INTRINSIC NEURAL ACTIVITY DIFFERENCES IN PSYCHOSIS BIOTYPES: FINDINGS FROM THE BIPOLAR-SCHIZOPHRENIA NETWORK ON INTERMEDIATE PHENOTYPES (B-SNIP) CONSORTIUM

by

OLIVIA THOMAS

(Under the Direction of BRETT CLEMENTZ)

ABSTRACT

The B-SNIP consortium proposed "Biotypes," subgroups of neuro-cognitively homologous psychosis cases. Neural/intrinsic activity (IA) unbound to stimulus-processing was important for differentiating Biotypes; high non-specific activity characterized Biotype-2. Initial Biotypes characterization did not include precise estimates of IA. This report hypothesizes IA is critical for differentiating psychosis Biotypes. Method: Recruitment included psychotic probands (schizophrenia, schizoaffective disorder, bipolar-I disorder), first-degree biological relatives, and healthy persons (N=1338). Probands were also sub-grouped by Biotype. IA was quantified using 64-sensor EEG during 10-sec inter-stimulus-intervals from an auditory paired-stimuli task. Frequency bands (delta/theta, alpha, beta, gamma), single-trial power, and connectivity were quantified. Results: Biotype-1 exhibited low and Biotype 2 exhibited high IA relative to HC. No difference in DSM groups vs. HC emerged. Discussion: Only Biotypes were differentiated by IA; Accentuation of IA characterized Biotype-2. Neurobiologically-defined subgroups may

facilitate use of IA in translation models aimed at developing effective treatments for psychosis-relevant neural deviations.

INDEX WORDS: intrinsic activity; B-SNIP; biotypes; DSM; psychosis; connectivity

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CHAPTER 1

INTRODUCTION

Of the 20% of the body's energy allocated to the brain, 95% of it is utilized in ongoing and unstructured neural activity called "intrinsic activity" (IA; Raichle, 2015). Despite such a great proportion of biological resources being allocated to the processes encompassed in IA, traditional research is oriented towards reactive responses that encompass the other 5% of the brain's energy budget; this is likely due to the ability to tightly control variables (Raichle & Mintun, 2006). Such control helps make possible the study of a single reactive phenomenon through the comparison of two or more groups differing upon only that phenomenon. In this traditional method, experimental groups are compared to "control groups" – a group that has not been given or does not contain the experimental stimuli, operating under the assumption that lack of an independent variable is enough to establish a "baseline", comparable group (Raichle, 2015). However, without definition of the intrinsic nature of the brain such comparisons must be left to depend on predictive models. Research of translational applications have found that diminished signal-to-noise ratios are associated with problems identifying stimulus salience. A signal-to-noise ratio is a measure used to quantify the strength/size of the applied/controlled signal relative to spontaneous fluctuations. Neural networks by nature contain noise, or random neuronal spiking, occurring alongside active network states. The frequency of random spiking controls the ratio of active signal-to-noise. Neural dysfunction resulting in increased noise can limit the ability of the brain to detect stimulus salience, presenting a promising way of identifying physiological mechanisms for psychosis manifestation (Rolls et al., 2008).

Psychosis, in which an individual loses touch with reality to varying degree, is present in certain mental disorders. Such disorders investigated in the Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) project included schizophrenia (SZ), schizoaffective disorder (SAD), and bipolar-I disorder (BD). There are current investigations being undertaken in effort to potentially further translational psychosis research, though attempts have been surprisingly unsuccessful to find meaningful and consistent endophenotypes (a.k.a. intermediate phenotypes) (Tamminga et al., 2013; Insel & Cuthbert, 2009). An endophenotype is a measure, in this case of distinct brain functions, with specific features; it is able to be measured across diverse clinical and research environments, is quantifiable, heritable, cosegregates, and is expressed in family members that are unaffected themselves (Glahn et al., 2011; Miller & Rockstroh, 2016; Gottesman & Shields, 1973). Symptoms amongst the disorders overlap greatly, complicating both diagnosis and treatment. Risk genes and family lineages overlap between the diagnoses as well. Because all three disorders (SZ, SAD, BD) feature psychosis, it presented an ideal clinical phenotype to generate a cohort for genetic and molecular characterization of mental illness (van OS & Reininghaus, 2016). Specific anatomical architecture is plausibly associated with psychosis, such as can be seen between BD with and without psychosis (Maggioni et al, 2017).

In the investigation into the neurobiology of psychosis, the B-SNIP consortium anticipated some differences and similarities between DSM diagnoses in the realms of clinical, familial, and phenotypic characteristics (Tamminga et al., 2013; Keshavan et al., 2013). Definition of such characteristics could be paramount in the elucidation of the biology of psychosis and disorders presenting with psychosis. [Such molecular, cellular, and systems knowledge could provide clearer distinctions and similarities of the pathophysiology of and risk pathways between clinical disorders] (Tsuang et al., 2000). The goal of the B-SNIP consortium

was to expand knowledge of psychosis endophenotypes, pursued through collaboration between 5 sites in 5 US states. Great care was taken to maintain consistency in site-to-site data acquisition. Diagnostic and clinical assessment techniques were identical, and all had similar approaches to recruitment. Each site had a recruitment goal of 200 probands with SZ, SAD, and BD, at least one of each probands' first-degree relatives, and 100 healthy comparison participants. All sites recruited within 20% of this goal. Probands included were in a clinically stable, non-acute symptom state, as assessed by trained research clinicians. Participants were also assessed using a variety of other methods (including the SCID, BACS, PANSS; see methods – chapter 2). Neurophysiological phenotyping included ocular motor testing with smooth pursuit and saccade paradigms; resting-state EEG; auditory event-related-potentials; structural, diffusion tensor, and resting-state functional brain imaging; and a blood sample to be used for genetic analysis (Tamminga et al., 2013).

The B-SNIP consortium aimed to recruit a sample representative of serious mental illnesses featuring psychosis. Proband diagnoses were limited to SZ, SAD, and BD because prevalence of psychosis was highest within them. To maintain inter-site reliability cross-site conference calls to discuss clinical assessments were carried out monthly and research clinicians refreshed their training at an in-person meeting every year. Statistical data analyses conducted using NCSS software included one-way ANOVAs, Tukey-Kramer multiple comparisons where appropriate, and Yates chi-squared tests. Alpha for these was set at 0.01 (Tamminga et al., 2013).

Notable endophenotypic overlap was observed across diagnoses along with several clinical, demographic, and genetic findings (Clementz et al., 2016; Tamminga et al., 2013). There were less women than men in the group of probands diagnosed with SZ. They exhibited more severity of psychosis symptoms, had less education, decreased IQ, and decreased literacy

level than other groups. Additionally, they exhibited decreased psychosocial functioning regardless of psychosis state. Clinical and demographic characteristics within the SAD and SZ proband groups were most similar to each other. Both groups (SADP and SZP) had lower numbers of Caucasians than BDP, which was mirrored in relative groups. Both had less education and higher PANSS scores than BDP. Probands with SZ historically have shown a lower number of previous suicide attempts, but SADP had the highest frequency (Nordentoft et al., 2011), possibly due to increased cognitive function associated in previous research with greater suicidal ideation; this information brings forth the idea rational considerations and depressed mood could drive suicides (Delaney et al., 2012).

The B-SNIP 1 study found "pure" and "mixed" lineages between SZP and BDP, suggesting and implicating common genetic mechanisms between both groups. Statistically, SZ, SAD, and BDP differed on multiple measures of brain function and structure, but this does not negate their internal disparity nor shared variance (Clementz et al., 2016; Tamminga et al., 2014; Pearlson et al., 2016; Hill et al., 2013; Ivleva et al., 2013; Hamm et al., 2014; Ethridge et al., 2015). When stripped of diagnosis and empirically assessed by clustering analyses, three groups of probands with distinct neurobiological profiles ("Biotypes") emerged that more efficiently predicted external measures of validation (Meda et al., 2016; Ivleva et al., 2017). One composite measure, "sensorimotor reactivity", is a defining characteristic of the biotypes; it is a measure of neural response to sensory stimuli, and each Biotype differed in this ability. The Biotypes showed a predictable pattern of neural response during auditory stimulation tasks, featuring deficiency (Biotype-1), relative normativity (Biotype-3), and accentuation (Biotype-2). Biotype-1 and Biotype-2 significantly differed from HC, but Biotype-3 had only mild deviations from healthy on these measures. Though Biotype-2's response amplitudes to auditory stimuli were in

some cases similar to healthy people (e.g., n100, p200, p300 ERPs), other measures related to ongoing activity (not specifically stimulus-related) were significantly elevated (Clementz et al., 2016; Hudgens-Haney et al., 2017). One such bio-factor (integrated biomarkers) initially called "intrinsic activity" is more accurately described as "ongoing high frequency activity". This bio-factor was comprised of preparatory and induced high frequency signals from oddball and paired-stimuli tasks (Clementz et al., 2016).

