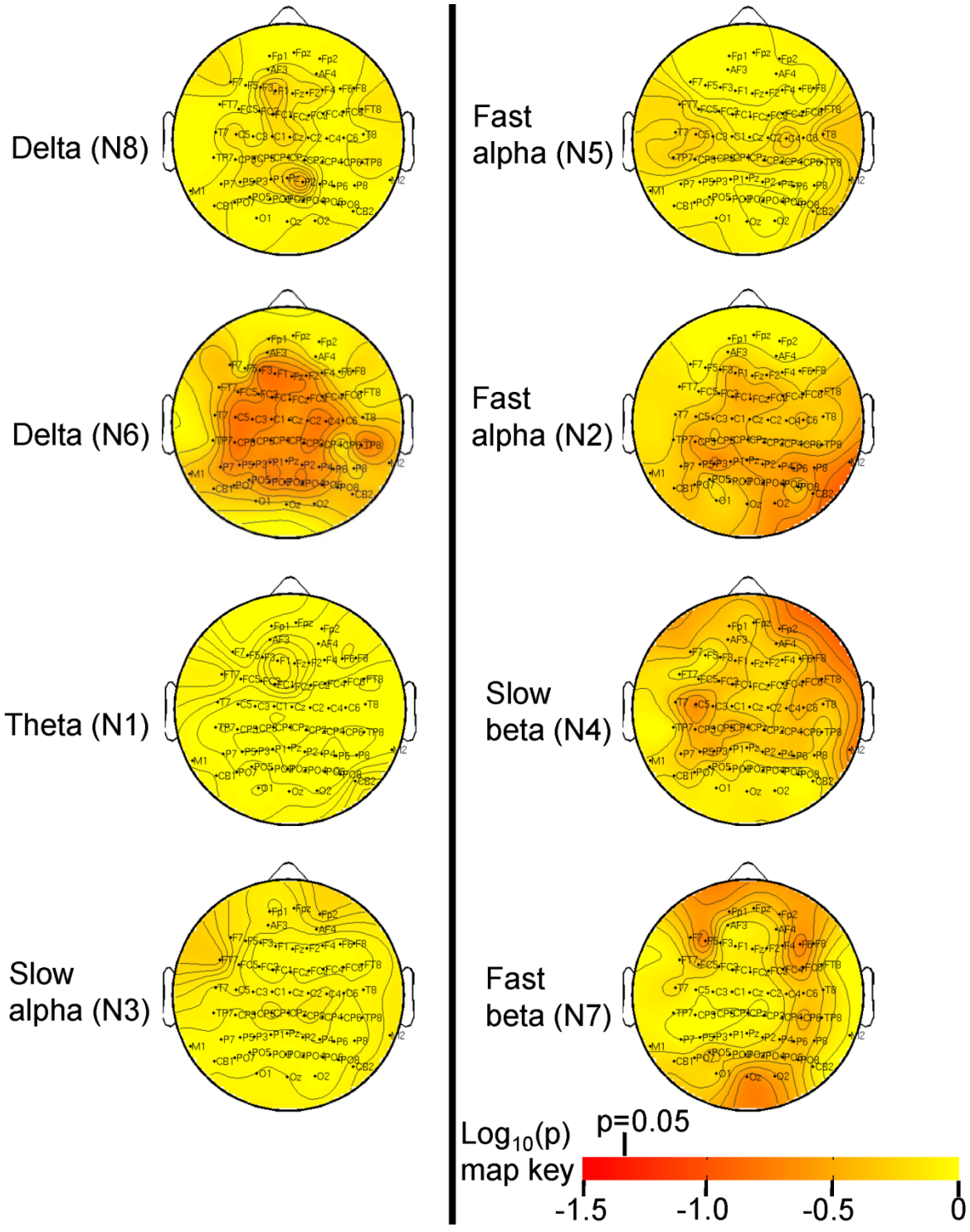

Figure S3. Significance levels for group-by-site interactions associated with various spectral components.

