Event-Related Potential and Time-Frequency Endophenotypes for Schizophrenia and Psychotic Bipolar Disorder

Supplemental Information

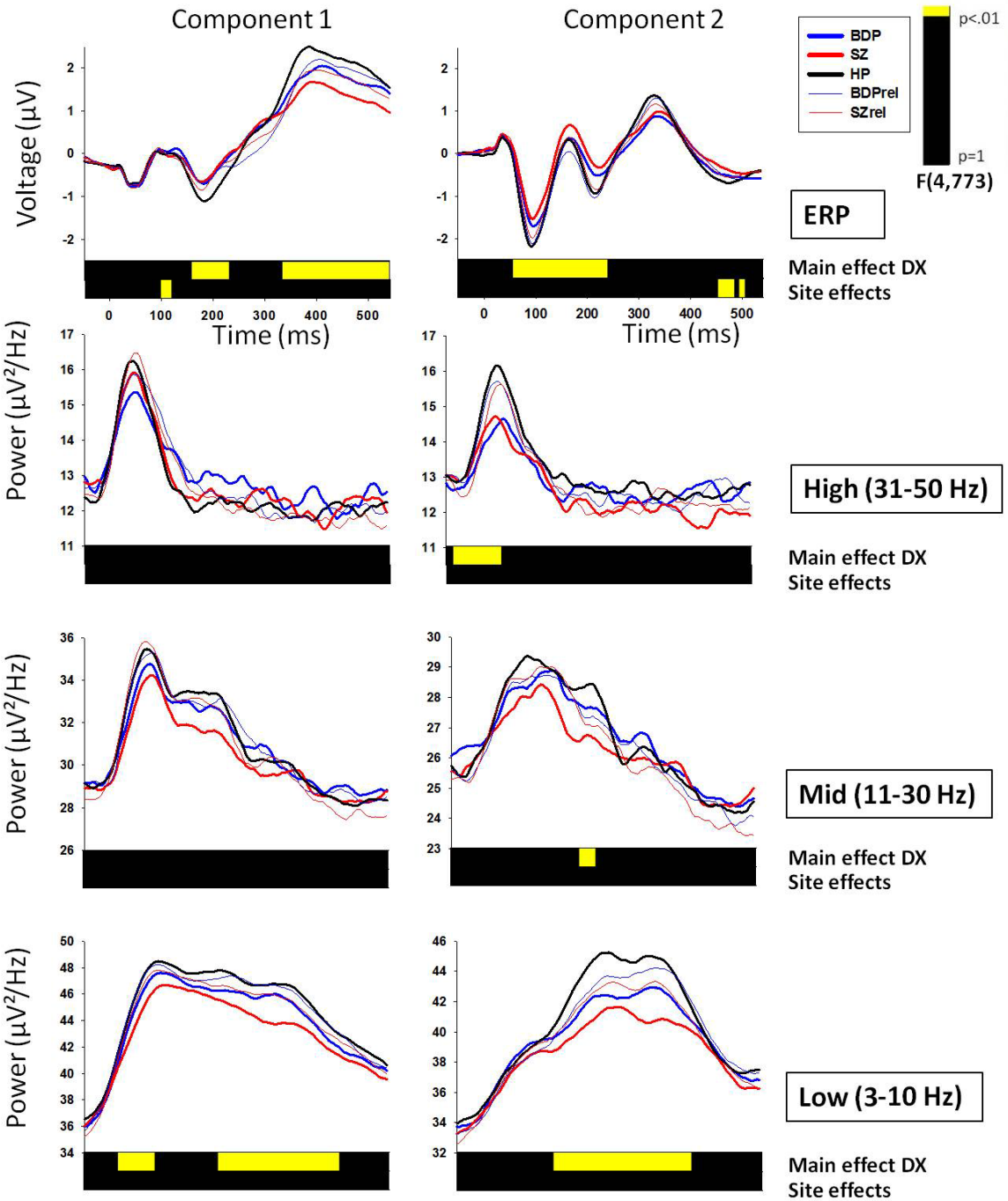

Figure S1. Site effects (site x DX interaction) for targets are minimal and show no overlap with main effects of DX. BDP, bipolar disorder with psychosis; DX, diagnosis; ERP, event-related potential; HP, healthy subjects; rel, relatives; SZ, schizophrenia.