As the original measure of intrinsic activity included in Biotype construction did not adequately quantify direct, ongoing, and unstructured neural activity, such a measure was sought for future analyses, once more utilizing auditory paired-stimuli data. During this task, stimuli are presented in pairs separated by 500-ms followed by a 10-sec inter-pair interval (Figure 1). Paired-stimuli variables used in Biotypes creation came from the period 200-ms before the first stimulus to 400-ms after the second stimulus, leaving the middle 10-sec inter-pair interval available for direct IA quantification. During this period, participants are awaiting the next stimulus pair but have no structured task or stimulus processing requirements. In contrast to the original induced activity bio-factor, this lack of structure provides a different and perhaps better index of ongoing neural activity.

In this endeavor we sought to improve upon the biomarker IA, a theoretically and practically important differentiator of psychosis subgroups potentially useful in future translational and treatment outcome investigations. The purpose of these analyses was to evaluate the following hypotheses: (i) DSM psychosis subgroups do not differ on level of IA; (ii) Biotype-1 cases have reduced levels of IA compared to all other groups; (iii) Biotype-2 cases have enhanced levels of IA compared to all other groups; and (iv) the initial bio-factors used to

characterize exuberant neural activity in Biotype-2 are highly correlated with a more direct measure of IA.

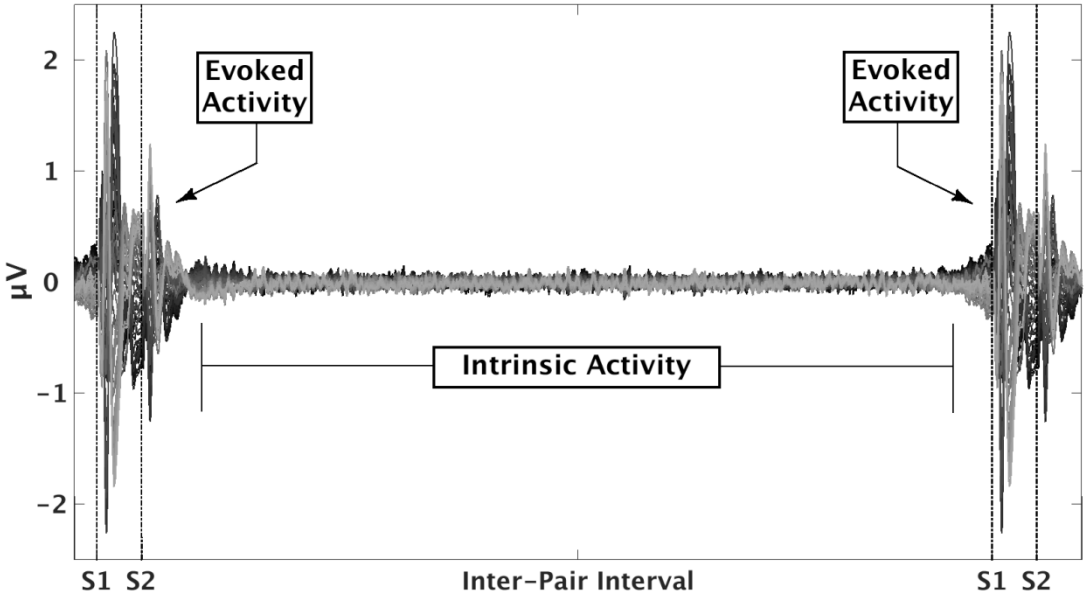

Figure 1: Intrinsic Activity. Average voltage response averaged over all trials averaged over all healthy participants (N=213). Evoked activity is in response to a paired click stimuli (500 ms interval between clicks). Intrinsic activity was quantified using the intervals between each paired click stimuli.

CHAPTER 2

METHODS

2.1 Participants

Laboratory data collection, participant recruitment, and interviews were completed at the Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) consortium sites as described in Chapter 1 (Tamminga et al., 2013).

Data analysis was performed at the University of Georgia in Athens, Georgia. Probands with psychosis (N=531), their first-degree relatives (N=589), and demographically comparable healthy people (N=218) were fully clinically characterized (Tamminga et al., 2013). Probands were assessed with the Structured Clinical Interview for DSM-IV-TR (First et al., 1997) while their relatives were given the Structured Interview for DSM-IV Personality Disorders (Zanarini et al., 1996) to measure psychosis spectrum personality traits. Those probands that met DSM-IV criteria for either SZ, SAD, or BDP were administered the Wide Range Achievement Test (WRAT; Wilkinson & Robertson, 2006), Positive and Negative Symptom (PANSS; Lançon et al., 2000), Montgomery- Åsberg Depression Rating (MADRS; Montgomery & Åsberg, 1979), Young Mania Rating (YMRS; Young et al., 1978), Global Assessment of Functioning (GAF; First et al., 1997), and Birchwood Social Functioning (SFS; Birchwood et al., 1990) scales (Tamminga et al., 2013; see Tables 1a-b, Supplemental Tables 1a-b). Healthy participants had no personal history of lifetime psychotic disorders, and no first-degree relatives with a history of psychotic or bipolar disorder as assessed by Family History Research Diagnostic Criteria (Andreasen et al., 1977). The majority of probands and a small subset of their relatives were taking psychotropic medication (Supplemental Tables 2a-d).

Table 1: Sociodemographic and Clinical characteristics of Probands and HC. 1a) Sample characteristics by Biotype constructs.

Table 1a	**Sample Characteristics by Biotype Constructs**					
	HC (*n*=218)	**B1 (*n*=148)**	**B2 (*n*=169)**	**B3 (*n*=214)**	**Test Statistic**	***P* Value**
Sociodemographic Characteristics						
Age, Years, Mean (SD)	37.43 (12.39)	37.42 (13.26)	35.29 (12.22)	35.01 (12.48)	$F_{6.1330}$=9.927	<.001
Sex/Male, *n*(%)	93 (42.7)	77 (52.0)	86 (50.9)	114 (53.3)	X^2_6 = 43.08	<.001
Handedness, *n*(%)					X^2_6 = 13.40	0.341
Right	189 (86.7)	117 (80.7)	149 (88.7)	180 (84.9)		
Left	26 (11.9)	23 (15.5)	16 (9.5)	29 (13.7)		
Ambidextrous	3 (1.4)	5 (3.4)	3 (1.8)	3 (1.4)		
Ethnicity/Hispanic, *n*(%)	21 (9.6)	15 (10.1)	18 (10.7)	14 (6.5)	X^2_6 = 11.798	0.067
Race, *n*(%)						
White	148 (67.9)	69 (46.6)	116 (68.6)	150 (70.1)	X^2_6 = 57.194	<.001
African American	56 (25.7)	77 (52.0)	50 (29.6)	60 (28.0)	X^2_6 = 61.901	<.001
Other	4 (1.8)	3 (2.0)	2 (1.2)	3 (1.4)	X^2_6 = 1.221	0.976
Education, years, Mean (SD)	15.26 (2.62)	12.41 (2.08)	13.16 (2.32)	14.15 (2.31)	$F_{6.1327}$=27.85	<.001
Clinical Characteristics, Mean (SD)						
Age of Illness Onset, Years	-	17.55 (6.99)	17.55 (7.76)	17.38 (7.90)	$F_{6,760}$=12.346	<.001
Age of First Hospitalization, Years	-	21.47 (7.72)	23.11 (8.35)	23.73 (8.83)	$F_{6,541}$=1.222	0.3
No. of Lifetime Hospitalizations	-	7.24 (7.18)	5.89 (6.55)	4.69 (5.43)	$F_{6,497}$=2.835	<.05
PANSS						
Total	-	64.33 (17.96)	64.99 (17.65)	60.12 (16.50)	$F_{6,593}$=5.163	<.001
Positive Subscale	-	16.41 (5.55)	16.29 (5.77)	14.93 (5.15)	$F_{6,594}$=4.025	<.005
Negative Subscale	-	16.27 (5.88)	15.45 (5.27)	13.92 (5.30)	$F_{6,594}$=6.510	<.001
General Symptoms Subscale	-	31.68 (9.18	33.30 (9.20)	31.28 (8.73)	$F_{6,595}$=3.498	<.005
YMRS	-	5.49 (5.98)	6.38 (6.22)	5.73 (5.97)	$F_{6,656}$=3.812	<.005
MADRS	-	10.01 (9.73)	11.54 (9.15)	10.52 (5.97)	$F_{6,656}$=6.174	<.001
GAF	86.52 (6.60)	49.09 (12.08)	52.66 (13.63)	56.04 (13.68)	$F_{6,1315}$=232.947	<.001
WRAT-4 IQ	103.45 (14.20)	90.01 (13.79)	94.85 (13.92)	105.36 (14.03)	$F_{6,1310}$=31.905	<.001

Table 1: Sociodemographic and Clinical characteristics of Probands and HC. 1b) Sample characteristics by conventional diagnoses.