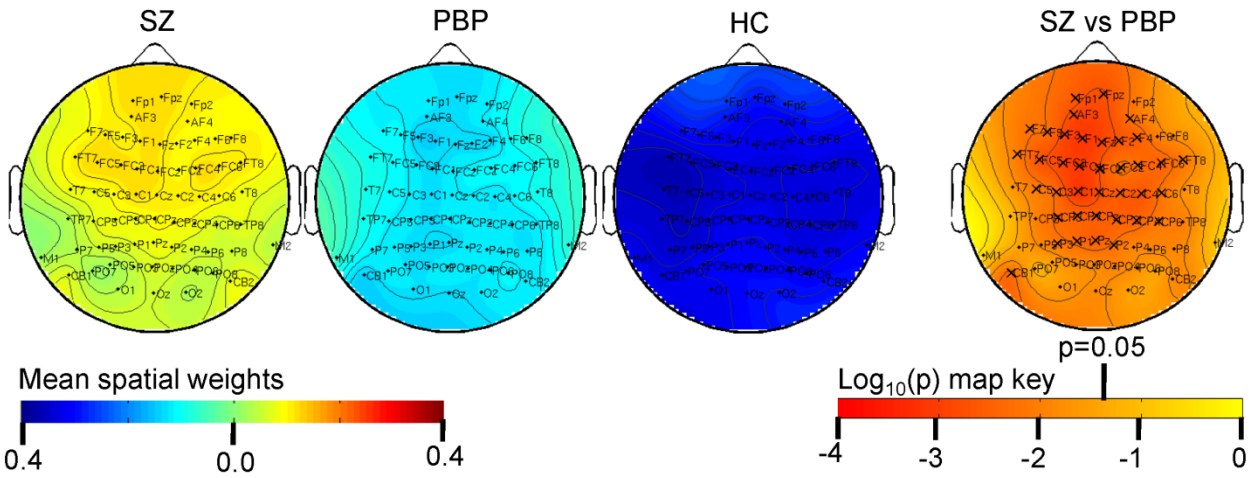

Figure S4. Mean spatial weights for theta (N1) activity in schizophrenia (SZ), psychotic bipolar disorder (PBP) and healthy controls (HC) and significance level associated with SZ vs PBP comparison. No other oscillatory networks differed between SZ and PBP. 'X' indicates significant after multiple comparison correction for 5 comparisons (p = 0.05/5). Activity and P maps are shown at all leads for continuity, but only leads significant in the omnibus analysis of covariance test are highlighted.