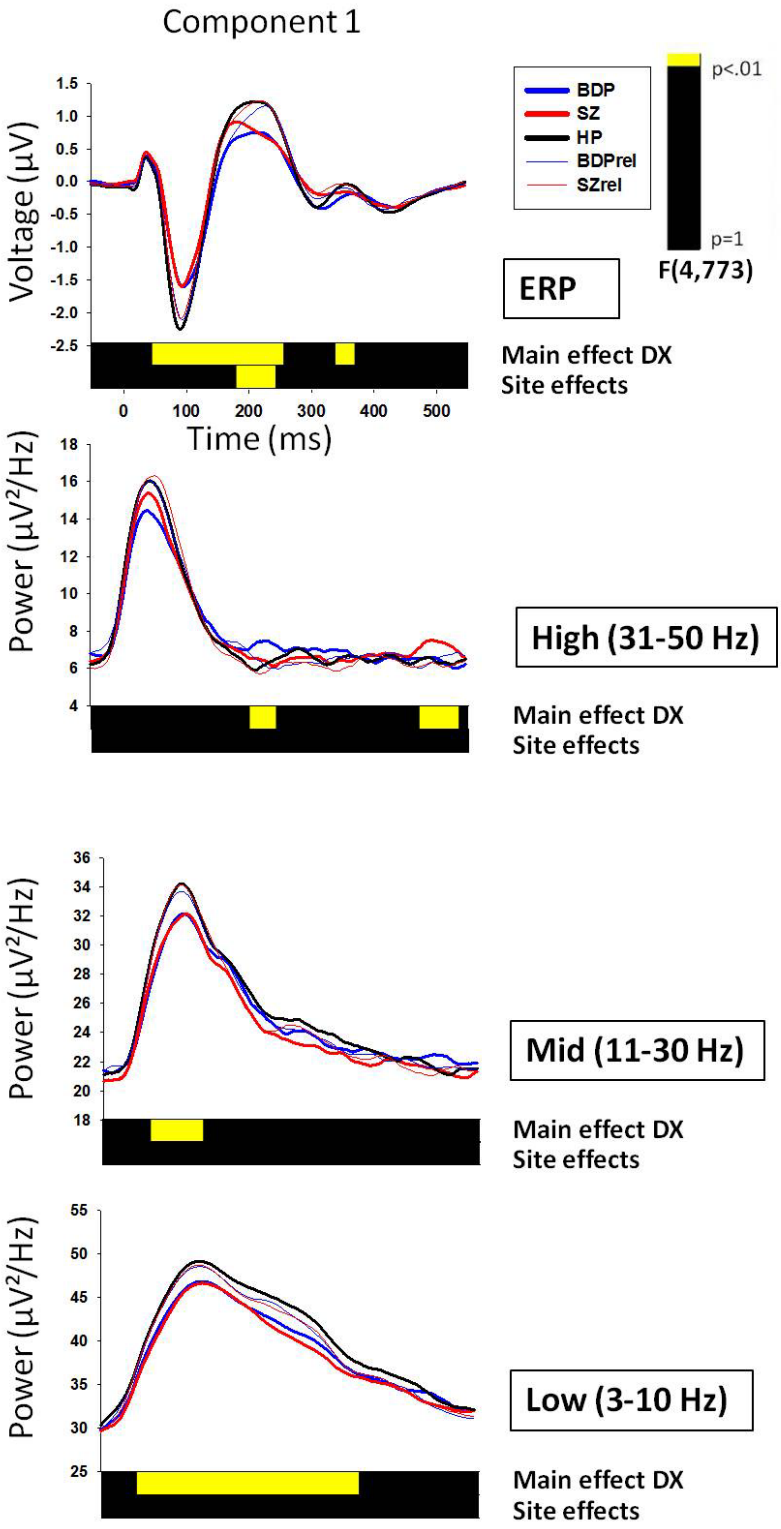

Figure S2. Site effects (site x DX interaction) for standards are minimal and show little overlap with main effects of DX. See Figure S1 for abbreviations.