Table 1b	**Sample Characteristics by Conventional Diagnoses**					
	HC (*n*=218)	**SZ (*n*=223)**	**SAD (*n*=130)**	**BD (*n*=178)**	**Test Statistic**	***P* Value**
Sociodemographic Characteristics						
Age, Years, Mean (SD)	37.43 (12.39)	35.22 (12.78)	36.51 (12.20)	35.92 (12.81)	$F_{6.1330}$=9.728	<.001
Sex/Male, *n*(%)	93 (42.7)	148 (66.4)	57 (43.8)	72 (40.4)	X^2_6 = 73.830	<.001
Handedness, *n*(%)					X^2_6 = 16.581	0.166
Right	189 (86.7)	185 (84.5)	112 (86.2)	149 (84.7)		
Left	26 (11.9)	30 (13.7)	12 (9.2)	26 (14.8)		
Ambidextrous	3 (1.4)	4 (1.8)	6 (4.6)	1 (0.6)		
Ethnicity/Hispanic, *n*(%)	21 (9.6)	19 (8.5)	15 (11.5)	13 (7.3)		
Race, *n*(%)						
White	148 (67.9)	112 (50.2)	87 (66.9)	136 (76.4)	X^2_6 = 62.266	<.001
African American	56 (25.7)	104 (46.6)	47 (36.2)	36 (20.2)	X^2_6 = 66.695	<.001
Other	4 (1.8)	4 (1.8)	1 (0.80)	3 (1.7)	X^2_6 = 2.931	0.818
Education, years, Mean (SD)	15.26 (2.62)	12.78 (2.25)	14.20 (2.37)	36.51 (12.20)	$F_{6,1327}$=23.092	<.001
Clinical Characteristics, Mean (SD)						
Age of Illness Onset, Years	-	18.12 (6.16)	17.45 (8.91)	14.20 (2.37)	$F_{6,760}$=12.483	<.001
Age of First Hospitalization, Years	-	22.19 (7.05)	23.60 (9.59)	23.10 (8.89)	$F_{5,541}$=0.621	0.684
No. of Lifetime Hospitalizations	-	5.11 (4.97)	6.00 (7.59)	6.75 (6.80)	$F_{5,498}$=1.923	0.089
PANSS						
Total	-	67.04 (17.31)	53.13 (13.59)	68.98 (16.61)	$F_{6,593}$=21.018	<.001
Positive Subscale	-	16.98 (5.48)	12.67 (4.30)	17.96 (5.15)	$F_{6,594}$=10.831	<.001
Negative Subscale	-	17.00 (5.86)	11.99 (3.76)	15.97 (5.23)	$F_{6,594}$=21.178	<.001
General Symptoms Subscale	-	33.10 (9.05)	28.47 (7.99)	35.06 (8.86)	$F_{6,595}$=10.927	<.001
YMRS	-	5.84 (5.80)	5.21 (5.89)	6.86 (6.59)	$F_{6,656}$=4.145	<.001
MADRS	-	8.63 (8.27)	10.46 (9.30)	14.51 (10.39)	$F_{6,656}$=11.367	<.001
GAF	86.52 (6.60)	49.19 (12.37)	61.02 (12.54)	48.63 (11.73)	$F_{6,1314}$=261.329	<.001
WRAT-4 IQ	103.45 (14.20)	94.96 (16.19)	101.72 (13.57)	97.03 (15.19)	$F_{6,1310}$=9.278	<.001

There were minimal associations between clinical and/or medication variables and biomarker outcomes (Clementz et al., 2016). The project was approved by IRBs at the participating institutions. All participants provided informed consent prior to inclusion after they obtained a complete description of the study.

2.2 Procedures

Across sites, testing and recording conditions were similar; stimulus presentation and recording equipment were identical. Experimenters were trained and continually monitored across sites to ensure data collection procedures were comparable. Previous studies confirmed there were no group by site effects on the EEG data (Hamm, Ethridge et al., 2014).

2.3 Stimuli

Participants sat in a shielded booth during the paired-stimuli task, and listened to 150 binaural broadband auditory click pairs (4-ms duration at 75 dB with a 500-ms inter-click interval) occurring every 9-10 for an average of 9.5 seconds. Clicks were presented through etymotic ear inserts. Participants were told to count click pairs (Hamm et al., 2014).

2.4 EEG Recording

Electroencephalogram (EEG) from 64 Ag/AgCl sensors with impedance less than 5 KΩ using a Quik-Cap from Compumedics Neuroscan (El Paso, TX). Resulting data was digitized (1000 Hz) and amplified (x12,500) using the Neuroscan Acquire and Synamps2 recording systems from Compumedics Neuroscan. A standard placement of the 10-10 EEG system (including mastoids, CP1/2 locations, a nose reference, and a forehead ground) was employed in order to provide sampling below the canthomeatel line (Hamm et al., 2014; Supplemental Methods).

2.5 Data Processing

EEG data were pre-processed in BESA 5.3 to remove artifacts and bad sensors, with such sensors being interpolated using spherical spline interpolation (MEGIS Software, Gräfelfing, Germany). Less than 5% of sensors were interpolated for any one participant. After conversion to average reference, data were digitally band-pass filtered (low: 0.5 Hz; High: 55 Hz; zero phase filter; rolloff: 6 and 48 dB/octave, respectively). Removed artifacts were comprised of muscle tension, blinks, and cardiac artifacts identified using an independent components analysis (EEGLAB 9.0; Hamm et al., 2014; Supplemental methods). The data from 500 ms after the second click of each trial and 500 ms before the next trial were then extracted. Epochs containing activity ±125 μV at any sensor at any time point were excluded from any subsequent analysis. Any participant that did not have at least 30 epochs (270 seconds) was excluded from subsequent analysis.

2.6 Time-Frequency Transformation

Data were transformed into the time-frequency (TF) domain using the following approach. In EEGlab, FFTs were computed on 50% overlapping Hanning tapered windows (1-55 Hz, 1000ms steps, 1 Hz resolution) for each 9-second inter-pair epoch, resulting in 17 time bins per epoch [500-8500 ms in 500 ms bins]. Power values (squared absolute values of complex FFT outputs) were then converted to decibels (10*log10). To determine the stability of the Power values across time, intraclass correlation was calculated across time bins for each sensor and frequency using all participants' data. Since all ICCs were > .96, power values were averaged over time bins. In order to capture maximum explanatory variance across variables, avoid information redundancy, and reduce the number of statistical comparisons, frequency data

reduction was accomplished by principal component analysis (PCA, see Supplemental Methods; Figure 2).

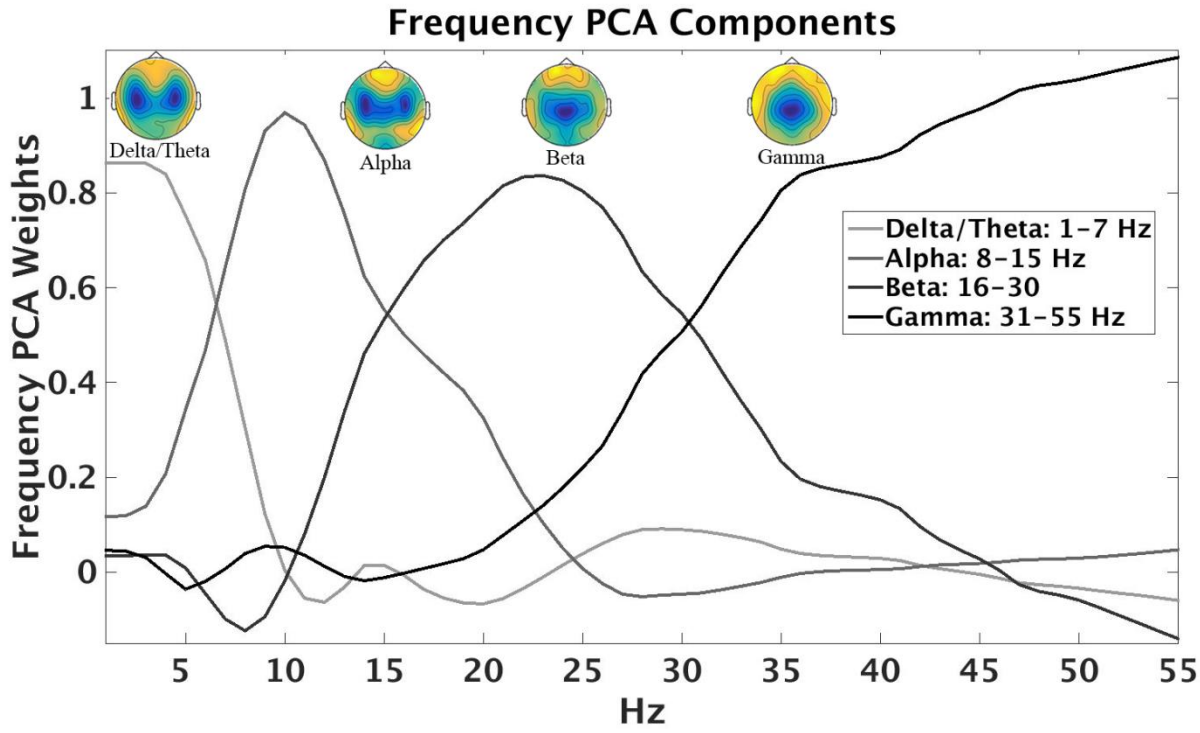

Figure 2: Empirically derived frequency bands. Each line represents the factor pattern matrix results for each frequency (1-55 Hz) for each component. Topographies show averaged neural response from all participants for each frequency component.