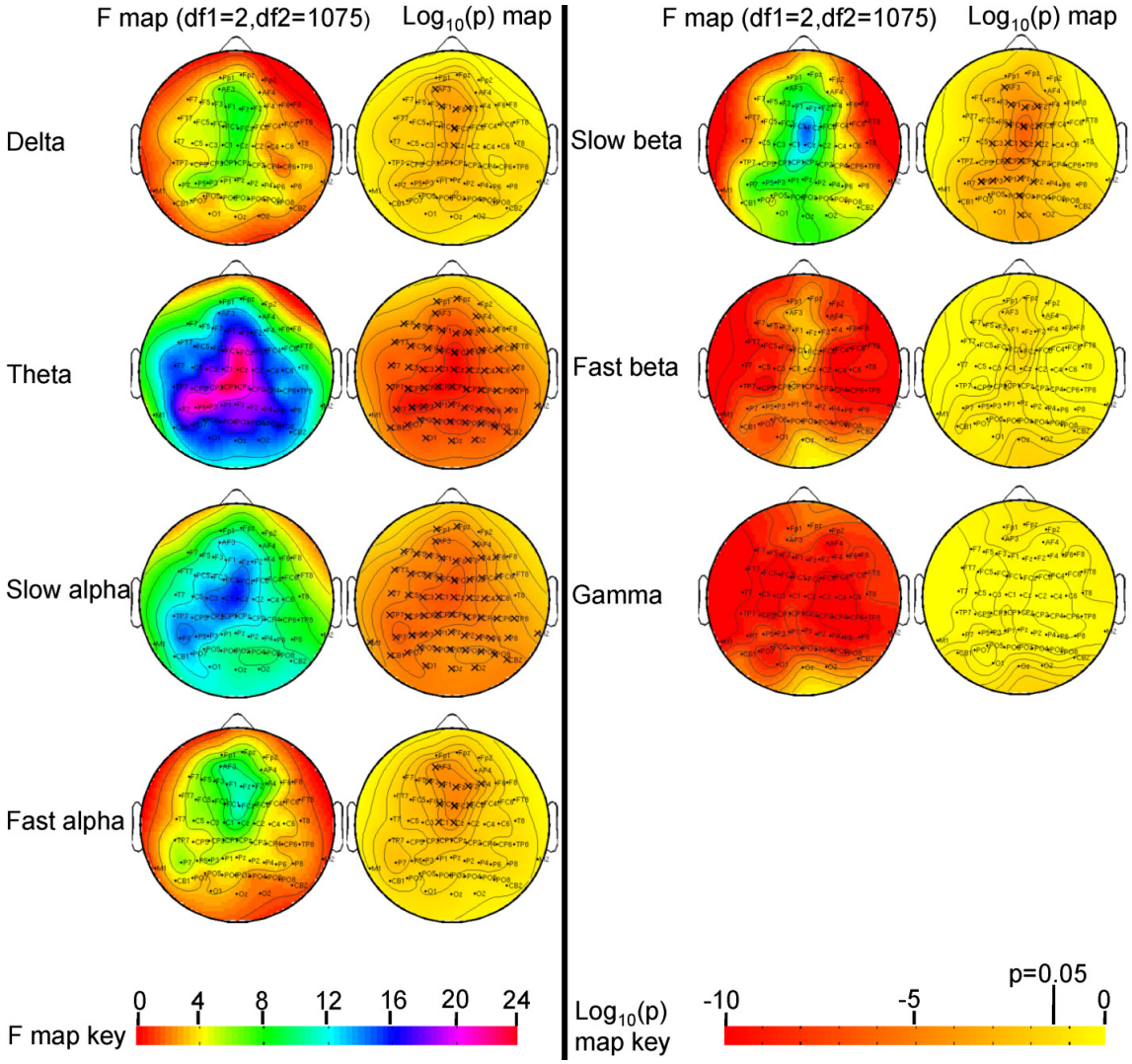

Figure S5. F-maps and significance levels from the omnibus analysis of covariance test comparing EEG spectral amplitude from various frequency bands across three groups. Data epochs were subjected to spectral transformation and averaged to yield the spectral curve at each lead. The amplitude was evaluated by computing area under the curve within traditional frequency bands including delta (1.5-4 Hz), theta (4.15-8 Hz), slow alpha (8.15–10 Hz), fast alpha (10.15-12 Hz), slow beta (12.15-20 Hz), fast beta (20.15-30 Hz) and gamma (30.15–50 Hz).

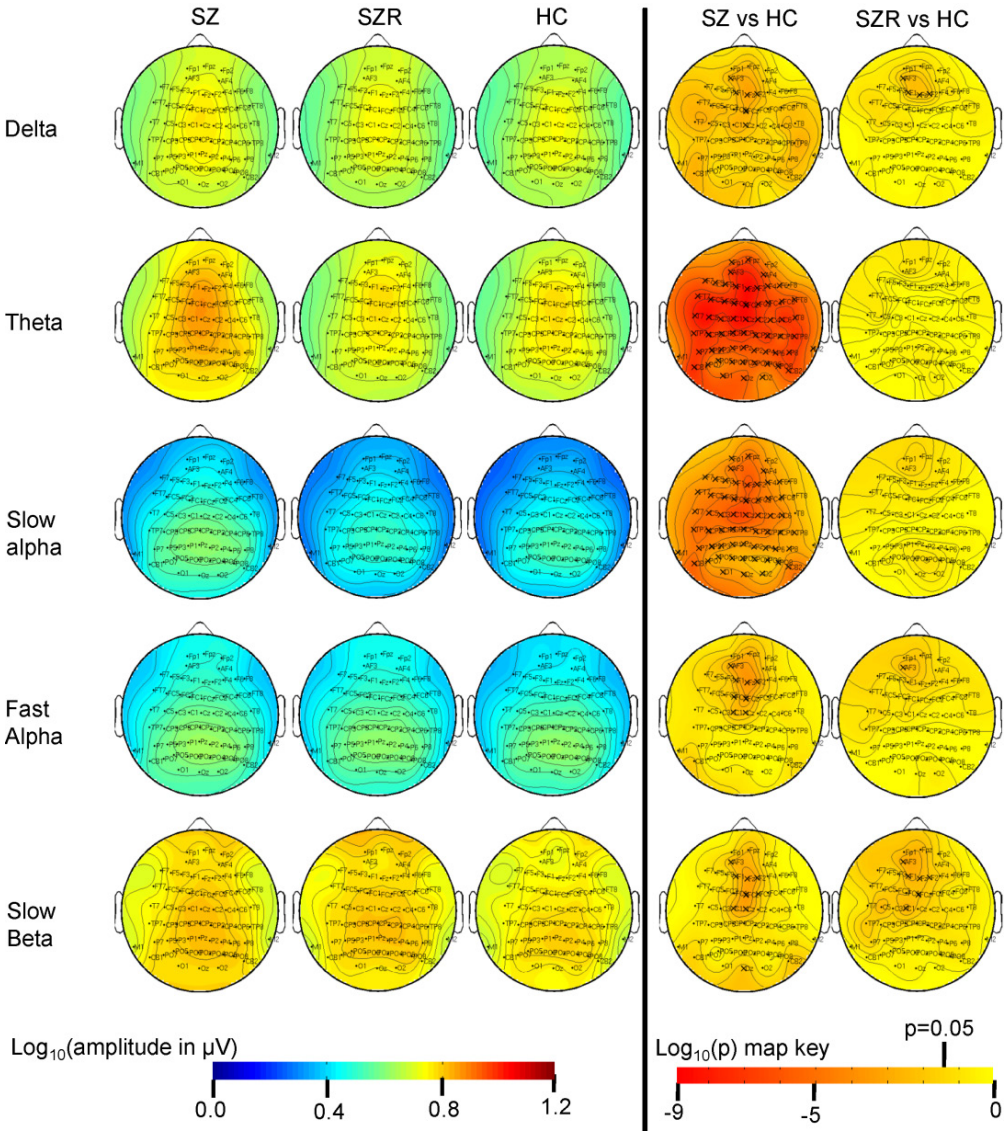

Figure S6. Mean spectral amplitude in various frequency bands in schizophrenia (SZ) probands, their relatives (SZR) and healthy controls (HC) and significance levels from pairwise post-hoc *t*-tests. 'X' indicates significant after multiple comparison correction for 5 comparisons (p = 0.05/5). Spatial leads significant in the analysis of covariance and significantly different in probands and relatives vs HC are highlighted in relatives. The abnormality expressed in the relatives was in the same direction of probands.