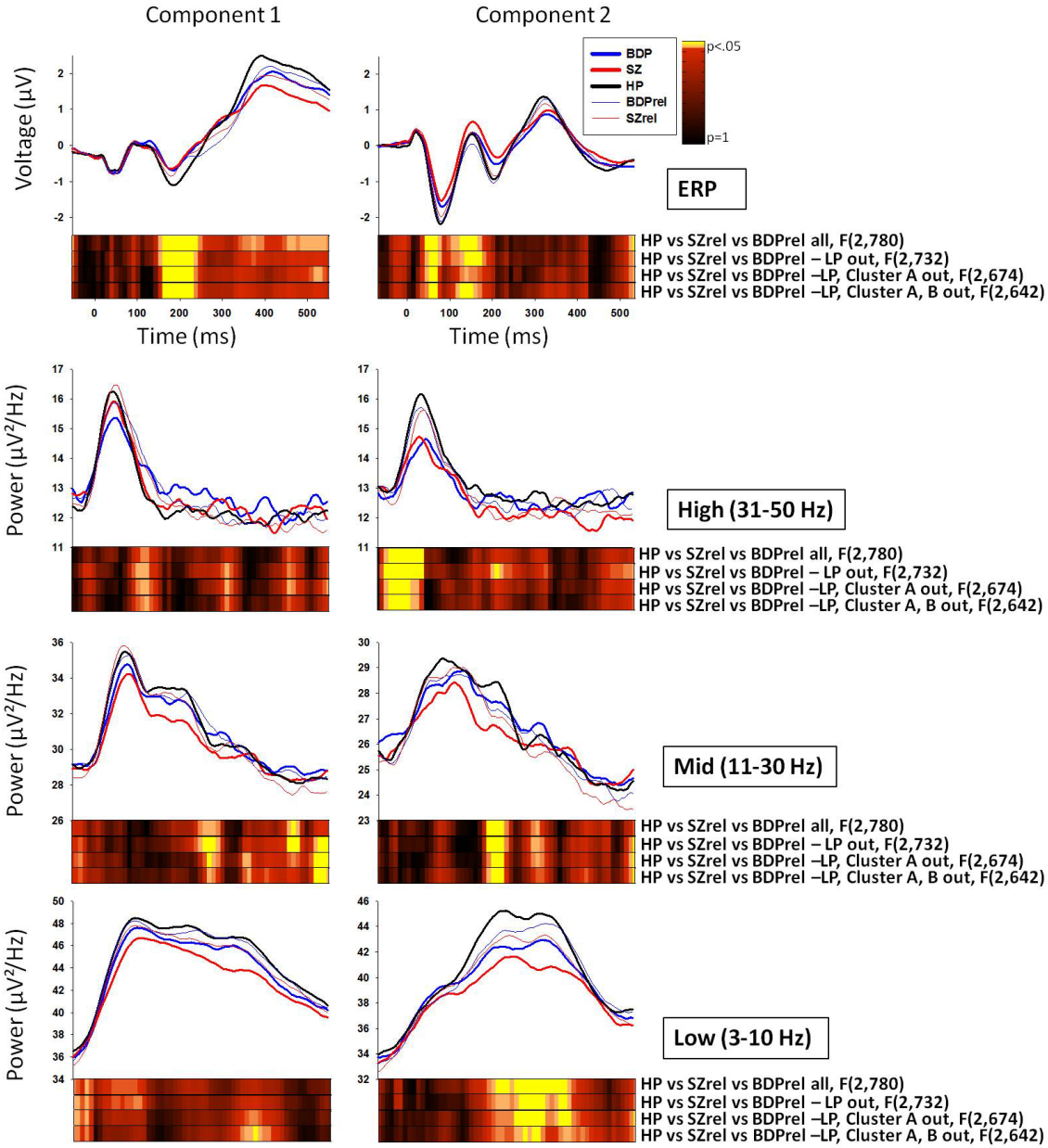

Figure S3. Targets. Full range of *p* values for group comparisons on relatives, first with all relatives, then leaving out those with a lifetime history of psychosis (LP), then those with Cluster A diagnoses, then Cluster B diagnoses. For most time-bins, group differences are remarkably consistent, suggesting primarily constitutional rather than disease-related neural abnormalities in those at risk for psychosis. See Figure S1 for abbreviations.