The 55 frequencies were reduced to four primary bands (97% variance accounted): delta/theta (1-7Hz), alpha (8-15 Hz), beta (16-30 Hz), and gamma (31-55 Hz), as shown in Figure 2. An additional spatial PCA (variance range: 37-49%) was performed on each frequency band in order to reduce the data from 64 sensors to one virtual sensor (Hamm et al., 2014; Ethridge et al., 2015; Supplemental Methods).

2.7 Connectivity Analyses

Organization of brain activity within and between brain regions is an important compliment to assessing the magnitude of intrinsic activity (Wang et al., 2017). To assess this

additional feature, the debiased weighted phase-lag index (dbWPLI) was employed as computed in Fieldtrip (Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands: https://www.ru.nl/neuroimaging/fieldtrip) using all 2016 sensor pairs from the concatenated complex output of the FFTs using all time bins from each epoch (1-55 Hz; output is averaged connectivity across all epochs). The dbWPLI method minimizes associations that may result from erroneous inflation of EEG connectivity caused by volume conduction. It does so by calculating an unbiased index of phase synchronization (2 or more signals oscillating with similar phase angles) between two time series that are then weighted by the magnitude of the imaginary component of the cross-spectrum (Vinck et al., 2011; Wang et al., 2017). The cross spectrum describes how much linear information of one signal is explained by another paired signal to estimate association between the two. The index values range from 0 to 1; 0 indicates the absence of phase-lagged coupling and 1 indicates the strongest possible coupling (Vinck et al., 2011; Wang et al., 2017). After dbWPLI calculation, the frequency PCA weights (delta/theta (1-7Hz), alpha (8-15 Hz), beta (16-30 Hz), and gamma (31-55 Hz) derived from the Power values were applied to each sensor pair for each participant in order to compare responses across the same frequency bands.

2.8 Statistical Analysis

All statistics were performed in SPSS Statistics version 23 (Armonk, NY: IBM Corp.). The following analyses were performed on each Power PCA component. Each PCA component's age effects were calculated using a linear regression analysis on healthy participants (Dukart et al., 2011). Components with significant age effects were adjusted for all participants by subtracting the product of the linear regression coefficient and age for each individual (see Supplemental Methods). Analysis of variance (ANOVA) was used to evaluate for

group differences, separately for DSM and Biotype. Each component was analyzed with a 2 (gender) X 4 (DSM: [HC, SZ, SAD, BDP]; Biotype: [HC, B1, B2, B3]) mixed model. This analysis was also performed for HC vs relative groups (DSM: [HC, SZR, SADR, BDPR]; Biotype: [HC, B1R, B2R, B3R]). Tukey post hoc tests were used to probe significant effects in the omnibus ANOVAs. In order to account for type-1 error inflation, a significant threshold of .0125 was set for these ANOVA comparisons. In order to determine if there was an interaction between DSM and Biotype designation, an additional DSM by Biotype ANOVA was performed using only psychosis probands ([SZ, SAD, BDP] vs. [B1, B2, B3]).

dBWPLI: For each of the 2,016 sensor pair connections at each frequency band component (4), a 1-way ANOVA was performed separately for DSM and for Biotype proband groups and separately for HC vs DSM and Biotype relative groups. Due to the large number of statistical tests, each set of ANOVAs was run 5,000 times (bootstrap procedure) with group membership randomly shuffled at each step (sampling with replacement). Probability estimates of the actual F-values were then calculated as the proportion of randomly generated F-values greater than the actual estimate (Hamm et al., 2014). To correct for the effect of multiple comparisons, the resulting distributions of p-values were converted with the false discovery rate procedure (Hochberg and Benjamini, 1990) to adjusted p-values, which minimized falsely rejected null hypotheses to 5%. The resulting set of significant sensors pairs were then averaged. All statistical steps used to compare Power by groups were performed on the averaged dBWPLI values.

2.9 Post Hoc Analyses: Canonical Correlation and Discriminant Analysis

To summarize variables that efficiently differentiated groups based on intrinsic neural responses, EEG Power/dbWPLI variables significant in the group comparisons were subjected to

canonical discriminant analysis (CDA) (Hamm et al. 2014; supplemental methods) separately by DSM [HC, SZ, SAD, and BDP] and Biotype [HC, B1, B2, and B3]. For each significant canonical variate, means and standard error of the mean were generated. A post hoc Tukey's B test was performed to identify homogenous sub-groupings. To parsimoniously evaluate the relationships between the significant neural components and clinical measures (GAF, SFS, PANSS Negative, PANSS Positive, PANSS General, YMRS, MADRS), canonical correlation analyses (CCA) across all psychosis proband groups were performed (Lambert et al., 1988; Supplemental Methods).

Finally, we also used Pearson correlations to quantify associations between IA measures from the above analyses and the two bio-factors on which Biotype-2 had exuberant activity (what we previously called the 'intrinsic activity' and 'P200' bio-factors; Clementz et al., 2016) across all proband participants. This allowed us to test if those bio-factors were specifically indexing intrinsic neural activity.

CHAPTER 3

RESULTS

3.1 Probands: Biotypes Versus HC.

Probands grouped by the Biotype versus HC detected a significant group effect for Power in each of the 4 frequency components [delta/theta: $F(3, 745)= 18.233$, $p<.001$; alpha: $F(3, 745)=29.570$, $p<.001$; beta: $F(3, 745)= 39.232$, $p<.001$; gamma: $F(3, 745)= 16.736$, $p<.001$]. For each frequency band Tukey B follow up tests identified three unique subgroups of B2> [HC/B3] > B1 (see Figure 3; Supplemental Figure 1a-d).

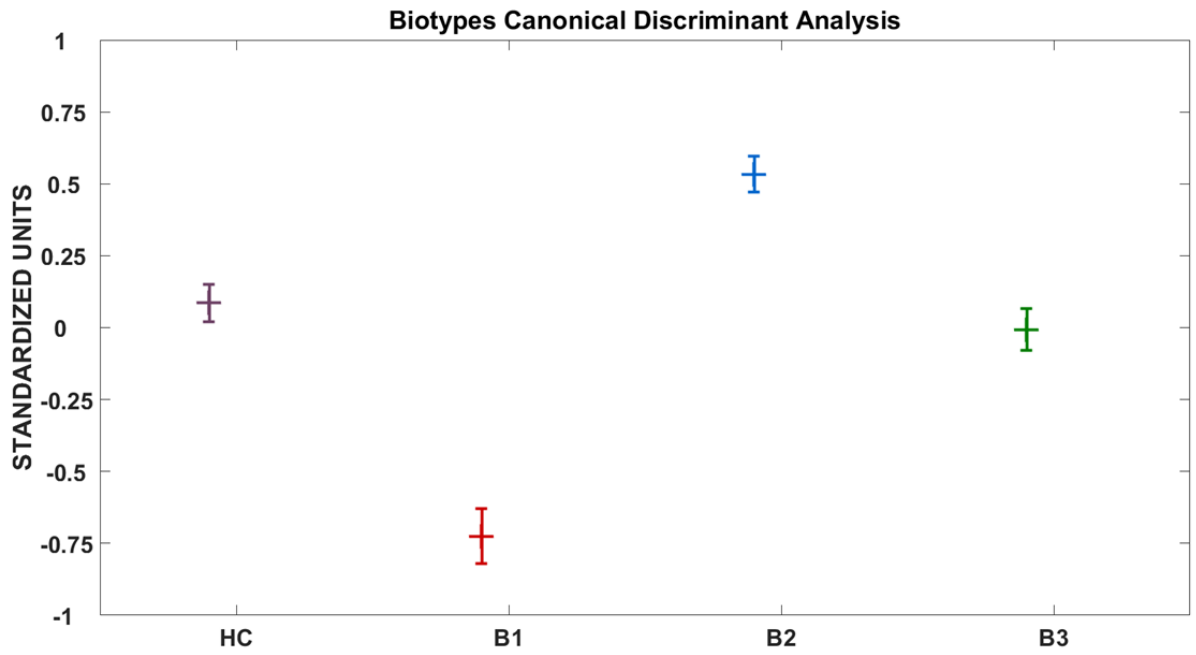

Figure 3: Canonical Variate means. Shown is a pattern of B2>HC/B3>B1. The variate correlated the strongest with Alpha and Beta Power components. HC, Healthy Comparison subjects (n=218); B1, Biotype-1 (n=148); B2, Biotype-2 (n=169); B3, Biotype-3 (n=214). Values are in standardized units. Error bars = SEM.