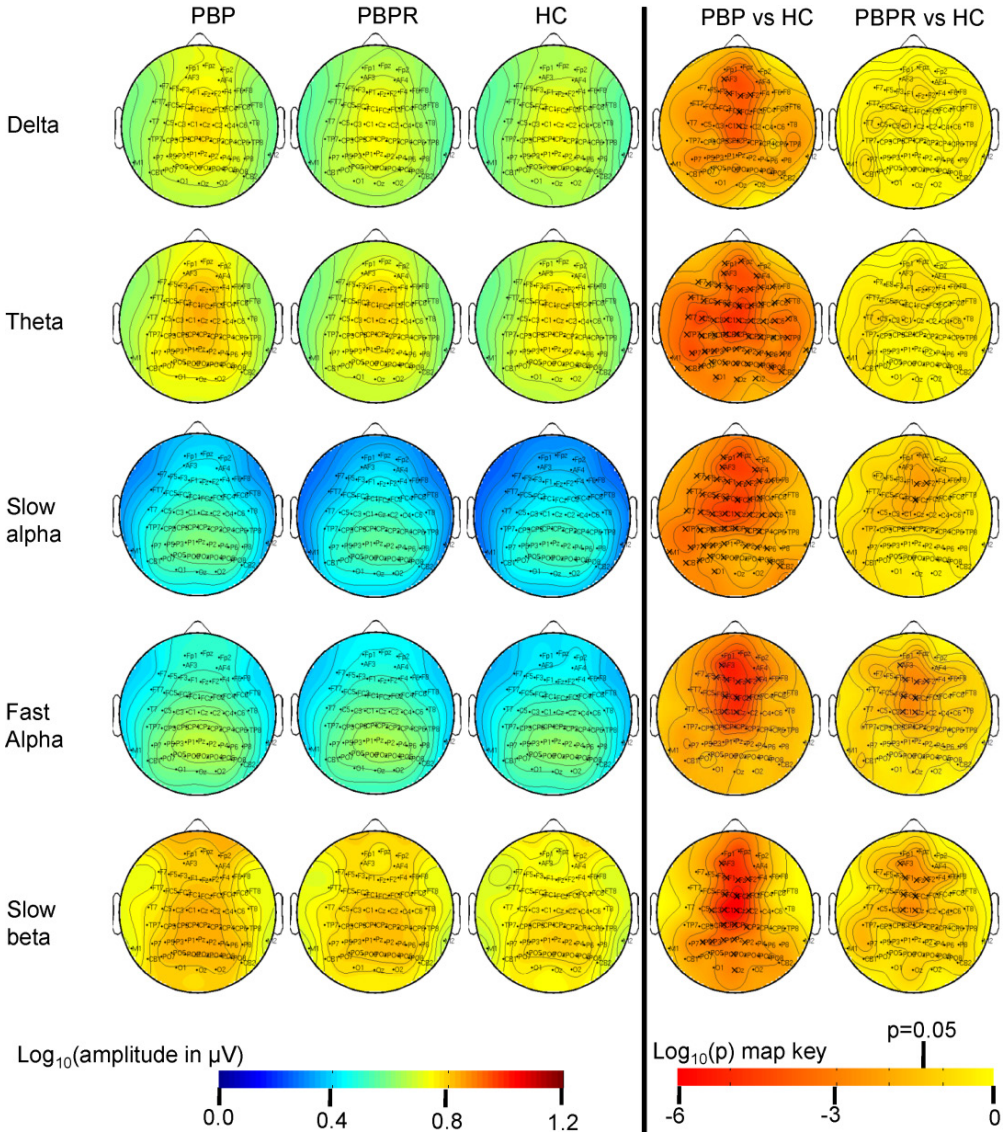

Figure S7. Mean spectral amplitude in various frequency bands in psychotic bipolar (PBP) probands, their relatives (PBPR) and healthy controls (HC) and significance levels from pairwise post-hoc *t*-tests. 'X' indicates significant after multiple comparison correction for 5 comparisons (p = 0.05/5). Spatial leads significant in the analysis of covariance and significantly different in probands and relatives vs HC are highlighted in relatives. The abnormality expressed in the relatives was in the same direction of probands.