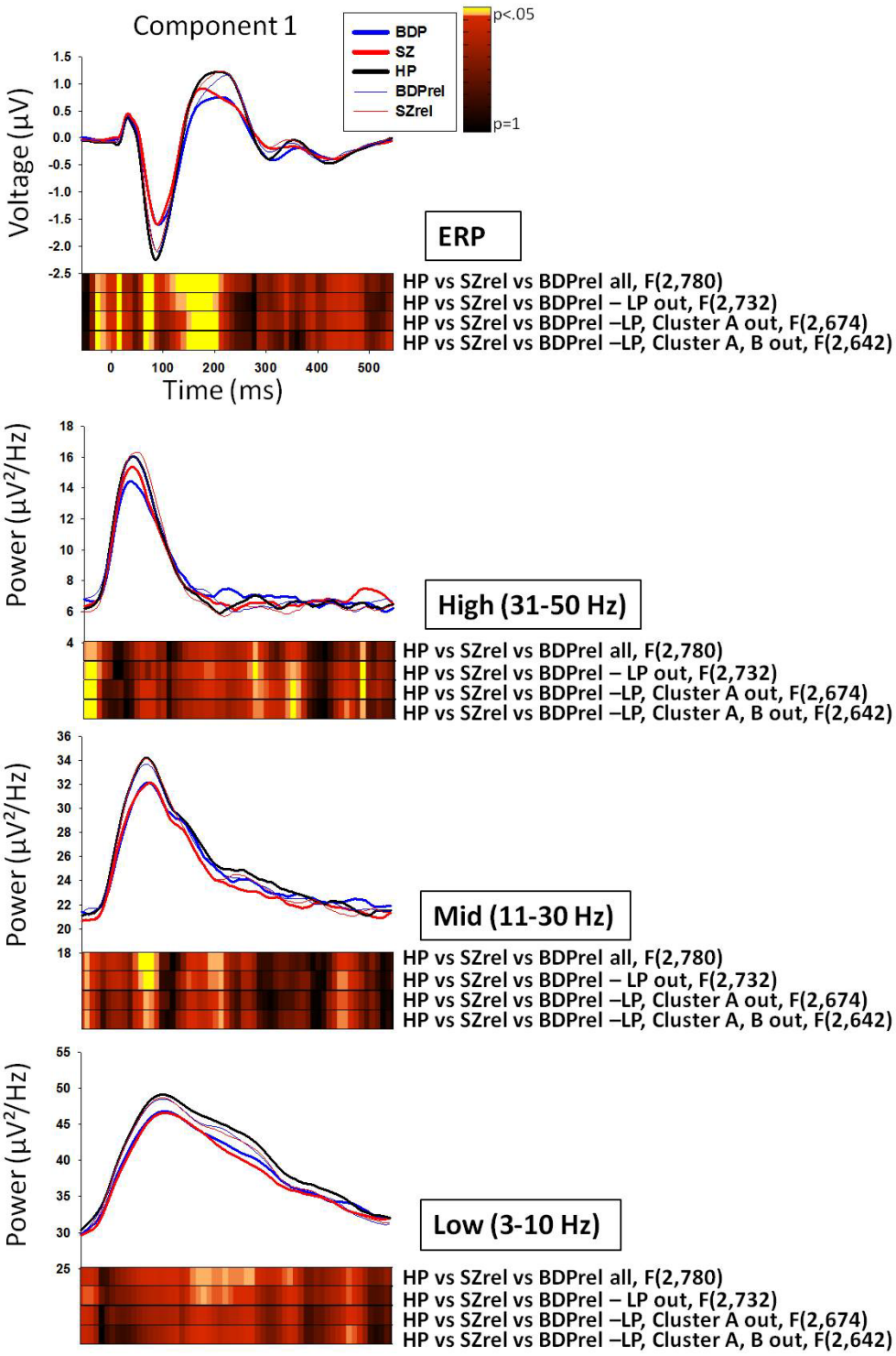

Figure S4. Standards. Full range of *p* values for group comparisons on relatives, first with all relatives, then leaving out those with a lifetime history of psychosis (LP), then those with Cluster A diagnoses, then Cluster B diagnoses. For most time-bins, group differences are remarkably consistent, suggesting primarily constitutional rather than disease-related neural abnormalities in those at risk for psychosis. See Figure S1 for abbreviations.