For dbWPLI, only the alpha frequency component showed an above chance number of sensor pairs (225) that remained significant after FDR correction. In alpha, the Biotype versus HC model detected a significant between-groups effect [$F(3, 745)= 11.063$, $p<.001$]. The Tukey B follow up tests identified three unique subgroups of B2> [HC/B3] > [HC/B1] (see Figure 4).

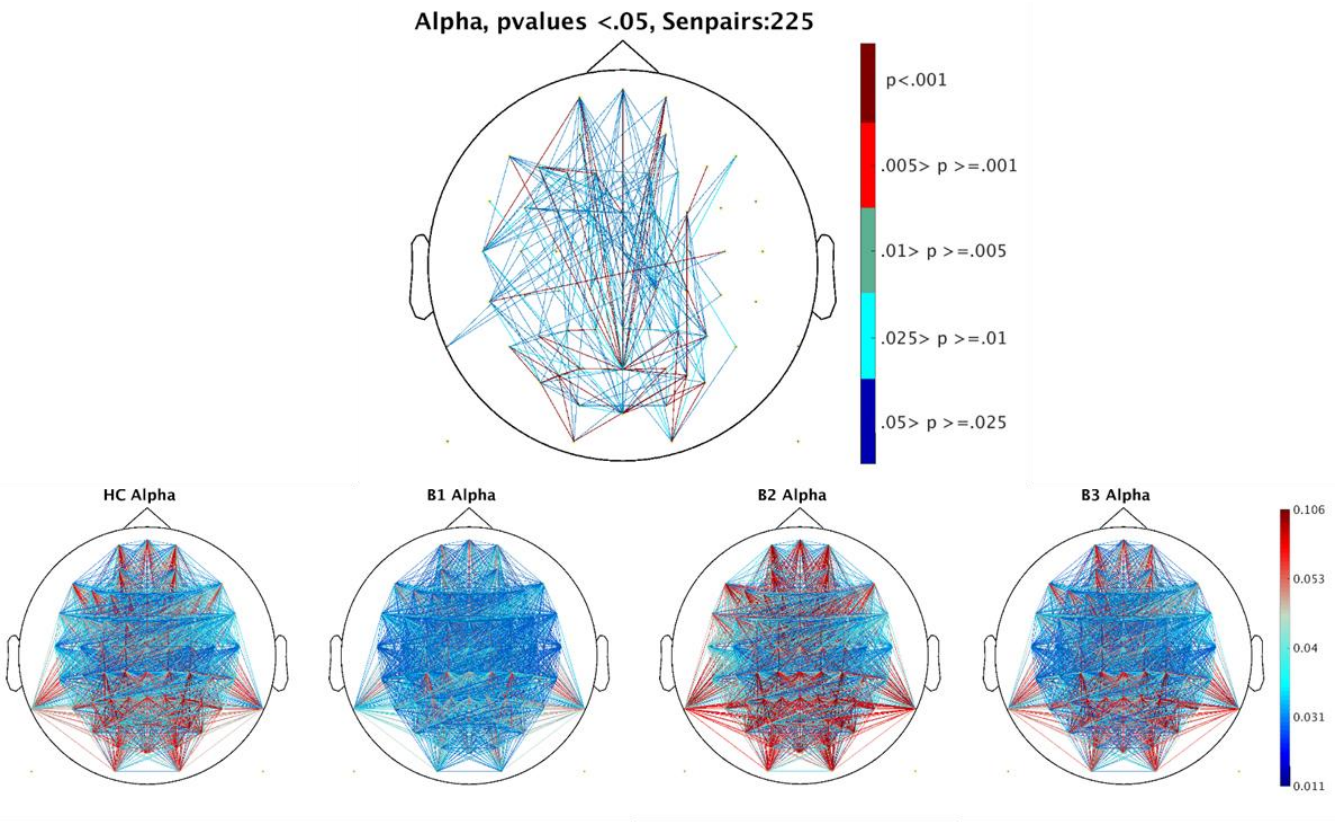

Figure 4: Debiased Weighted Phase lab index for each sensor pair (2016) after Power frequency PCA weights had been applied to the data. A) FDR corrected significant (p<.05) sensor pair group ANOVA results by biotype sub-grouping. B) Group averages by biotype for the alpha frequency band (8-15Hz). Values range from 0-1. 0 indicates the absence of phase-lagged coupling and 1 indicates the strongest possible coupling. Due to its non-normal distribution, scaling is based off of distribution percentiles from the grand average responses across groups. Tick marks indicate 25th percentiles.

3.1.2 Probands: DSM Diagnosis Versus HC.

Probands grouped by the DSM versus HC did not detect significant between-group effects for Power in any of the 4 frequency components [delta/theta: $F(3, 745)= .364$, $p=.779$; alpha: $F(3, 745)= .694$, $p=.556$; beta: $F(3, 745)= 1.867$, p=.134; gamma: $F(3, 745)= .546$, $p=.651$]. For dbWPLI, no sensor pairs survived FDR correction when grouped by DSM diagnosis (see Figure 4; Supplemental Figures 1 and 3).

3.1.3 Probands: Interaction between DSM Diagnosis and Biotypes.

The follow up DSM by Biotype ANOVAs using only the psychosis probands did not show any significant interactions for Power or dbWPLI components: (delta/theta, alpha, beta, and gamma Power, alpha dbWPLI) [$F(4,739)>.752$, p's$>.171$].

3.2 Relatives: Biotypes Versus HC.

Relatives grouped by the Biotypes versus HC model did not detect significant between group effects for Power in three power frequency components [delta/theta: $F(3, 803)= .590$, $p=.621$; alpha: $F(3, 803)= 1.838$, $p=.139$; gamma: $F(3, 803)= 2.093$, $p=0.100$] (see Supplemental Figures 2 and 3). There was a significant group difference at beta [$F(3, 803)= 3.061$, $p<.05$], B1R being significantly different from B2R ($p<.05$). For dbWPLI, no sensor pairs survived FDR correction when grouped by Biotype.

3.2.1 Relatives: DSM Versus HC.

Relatives grouped by the DSM versus HC did not detect significant between group effects for Power in any of the 4 power frequency components [delta/theta: $F(3, 803)= 1.295$, $p=.275$; alpha: $F(3, 803)= 1.107$, $p=.345$; beta: $F(3, 803)= .614$, $p=.606$; gamma: $F(3, 803)= 1.076$, $p=.358$] (see Supplemental Figure 2a-d). For dbWPLI, no sensor pairs survived FDR correction when grouped by DSM diagnosis.

3.3 Canonical Discriminant Analysis

3.3.1 Probands: Biotypes Versus HC.

The 5 components that showed significant group differences (delta/theta, alpha, beta, gamma Power, and alpha dbWPLI) were used in the CDA to efficiently summarize group differentiations (HC, B1, B2, B3; no variables significantly differentiated the DSM groups). Only the first variate ($\not\subset$ =.387, Wilks' Lambda= .833, Chi=136.1, df=15, p<.001) was statistically significant (see Table 2 for canonical loadings).

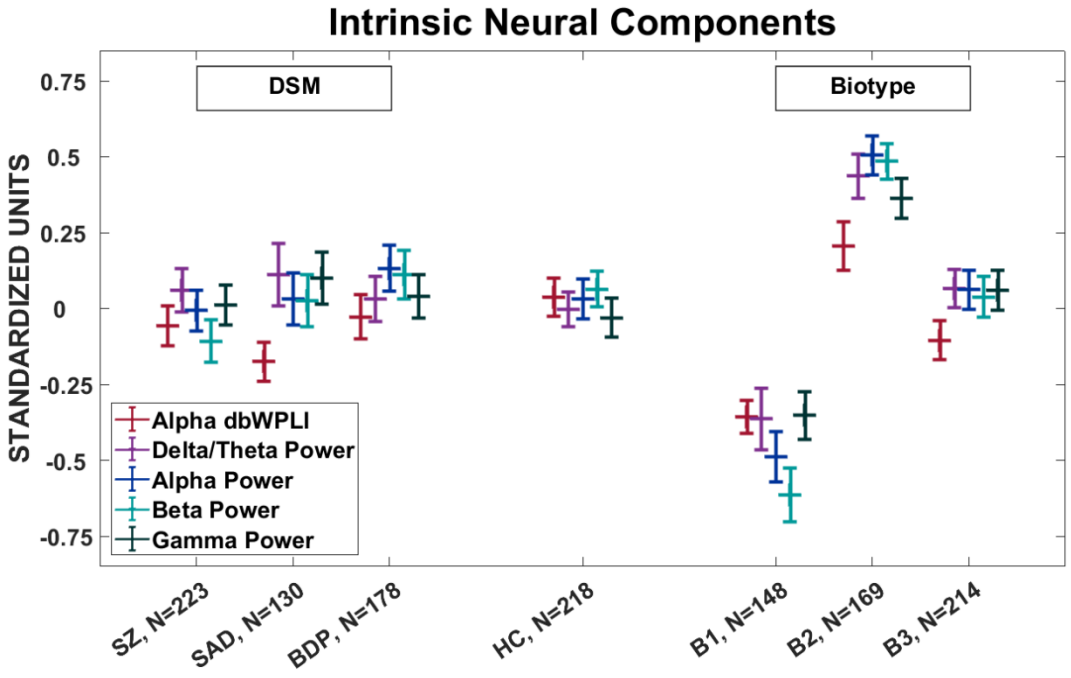

Figure 5: Final Component values for each of the 5 significant components (Delta, Alpha, Beta, & Gamma Power and Alpha dbWPLI). Each component showed a highly similar pattern for DSM (HC and probands showed a similar response) and Biotype groupings (B2> HC/B3> B1). A) Values sorted by DSM categories. HC, Healthy Comparison subjects (n=218); SZ, probands with schizophrenia (n=223); SAD, probands with schizoaffective disorder (n=130); BDP, probands with bipolar disorder I with psychosis (n=178). B) HC, Healthy Comparison subjects (n=218); B1, Biotype-1 (n=148); B2, Biotype-2 (n=169); B3, Biotype-3 (n=214). Values are in standardized units. Error bars=SEM.