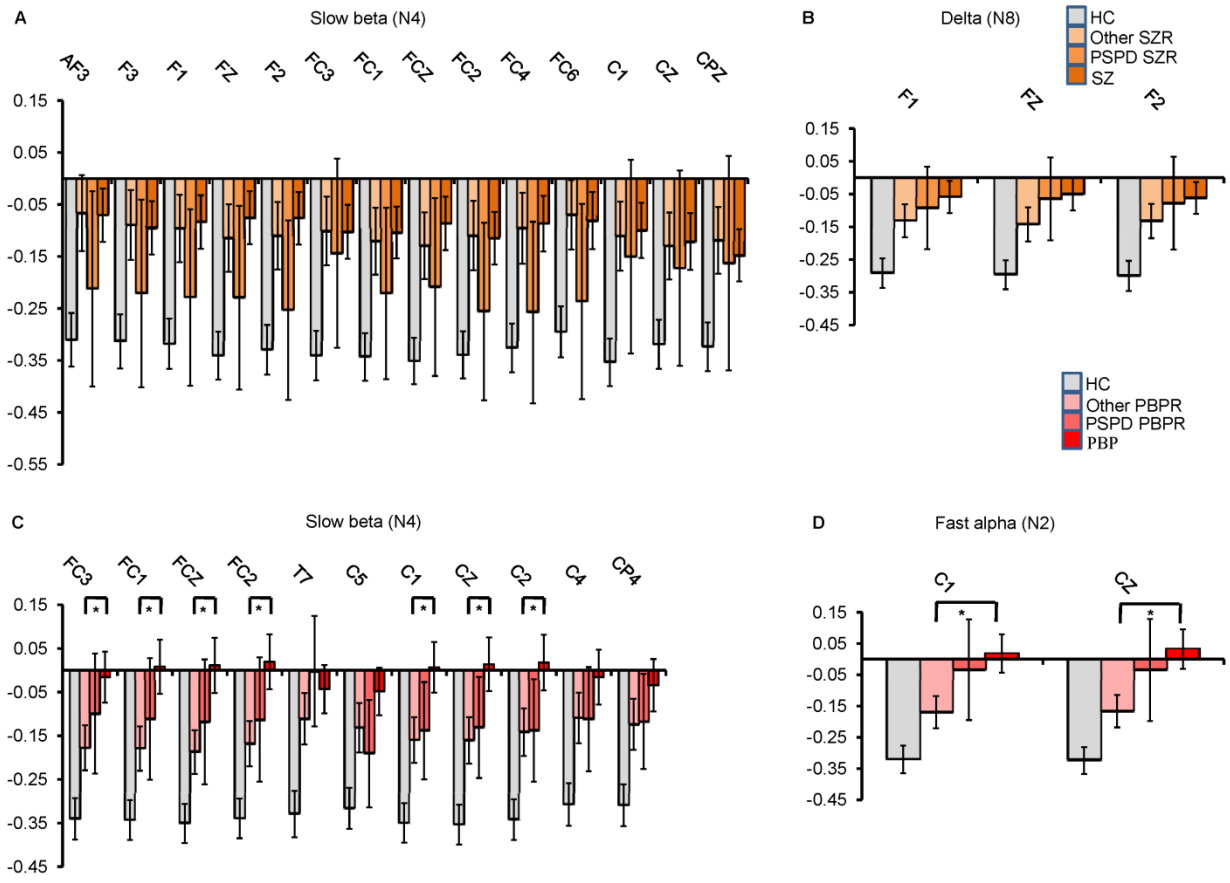

Figure S8: Mean spatial weights for clinically relevant leads in schizophrenia (SZ) and psychotic bipolar disorder (PBP) probands, healthy controls (HC) and relatives with psychosis spectrum disorder (PSPD). (**A**) Slow beta (N4) and (**B**) delta (N8) activity in HC (*n* = 200), other relatives of SZ proband (SZR) (*n* = 180), SZR with PSPD (*n* = 21) and SZ (*n* = 225) probands. (**C**) Slow beta (N4) and (**D**) fast alpha (N2) activity in HC (*n* = 200), other relatives of PBP proband (PBPR) (*n* = 207), PBPR with PSPD (*n* = 24) and PBP (*n* = 234) probands. Other SZR and PBPR refer to SZR and PBPR with non-psychotic Axis 1 disorders and diagnoses-free relatives with neither Axis 1 nor cluster A or B diagnoses. *T*-tests were carried out between proband vs PSPD relatives and proband vs other relatives in both SZ and PBP. * indicates significant at $p < 0.05$ uncorrected. Error bars represent SEM.