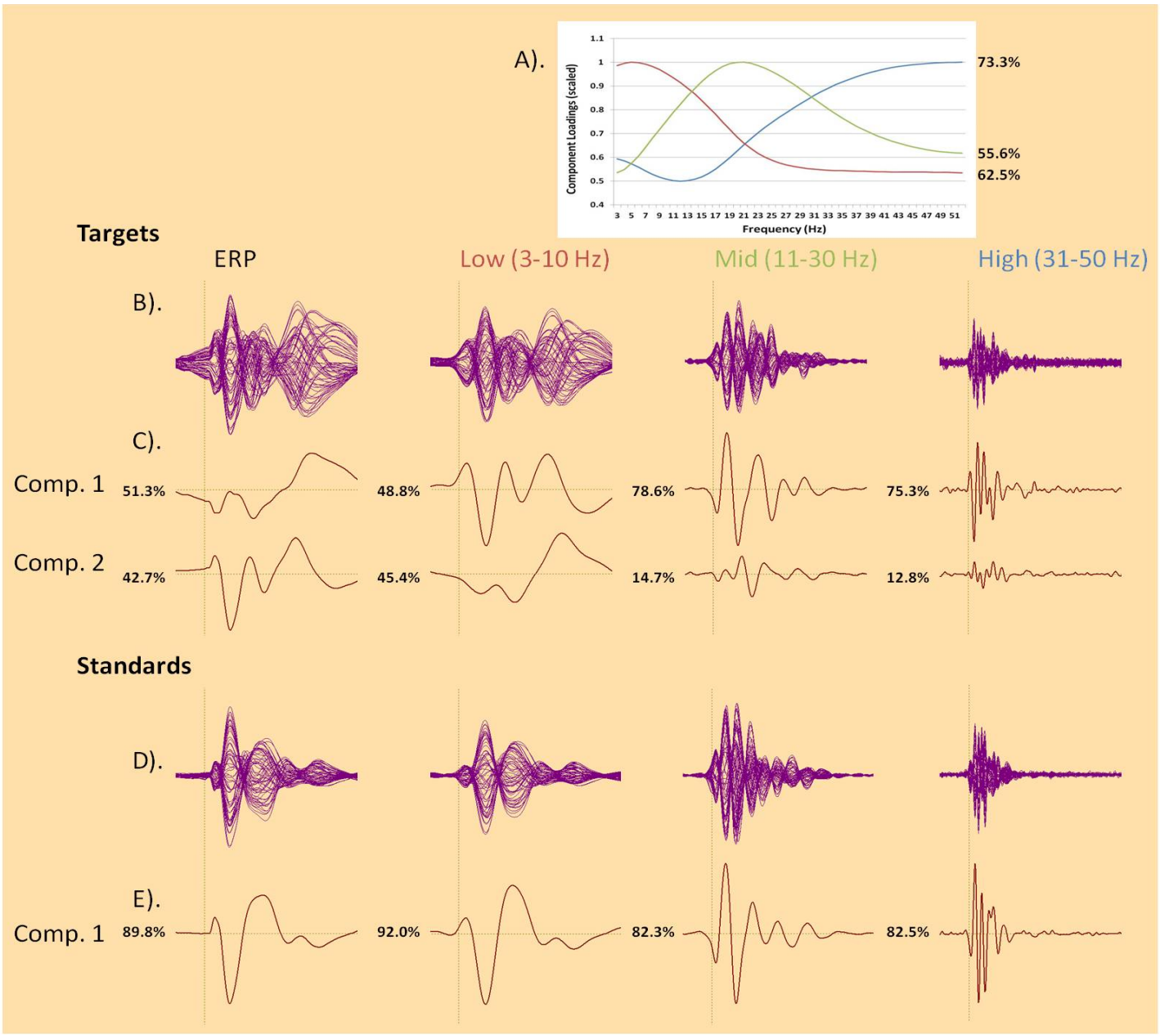

Figure S5. Principal component analysis (PCA) component structure for frequency and spatial PCAs. (**A**) Frequency PCA (PCA1) component waveforms and percent variance accounted for. These 3 components formed the basis for the 3 data-driven frequency bands into which the event-related potential (ERP) was filtered prior to spatial PCA (below, headings match PCA1 waveforms in color) and wavelet transformation. (**B**) Butterfly plots for the target ERP and then with each frequency component filter applied. (**C**) Target spatial PCA (PCA2) component waveforms and percent variance accounted for. (**D**) Butterfly plots for the standard ERP and then with each frequency component filter applied. (**E**) Standard spatial PCA (PCA2) component waveforms and percent variance accounted for.

Table S1. As a comparison with the findings for the primary methodology used in this study, this table shows P3 amplitude and latency defined by the maximum amplitude of the Target ERP Component 1 waveform (this waveform captured the traditional P3b topography most compared in the literature) between 250 and 550 ms post-stimulus. Omnibus *F* values for group differences and proband comparisons to healthy subjects for P3 amplitude and latency at the P3 peak. Effect sizes represent group differences from healthy subjects (HP means) and are calculated using Glass's delta with bootstrapped two-tailed significance values. Positive effect sizes indicate a larger amplitude response in healthy subjects.