The canonical variate (plotted in Figure 5, values in standardized units) was associated with higher beta (r=.944), and alpha Power (r=.810), and showed a pattern of B2 (mean=.528, SEM=.063) >HC (mean=.089, SEM= .066), B3 (mean=.008, SEM=.072) > B1 (mean= -.747, SEM=.094). A follow up Tukey B post-hoc test identified three homogenous sub-groups: B2> HC/B3> B1. Correlations between each component and the canonical variate are provided in Table 2.

3.3.2 DSM Probands & DSM, Biotypes Relatives Versus HC.

Since there were no significant results for DSM probands or relatives, and only one for Biotype relatives, no post-hoc CDAs were performed.

3.4 Canonical Correlations:

Only the first canonical variate was significant [canonical correlation=0.40, Wilk's lambda=0.76, $F(40, 1585)=2.61$, $p<.001$]. Correlation loadings for each variable with its canonical variate are provided in Supplemental Table 3 (Hair Jr. et al., 1998). The loadings indicate current general psychosis-related clinical features are positively and most closely associated with magnitude of neural activity in lower frequency ranges (beta, alpha, and delta/theta).

3.4.1 Canonical Correlations by Groups

In order to find the strength of the CCA associations as function of group membership, the canonical coefficients for the intrinsic activity variate and clinical symptom variate were averaged together for each individual. This step was taken since both variates index the same construct. High averaged coefficients mean high intrinsic neural activity was associated with more psychosis symptoms, and low averaged coefficients mean low intrinsic neural activity was associated with fewer psychosis symptoms (see Figure 6).

Table 2: Canonical Discriminant Analysis Results for the Biotype Canonical Variate. Correlations at each frequency band are present, as well as group centroids correlations with SD and lower/upper 95th percentiles.

Table 2	**Canonical Discriminant Analysis Results**				
	Eigenvalue	**% of Variance**	**Cumulative %**	**Canonical Correlation**	
Biotypes Canonical					
Variate 1:	0.176	89.5	89.5	0.387***	
	Wilks' Lambda	**Chi-Square**	**Df**	**Sig.**	
Biotypes Canonical					
Variate 1:					
Correlations:	0.833	136.055	15	<0.001	
	Delta/Theta STP	***Alpha STP***	***Beta STP***	***Gamma STP***	***Alpha dbWPLI***
Biotypes Canonical					
Variate 1:	-0.011	-0.043	1.037	-0.151	0.31
Group Centroids:					
Biotypes Canonical					
Variate 1:	***N***	***Mean***	***SD***	***Lower 95%***	***Upper 95%***
HC	218	0.089	0.971	-0.04	0.219
B1	148	-0.747	1.144	-0.932	-0.561
B2	169	0.528	0.823	0.403	*0.653*
B3	214	0.008	1.05	-0.133	0.149
*Note: *p<.05, **p<.01, ***p<.001.*					

The DSM groups did not differ on magnitude of the averaged coefficients ($F(2, 373)= 0.900$, $p=0.408$). The Biotype groups, however, significantly differed on the averaged coefficients ($F(2, 373)= 30.55$, $p<.001$). According to Tukey's b post-hoc test, B1 and B2 ($p<.001$), and B1 and B3 ($p<.001$), significantly differed. B2 and B3 did not differ significantly on strength of the relationship between intrinsic activity and general psychosis symptoms ($p=.066$). The pattern of group differences indicates that the high B2 intrinsic activity was associated with increased current psychosis symptoms, while the low B1 intrinsic activity was associated with fewer current psychosis symptoms.

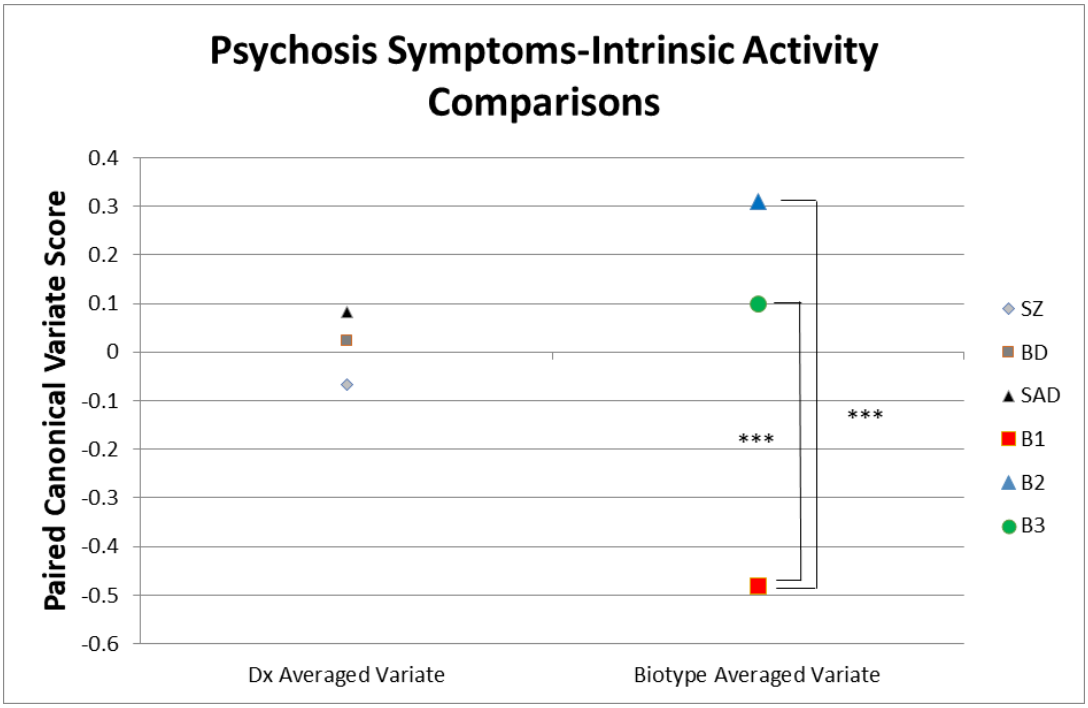

Figure 6: Average of the two canonical correlation variates using probands only (82% of proband sample). One variate was comprised of EEG variables (Delta/Theta, Alpha, Beta, Gamma Power, and Alpha dbWPLI) and one variate was comprised of clinical variables (GAF, SFS, YMRS, MADRS, WRAT, PANSS (Positive, Negative, General)). Coefficients are listed in supplemental table 3. Values are for participants when organized by DSM diagnoses and biotype. Significant differences are shown with asterisks for B1<B3 and B1<B2.

3.5 Correlation of IA Measures with Bio-Factors

Across the proband sample the IA measures across frequency bands were strongly correlated with the ongoing high frequency (previously called “intrinsic activity”) bio-factor [delta/theta: r=0.558, p<.001; alpha: r=0.614, p<.001; beta: r=0.741, p<.001; gamma: r=0.640, p<.001]. The IA measures had a weaker correlation with the “p200” bio-factor: delta/theta: r=0.136, p<.005; alpha: r=0.239, p<.001; beta: r=0.302, p<.001; gamma: r=0.317, p<.001.

CHAPTER 4

DISCUSSION

Level of intrinsic neural activity is important for understanding psychosis neurophysiology, the proposition of which is evidenced in multiple cases (Rolls et al., 2008; Hudgens-Haney et al., 2017; Spencer, 2014). Differences in level of IA across several frequencies or within specific ranges of neural oscillation may be important translational biomarkers, especially for studying mechanisms supporting specific pharmacological interventions (Rolls et al., 2008; Spencer, 2014). The biomarker panel used in developing proposed psychosis Biotypes by B-SNIP (Clementz et al., 2016) did not include a direct index of IA, though Biotype-2 was characterized by exuberant neural activity on two bio-factors. The initial "intrinsic activity" bio-factor was significantly more highly correlated than the "p200" bio-factor with the direct measure of IA described in this paper. Additionally, this new, direct measure of IA distinguished groups as well as, or better than, the bio-factor statistically used to maximally differentiate groups (Glass Δ, present in Table 3). The differences in level of IA seen here, therefore, increase the possibility of more specific target engagement for interventions aimed at moderating a physiological deviation associated with a subset of psychosis features.