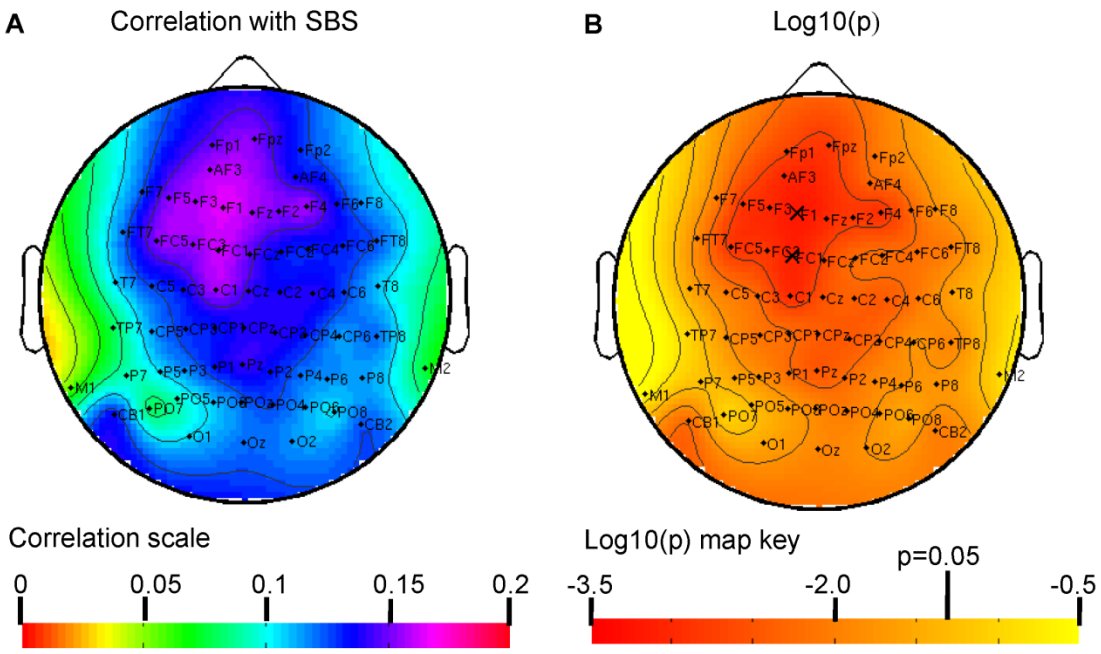

Figure S9. Clinical correlation with schizo-bipolar scale (SBS). (**A**) Pearson correlation of spatial weights of theta (N1) activity with SBS and (**B**) associated significance level in logarithmic scale. 'X' indicates significant after Bonferroni correction (p = 0.05/63) for 63 leads from omnibus analysis of covariance test.

Table S1. Medication information for subjects across diagnostic groups.

	SZP (*n* = 225)	**PBP (*n* = 234)**	**SZR (*n* = 201)**	**PBPR (*n* = 231)**	**HC (*n* = 200)**
Unknown Medication History, % (*n*)	1.9 (4)	1.9 (4)	1.3 (3)	0.8 (2)	7.0 (14)
Medication data below are for subjects with medication history reported	***n* = 221**	***n* = 230**	***n* = 198**	***n* = 229**	***n* = 186**
No Medication taken, % (*n*)	3.1 (7)	3.4 (8)	34.0 (67)	28.3 (65)	55.3 (103)
Not on Psychotropic Medications, % (*n*)	6.3 (14)	5.8 (13)	78.3 (155)	71.3 (163)	96.3 (179)
Antiparkinsonian, % (*n*)	19.2 (42)	8.4 (19)	0.0 (0)	0.0 (0)	0.0 (0)
Antidepressant (Any), % (*n*)	38.4 (85)	48.3 (111)	15.3 (30)	21.3 (49)	1.4 (3)
Tricyclic	1.2 (3)	1.9 (5)	0.4 (1)	1.2 (3)	0.0 (0)
Other (SSRI, SNRI, tetracyclic, other)	36.9 (82)	46.4 (107)	15.3 (30)	20.2 (46)	1.4 (3)
Antipsychotic (Any), % (*n*)	92.2 (204)	74.3 (171)	2.1 (4)	2.3 (5)	0.0 (0)
Typical	10.6 (23)	6.5 (15)	0.0 (0)	0.0 (0)	0.0 (0)
Atypical	81.2 (179)	67.8 (156)	2.1 (4)	2.3 (5)	0.0 (0)
Anxiolytic/Hypnotic, % (*n*)	21.2 (47)	29.5 (68)	9.8 (19)	8.5 (19)	0.0 (0)
Mood Stabilizer (Any), % (*n*)	2.1 (5)	67.8 (156)	28.2 (56)	5.0 (11)	0.0 (0)
Lithium	5.9 (13)	21.0 (48)	0.4 (1)	1.2 (3)	0.0 (0)
Other	22.4 (50)	46.7 (107)	1.7 (3)	3.9 (9)	0.0 (0)
Miscellaneous, Centrally Active, % (*n*)	0.8 (2)	0.4 (1)	0.4 (1)	0.0 (0)	0.0 (0)
Stimulants, % (*n*)	4.3 (11)	8.0 (18)	0.9 (2)	2.7 (6)	0.5 (1)

HC, healthy control; SZ, schizophrenia; SZR, first-degree relative of schizophrenia proband; PBP, psychotic bipolar disorder; PBPR, first degree relative of psychotic bipolar disorder proband; SSRI, selective serotonin reuptake inhibitor; SNRI; serotonin-norepinephrine reuptake inhibitor.