	Targets	
	P3 Amplitude	**P3 Latency**
Range for Peak Definition	250-550 ms	250-550 ms
Omnibus ANOVA *F* Value	8.04***	0.27
SZ vs HP *t* Value	5.60***	0.12
BDP vs HP *t* Value	3.13**	0.54
Familiality	0.30***	0.04
Effect Sizes		
HP mean	5.13 μV	384.91 ms
BDP	-0.29**	0.05
SZ	-0.51**	0.01
BDPrel	-0.07	0.09
BDPrel -psychosis	-0.05	0.07
BDPrel -psych/cluster A	-0.04	0.07
BDPrel -psych/cluster A/cluster B	-0.01	0.06
SZrel	-0.15**	0.04
SZrel -psychosis	-0.13*	0.08
SZrel -psych/cluster A	-0.11*	0.05
SZrel -psych/cluster A/cluster B	-0.11*	0.06

ANOVA, analysis of variance; BDP, bipolar disorder with psychosis; ERP, event-related potential; HP, healthy subjects; rel, relatives; SZ, schizophrenia.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

Table S2. Comparison of probands (SZ, BDP) and their first-degree relatives (SZrel or BDPrel) on variables surviving the discriminant analysis. Effect sizes represent relatives' group differences from their proband group (BDP vs BDPrel or SZ vs SZrel) and are calculated using Glass's delta with bootstrapped two-tailed significance values. Positive effect sizes indicate a larger amplitude response in probands, except in cases where the proband mean is negative (N1, N2, N2/P2).