Table 3: Glass Δ Effect Sizes for Biotype constructs and conventional diagnoses at each of the four frequency bands (Delta/Theta STP, Alpha STP, Beta STP, Gamma STP, and Alpha dbWPLI).

Glass Δ Effect Sizes	Biotype			Dx		
	B1	B2	B3	SZ	BD	SAD
Delta/Theta STP	-0.412	0.537	0.059	0.075	0.047	0.133
Alpha STP	-0.544	0.495	0.032	-0.04	0.106	0.001
Beta STP	-0.802	0.482	-0.013	-0.197	0.052	-0.042
Gamma STP	-0.359	0.41	0.115	0.045	0.071	0.14
Alpha dbWPLI	-0.018	0.008	-0.007	-0.004	-0.003	-0.01

As predicted based on Clementz et al. (2016), intrinsic neural activity was high in Biotype-2, low in Biotype-1, and similar to healthy levels in Biotype-3. IT is the unique contribution of this report that these differences spanned frequency bands but were most prominent in lower bands, including measures of power and distributed sensor-sensor connectivity. The gamma band is most closely associated with local sensory processing (Kaiser & Lutzenberger, 2005), so it is unsurprising neural activity in this frequency range contributed less to group discriminations using data collected during an inter-trial interval. Intrinsic activity measures were also associated with level of current psychosis symptoms: Biotype-2 showed high IA-high current symptoms and Biotype-1 showed low IA-low current psychosis symptoms, while Biotype-3 reflected healthy comparisons once more. When grouped by DSM subgroups minimal between-groups differences on intrinsic neural activity presented themselves, and no clear relationship between level of IA and current psychosis symptoms was uncovered (see Figure 6). There was little indication IA is a unique biomarker for any specific DSM psychotic disorder used in this report.

Differences from healthy persons on non-specific neural activity have been seen in psychosis as well as correspondingly low signal-to-noise ratios, using a multitude of measurement schemes, tasks, and quantification methods (Butler et al., 2001; Clementz & Blumenfeld, 2001; Clementz et al., 2004; Clementz et al., 2008; Ethridge et al, 2011; Hudgens-Haney et al., 2017; Krishnan et al., 2005; Narayanan et al., 2014[1]; Spencer et al., 2004; Wang et

[1] Narayanan et al., 2014 used a subset of the present sample (about 83%) and also forced SAD cases into the SZ and BDP subgroups based on depressive or manic subtype, respectively. They also used different data (a separate "resting EEG" period that was only available in a subset of B-SNIP participants) and a different frequency band extraction method (ICA). Nevertheless, the overall conclusion that low frequency activity deviations account for SZ-BDP effects is similar to the outcome of this study.

al., 2010; Winterer et al., 2000, 2006). Most of these reports involved exclusive evaluation of SZ cases (an exception being Kam et al., 2013, which included BD with psychosis), with findings driving theories of how intrinsic activity could be an important translational biomarker for an aspect of this psychosis syndrome (Rolls et al., 2008; Spencer, 2014). The present report supports this proposition, but adds deviant intrinsic activity can manifest divergently within SZ, and, more explicitly, may transcend psychosis syndromes. Biotype-2 cases, with high IA, consist of about 45% SZ, while Biotype-1 cases, with low IA, contain about 60% SZ (Clementz et al., 2016). No interaction between Biotype and DSM was found in our analysis. Prior conclusions drawn about intrinsic activity as a biomarker for SZ may therefore be dependent on the type of SZ subsample being recruited into each individual research project.

Neural oscillations measured with EEG derive from coordinated ensemble activity comprising thousands of neurons, with distinct frequencies typically associated with different functions and neural architectures. For instance, lower frequency oscillations (e.g., theta, alpha) are associated with cortico-cortical communication between distant brain regions. Theta and alpha oscillations are both theorized to be associated with and/or support various higher-level cognitive operations (Narayanan et al., 2014, 2015; Spencer, 2014). In addition, alpha oscillations may be associated with coordinating activity during idling states of the brain, elsewhere characterized as the "default mode" (Mantini et al., 2007), so it is perhaps unsurprising distributed sensor-sensor associations were only observed in this frequency range. The observation enhanced connectivity was only observed among Biotype-2s is consistent with a neuronal hyper-excitation model that may decrease the stability of cortical networks selected to support current behavioral requirements (e.g., Hudgens-Haney et al., 2017). Alternatively, low levels of neuronal activity among Biotype-1s in frequency ranges supporting distant cortico-

cortical communication may lead to difficulties modulating behavior in relation to changing behavioral contexts (Rolls et al., 2008). Given beta oscillations may be a gross index of cortical excitability (Rangaswamy et al., 2002), exuberant activity in Biotype-2 and reduced activity among Biotype-1 cases in this frequency range highlight differing functional cortical properties in these groups.

There are some limitations to be considered when evaluating this study. First, like most studies of mid-course psychosis, most probands were medicated (see Supplementary Table 1). However, the Biotype subgroups were similarly medicated, so it is unlikely pharmacological interventions account for between-groups differences. Second, there are differences in Biotype subgroup sample sizes, but this is a function of the apparent distribution of such cases in mid-course psychosis given that subgroups were empirically derived based on biomarker profiles. Third, although the number of participating relatives was large, there was only approximately one biological relative per proband, which is far from complete sampling of first-degree relatives. It is possible bias in those relatives willing to participate accounted for minimal differences between relatives and healthy subjects on IA. Finally, the current measure was extracted from the paired-stimuli task data, a task used in Biotypes construction. The purpose of the present report, however, was not to use intrinsic activity as an external validator but to clarify and examine the range of IA differences between psychosis subgroups to refine future Biotype construction and target engagement efforts. Effects spanned frequency ranges, indicating it may be critical to understand commonalities in generation of neural oscillations rather than focusing on a specific frequency range when building neurophysiological models of psychosis incorporating intrinsic neural activity (Spencer, 2014).

The results of this study suggest fundamental differences between comparison and psychosis groups in basic neural activity, challenging the traditional idea control groups and experimental groups differ on little other than the reactive stimuli being pursued. Work with awake, healthy rats showed evidence of non-random intrinsic connectional architecture within functional networks as well, drawing question to whether or not similar basic differences are also present in humans (Liang, King, & Zhang, 2011). In future studies it is important, within psychiatry and otherwise, to not only consider differences in the task-related neurophysiological data, but intrinsic data as well.

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CHAPTER 5

SUPPLEMENTAL METHODS

5.1 Recruitment:

Every proband included met diagnostic criteria for SZ, SAD, or BDP according to the SCID-IV-R, had at least one first degree relative available for participation, and were in a clinically stable, non-acute symptom state. The large geographical recruitment range served to enrich the participant sample with characteristics from broad geographical areas. Advertisement to probands and healthy participants consisted of a mixture of newspaper and community advertising in a similar manner across sites. Generalizability of the B-SNIP cohort is served by the large samples and broad geographical recruitment, as well as a more representative sample of the spectrum of psychosis than is typical.

5.2 Clinical Characterization

Along with previously described measures, psychiatric and medical histories, a modified family psychiatric history (see Table 1a-b), and concomitant medication information was recorded (see Supplemental Table 2a-d). First-degree relatives were assessed using the SCID-IV for Personality Disorders to evaluate personality traits, including those relevant to the psychosis spectrum represented by the cluster-A personality disorders (see Supplemental Tables 1a-b). Exclusion criteria for healthy comparison participants included a personal and familial (first- and second-degree relatives) history of schizophrenia-bipolar spectrum disorders or recurrent major depressive disorder. To establish a consensus “best-estimate” diagnosis, at least two experienced research clinicians met and reviewed the extensive clinical information obtained for each participant.

Supplemental Table 1(a-b): Sociodemographic and Clinical characteristics of Relatives and HC. 1a) Sample characteristics by Biotype constructs.