Table S2. Relative risk estimates and associated *P*-values at significant spatial leads for delta and slow beta activity in schizophrenia (SZ).

	Cutoff (SD)[b]	Delta				RR[a] (λ)	χ^2 df=1	*P*	Slow Beta				RR[a] (λ)	χ^2 df=1	*P*
		SZ Risk							SZ Risk						
		REL		HC					REL		HC				
		n	%	*n*	%				*n*	%	*n*	%			
AF3	1								47	23.3	26	13	1.79	7.25	0.007
	1.5								31	15.4	13	6.5	2.37	8.17	0.004
	2								17	8.4	8	4	2.11	3.4	0.06
F3									48	23.8	27	13.5	1.76	7.1	0.007
									28	13.9	15	7.5	1.85	4.33	0.03
									15	7.4	7	3.5	2.13	3.03	0.08
F1		47	23.3	28	14	1.67	5.8	**0.01**	47	23.3	29	14.5	1.61	5.14	0.02
		20	9.9	13	6.5	1.53	1.58	0.20	29	14.4	17	8.5	1.69	3.46	0.06
		13	6.4	7	3.5	1.84	1.28	0.25	18	8.9	10	5	1.79	2.41	0.12
FZ		47	23.3	29	14.5	1.61	5.14	0.02	48	23.8	26	13	1.83	7.88	0.004
		29	14.4	11	5.5	2.62	8.89	**0.002**	31	15.4	16	8	1.92	5.33	0.02
		14	6.9	5	2.5	2.78	3.49	0.06[c]	21	10.9	10	5	2.18	4.82	0.02
F2		44	21.8	28	14	1.56	4.23	0.03	45	22.3	24	12	1.86	7.59	0.005
		27	13.4	12	6	2.23	6.3	**0.01**	31	15.4	16	8	1.92	5.33	0.02
		13	6.4	5	2.5	2.58	2.8	0.09[c]	21	10.4	10	5	2.08	4.17	0.04
FC3									48	23.8	25	12.5	1.91	8.71	**0.003**
									34	16.9	15	7.5	2.25	8.28	0.004
									20	9.9	10	5	1.99	3.54	0.06
FC1									51	25.3	30	15	1.69	6.69	0.009
									29	14.4	17	8.5	1.69	3.46	0.06
									20	9.9	10	5	1.99	3.54	0.06
FCZ									49	24.3	26	13	1.87	8.53	**0.003**
									29	14.4	17	8.5	1.69	3.46	0.06
									21	10.4	8	4	2.61	6.21	0.01
FC2									52	25.8	26	13	1.99	10.5	**0.001**
									32	15.9	18	9	1.76	4.39	0.03
									23	11.4	11	5.5	2.08	4.56	0.03
FC4									49	24.3	22	11	2.21	12.3	**0.0004**
									33	16.4	18	9	1.82	4.9	0.02
									24	11.9	9	4.5	2.65	7.3	0.006
FC6									49	24.3	24	12	2.03	10.3	**0.001**
									30	14.9	14	7	2.13	6.44	0.01
									22	10.9	9	4.5	2.43	5.83	0.01
C1									50	24.8	27	13.5	1.84	8.36	0.003
									40	19.9	14	7	2.84	14.3	**0.0001**
									21	10.4	10	5	2.08	4.17	0.04
CZ									50	24.8	27	13.5	1.84	8.36	0.003
									30	14.9	15	7.5	1.99	5.54	0.01
									20	9.9	11	5.5	1.80	2.78	0.09
CPZ									47	23.3	28	14	1.67	5.8	0.01
									31	15.4	15	7.5	2.05	6.19	0.01
									19	9.4	10	5	1.89	2.96	0.08

[a]Relative risk (RR) is defined as the ratio of fraction of relatives (REL) classified as affected to the fraction of the healthy controls (HC) designated as affected.

[b]Cutoff is the number of standard deviations (SD) above the mean of healthy controls used to classify a subject as affected. Three different cutoff criterion including 1, 1.5 and 2 SD were used.
[c]Yates correction applied.
Bold *p* values are significant after Bonferonni correction ($p = 0.05/3$ for fast alpha and $p = 0.05/14$ for slow beta).

Table S3. Relative risk estimates and associated *P*-values at significant spatial leads for fast alpha and slow beta activity in psychotic bipolar disorder (PBP).