	Standards					**Targets**			
	N1	**P2**	**Mid freq**	**High freq**	**High freq**	**Comp1 N2**	**Comp2 P2/N2**	**Comp1 P3b**	**Comp1 Low freq**
Range (in ms)	50-130	130-250	30-110	200-240	460-520	160-230	140-240	330-540	20-90
BDP vs BDPrel *t* Value	3.07**	1.61	2.21*	2.55*	0.32	0.41	3.69**	2.41*	1.43
SZ vs SZrel *t* Value	3.35**	1.27	2.49*	1.42	3.29**	0.20	5.29**	5.37**	2.44*
Effect Sizes									
BDP vs BDP relatives									
BDPrel	.30**	-.14	-.20*	.24**	.03	-.04	.35**	-.22*	-.13
BDPrel -psychosis	.34**	-.17	-.22*	.24*	.04	-.03	.37**	-.26**	-.15
BDPrel -psych/cluster A	.31**	-.17	-.23*	.22*	.02	.03	.36**	-.28**	-.14
BDPrel -psych/cluster A/cluster B	.33**	-.17	-.24**	.24*	.03	.01	.38**	-.29**	-.18
SZ vs SZ relatives									
SZrel	.31**	-.12	-.23**	.13	.28**	-.02	.51**	-.49**	-.21**
SZrel -psychosis	.33**	-.15	-.23**	.16	.31**	.01	.54**	-.53**	-21**
SZrel -psych/cluster A	.34**	-.23*	-.29**	.13	.31**	.07	.51**	-.55**	-.26**
SZrel -psych/cluster A/cluster B	.35**	-.19	-.26*	.13	.30**	.05	.50**	-.56**	-.28**

BDP, bipolar disorder with psychosis; ERP, event-related potential; HP, healthy subjects; rel, relatives; SZ, schizophrenia.
* $p < .05$.
** $p < .01$.

Supplemental Methods

Event-Related Potential (ERP) Spatial Principal Component Analysis (PCA)

For each condition, PCA with promax (oblique) vector rotation and Kaiser normalization (1) was calculated on a 64 x 64 sensor covariance matrix (1000 time-points as observations). Scree tests (2) identified 2 components for the target condition (accounting for 65.7 and 29.6 percent of the variance) and 1 component (86.8 percent of the variance) for the standard condition. Each set of component weights was multiplied by each subject's averaged data, summed across sensors, and divided by the sum of the component weights, reducing waveforms from one for each sensor to one waveform per component for each subject for targets and standards (Figures 1 and 2).

Time-Frequency PCA

PCA with promax (oblique) vector rotation and Kaiser normalization (1) was calculated on a 50 x 50 frequency covariance matrix (1204 subjects concatenated across targets and standards for a total of 2408 observations, collapsed across time and channels). For ease of explanation this step will be referred to as PCA1. A scree test (2) identified 3 frequency bands: high (31-50 Hz), low (3-10 Hz) and mid-range (11-30 Hz). Then, to reintroduce temporal information and obtain spatial topographies for each frequency band component, the frequency band delimiters were used to guide high and low pass filter cutoffs for a subsequent spatial PCA (which will be referred to as PCA2) of the grand average ERP separately for targets and standards utilizing only the frequency information within that data-driven band. For each of the three frequency band spatial PCAs (PCA2), scree tests consistently identified 2 components for targets and 1 for standards (9 total frequency components, see Figure 1 for targets and Figure 2 for standards). Each set of PCA2 weights was multiplied by each subject's averaged data,

summed across sensors, and divided by the sum of the component weights, reducing waveforms from one for each sensor to one waveform per component for each subject for targets and standards. These frequency waveforms were then subjected to the same modified Morlet wavelet transformation described in the main text. For all PCA2 components and the resulting power information was averaged across the delimited frequency band to obtain EEG oscillatory power information across time by individual and frequency band component topography.

Supplemental References

1. Dien J, Khoe W, Mangun GR (2007): Evaluation of PCA and ICA of simulated ERPs: Promax vs. Infomax rotations. *Hum Brain Mapp* 28(8):742-763.
2. Cattell RB (1966): Evaluating therapy as total personality change: theory and available instruments. *Am J Psychother* 20(1):69-88.