	Cutoff (SD) [b]	Fast Alpha				RR[a] (λ)	χ^2 df=1	*P*	Slow Beta				RR[a] (λ)	χ^2 df=1	*P*
		PBP Risk							PBP Risk						
		REL		HC					REL		HC				
		n	%	*n*	%				*n*	%	*n*	%			
FC3	1								54	23.3	25	12.5	1.87	8.47	**0.003**
	1.5								27	11.6	15	7.5	1.55	2.13	0.14
	2								15	6.4	10	5	1.29	0.43	0.5
FC1									50	21.6	30	15	1.44	3.13	0.07
									25	10.8	17	8.5	1.27	0.65	0.41
									18	7.79	10	5	1.55	1.37	0.24
FCZ									48	20.7	26	13	1.59	4.56	0.03
									25	10.8	17	8.5	1.27	0.65	0.41
									19	8.2	8	4	2.05	3.2	0.07
FC2									49	21.2	26	13	1.63	5.02	0.02
									27	11.6	18	9	1.29	0.82	0.36
									16	6.9	11	5.5	1.25	0.37	0.54
T7									51	22	28	14	1.57	4.67	0.03
									27	11.6	16	8	1.46	1.62	0.20
									11	4.7	6	3	1.58	0.87	0.34
C5									48	20.7	26	13	1.59	4.56	0.03
									29	12.5	12	6	2.09	5.34	0.03
									13	5.6	8	4	1.4	0.61	0.43
C1		51	22	26	13	1.69	6.02	**0.01**	55	23.8	27	13.5	1.76	7.39	0.006
		30	12.9	15	7.5	1.73	3.45	0.06	26	11.2	14	7	1.6	2.3	0.12
		20	8.6	9	4.5	1.92	2.95	0.08	19	8.2	10	5	1.64	1.77	0.18
CZ		55	23.8	28	14	1.7	6.63	**0.01**	55	23.8	27	13.5	1.76	7.39	0.006
		32	13.8	14	7	1.97	5.28	**0.02**	26	11.2	15	7.5	1.5	1.75	0.18
		20	8.6	8	4	2.16	3.82	0.05	17	7.3	11	5.5	1.33	0.61	0.43
C2									57	24.6	27	13.5	1.82	8.53	**0.003**
									27	11.6	16	8	1.46	1.62	0.2
									16	6.9	11	5.5	1.25	0.37	0.54
C4									55	23.8	25	12.5	1.90	9.07	**0.002**
									32	13.8	19	9.5	1.45	1.94	0.16
									17	7.3	10	5	1.47	1.01	0.31
CP4									52	22.5	27	13.5	1.66	5.81	0.01
									33	14.2	16	8	1.78	4.2	0.04
									17	7.3	10	5	1.47	1.01	0.31

[a]Relative risk (RR) is defined as the ratio of fraction of relatives (REL) classified as affected to the fraction of the healthy controls (HC) classified as affected.

[b]Cutoff is the number of standard deviations (SD) above the mean of healthy controls used to classify a subject as affected. Three different cutoff criterion including 1, 1.5 and 2 SD were used.

Bold *p* values are significant after Bonferonni correction ($p = 0.05/2$ for fast alpha and $p = 0.05/11$ for slow beta).

Table S4. Heritability estimates and associated significance values at clinically relevant spatial leads.

Channels	Fast Alpha (N2)		Slow Beta (N4)		Delta (N8)	
	h^2	*p*	h^2	*p*	h^2	*p*
AF3	-	-	0.16	0.04	-	-
F3			0.19	0.02		
F1	-	-	0.20	0.01	0.30	0.0003*
FZ	-	-	0.22	0.009	0.28	0.0006*
F2	-	-	0.12	0.09	0.20	0.007*
FC3	-	-	0.25	0.002*	-	-
FC1	-	-	0.14	0.06	-	-
FCZ	-	-	0.1	0.13	-	-
FC2	-	-	0.183	0.02	-	-
FC4	-	-	0.183	0.02	-	-
FC6	-	-	0.189	0.02	-	-
T7	-	-	0.28	0.001*	-	-
C5	-	-	0.25	0.002*	-	-
C1	0.224	0.008*	0.17	0.02	-	-
CZ	0.222	0.009*	0.19	0.01	-	-
C2	-	-	0.21	0.009	-	-
C4	-	-	0.22	0.007	-	-
CPZ			0.29	0.001*		
CP4	-	-	0.31	0.0005*	-	-

Heritability was evaluated at leads significantly differing between healthy controls and both probands and their relatives ($n = 690$) in schizophrenia and/or psychotic bipolar disorder.

* indicates significant at $p < 0.05$ after multiple comparison correction for clinically relevant leads within each measure ($p = 0.05/2$ for fast alpha (N2), $p = 0.05/19$ for slow beta (N4) and $p = 0.05/3$ for delta (N8)).

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