Supplemental Table 1a		**Sample Characteristics by Biotype Relative Constructs**				
	HC (*n*=218)	**B1R (*n*=139)**	**B2R (*n*=195)**	**B3R (*n*=255)**	**Test Statistic**	***P* Value**
Sociodemographic Characteristics						
Age, Years, Mean (SD)	37.43 (12.39)	41.55 (15.31)	40.41 (15.36)	42.88 (15.88)	$F_{6.1310}$=31.905	<.001
Sex/Male, *n*(%)	93 (42.7)	50 (36.0)	67 (34.4)	78 (30.6)	X^2_6 = 43.08	<.001
Handedness, *n*(%)					X^2_6 = 13.40	0.341
Right	189 (86.7)	120 (87.0)	165 (85.5)	231 (90.9)		
Left	26 (11.9)	17 (12.3)	23 (11.9)	21 (8.3)		
Ambidextrous	3 (1.4)	1 (0.70)	5 (2.6)	2 (0.80)		
Ethnicity/Hispanic, *n*(%)	21 (9.6)	21 (15.1)	20 (10.3)	15 (5.9)	X^2_6 = 11.798	0.067
Race, *n*(%)						
White	148 (67.9)	69 (49.6)	141 (72.3)	192 (75.3)	X^2_6 = 57.194	<.001
African American	56 (25.7)	63 (45.3)	49 (25.1)	55 (21.6)	X^2_6 = 61.901	<.001
Other	4 (1.8)	3 (2.2)	3 (1.5)	6 (2.4)	X^2_6 = 1.221	0.976
Education, years, Mean (SD)	15.26 (2.62)	13.77 (2.76)	13.92 (2.41)	14.86 (2.76)	$F_{6.1310}$=31.905	<.001
Clinical Characteristics, Mean (SD)						
Age of Illness Onset, Years	-	-	-	-	$F_{6,760}$=12.346	<.001
Age of First Hospitalization, Years	-	-	-	-	$F_{6,541}$=1.222	0.3
No. of Lifetime Hospitalizations	-	-	-	-	$F_{6,497}$=2.835	<.05
PANSS						
Total	-	-	-	-	$F_{6,593}$=5.163	<.001
Positive Subscale	-	-	-	-	$F_{6,594}$=4.025	<.005
Negative Subscale	-	-	-	-	$F_{6,594}$=6.510	<.001
General Symptoms Subscale	-	-	-	-	$F_{6,595}$=3.498	<.005
YMRS	-	-	-	-	$F_{6,656}$=3.812	<.005
MADRS	-	-	-	-	$F_{6,656}$=6.174	<.001
GAF	86.52 (6.60)	72.99 (14.83)	75.32 (14.58)	75.69 (12.64)	$F_{6,1315}$=232.947	<.001
WRAT-4 IQ	103.45 (14.20)	93.02 (14.79)	99.50 (14.68)	104.32 (14.41)	$F_{6,1310}$=31.905	<.001

Supplemental Table 1(a-b): Sociodemographic and Clinical characteristics of Relatives and HC. 1b) Sample characteristics by conventional diagnoses.

Supplemental Table 1b	**Sample Characteristics by Conventional Diagnoses Relatives**					
	HC (*n*=218)	**SZR (*n*=236)**	**SADR (*n*=152)**	**BDR (*n*=201)**	**Test Statistic**	***P* Value**
Sociodemographic Characteristics						
Age, Years, Mean (SD)	37.43 (12.39)	43.14 (15.15)	41.49 (15.92)	40.31 (15.79)	$F_{6.1330}$=9.728	<.001
Sex/Male, *n*(%)	93 (42.7)	78 (33.1)	49 (32.2)	68 (33.8)	X^2_6 = 73.830	<.001
Handedness, *n*(%)					X^2_6 = 16.581	0.166
Right	189 (86.7)	206 (88.4)	135 (89.4)	175 (87.1)		
Left	26 (11.9)	24 (10.3)	12 (7.9)	25 (12.4)		
Ambidextrous	3 (1.4)	3 (1.3)	4 (2.6)	1 (0.50)		
Ethnicity/Hispanic, *n*(%)	21 (9.6)	23 (9.7)	18 (11.8)	15 (7.5)		
Race, *n*(%)						
White	148 (67.9)	137 (58.1)	101 (66.4)	164 (81.6)	X^2_6 = 62.266	<.001
African American	56 (25.7)	87 (36.9)	49 (32.2)	31 (15.4)	X^2_6 = 66.695	<.001
Other	4 (1.8)	7 (3.0)	2 (1.3)	3 (1.5)	X^2_6 = 2.931	0.818
Education, years, Mean (SD)	15.26 (2.62)	14.05 (2.49)	14.11 (2.97)	14.72 (2.65)	$F_{6,1327}$=23.092	<.001
Clinical Characteristics, Mean (SD)						
Age of Illness Onset, Years	-	-	-	-	$F_{6,760}$=12.483	<.001
Age of First Hospitalization, Years	-	-	-	-	$F_{5,541}$=0.621	0.684
No. of Lifetime Hospitalizations	-	-	-	-	$F_{5,498}$=1.923	0.089
PANSS						
Total	-	-	-	-	$F_{6,593}$=21.018	<.001
Positive Subscale	-	-	-	-	$F_{6,594}$=10.831	<.001
Negative Subscale	-	-	-	-	$F_{6,594}$=21.178	<.001
General Symptoms Subscale	-	-	-	-	$F_{6,595}$=10.927	<.001
YMRS	-	-	-	-	$F_{6,656}$=4.145	<.001
MADRS	-	-	-	-	$F_{6,656}$=11.367	<.001
GAF	86.52 (6.60)	74.46 (14.18)	74.23 (13.56)	76.01 (13.67)	$F_{6,1314}$=261.329	<.001
WRAT-4 IQ	103.45 (14.20)	97.80 (15.32)	99.71 (16.18)	102.92 (13.92)	$F_{6,1310}$=9.278	<.001

At study onset, each rater was trained face-to-face, with a reliability requirement of above 0.85. Monthly cross-site diagnostic conference calls chaired by two senior primary investigators and attended by 2-4 trained clinical assessors at each site were held featuring in-depth diagnostic discussions. Raters were retrained yearly to reestablish reliability. Sociodemographic and clinical data was statistically analyzed descriptively using NCSS software (http://www.ncss.com/software/ncss/). A one-way ANOVA and subsequent Tukey-Kramer multiple comparison test, in conjunction with the Yates-corrected chi-square test were used as appropriate. Alpha was set at 0.01 for all statistical analyses in light of the large study group.

Supplemental Table 2(a-d): Concomitant Medications of Probands and HC. 2a) Sample characteristics by Biotype constructs.

Supplemental Table 2a	**Sample Characteristics by Biotype Constructs**					
	HC (*n*=218)	**B1 (*n*=148)**	**B2 (*n*=169)**	**B3 (*n*=214)**	**Test Statistic**	***P* Value**
Concomitant Medications, *n*(%)						
Off Psychotropic Medications	207 (95.8)	1 (0.7)	12 (7.1)	19 (9.0)	-	-
Antipsychotics	0 (0)	133 (92.4)	145 (85.8)	164 (77.4)	-	-
CPZ-equivalents, Mean (SD)	-	517.83 (409.78)	488.25 (460.35)	429.45 (360.06)	$F_{5,361}$=2.058	0.07
Mood Stabilizers	0 (0)	65 (45.1)	82 (48.5)	110 (51.9)	-	-
Lithium	0 (0)	15 (10.4)	25 (14.8)	34 (16.0)	-	-
Anticonvulsant	0 (0)	50 (34.7)	57 (33.7)	76 (35.8)	-	-
Antidepressants	3 (1.4)	66 (45.8)	73 (43.2)	103 (48.6)	-	-
Anxiolytics/Hypnotics	6 (2.8)	44 (30.6)	43 (25.4)	56 26.4)	-	-
Anticholinergics	0 (0)	32 (22.2)	17 (10.1)	26 (12.3)	-	-
Stimulants	1 (0.5)	8 (5.6)	9 (5.3)	22 (10.4)	-	-

Supplemental Table 2(a-d): Concomitant Medications of Probands and HC. 2b) Sample characteristics by conventional diagnoses.

Supplemental Table 2b	**Sample Characteristics by Conventional Diagnoses**					
	HC (*n*=218)	**SZ (*n*=223)**	**SAD (*n*=130)**	**BD (*n*=178)**	**Test Statistic**	***P* Value**
Concomitant Medications, *n*(%)						
Off Psychotropic Medications	207 (95.8)	11 (5.0)	9 (6.9)	12 (6.8)	-	-
Antipsychotics	0 (0)	197 (90.4)	112 (86.2)	133 (75.1)	-	-
CPZ-equivalents, Mean (SD)	-	522.02 (408.59)	560.48 (479.69)	341.62 (310.97)	$F_{5,361}$=4.051	<.005
Mood Stabilizers	0 (0)	51 (23.47)	75 (57.7)	131 (74.0)	-	-
Lithium	0 (0)	13 (6.0)	14 (10.8)	47 (26.6)	-	-
Anticonvulsant	0 (0)	38 (17.4)	61 (46.9)	84 (47.5)	-	-
Antidepressants	3 (1.4)	86 (39.4)	74 (56.9)	82 (46.3)	-	-
Anxiolytics/Hypnotics	6 (2.8)	47 (21.6)	39 (30.0)	57 (32.2)	-	-
Anticholinergics	0 (0)	40 (18.3)	18 (13.8)	17 (9.6)	-	-
Stimulants	1 (0.5)	11 (5.0)	7 (5.4)	21 (11.9)	-	-

Supplemental Table 2(a-d): Concomitant Medications of Relatives and HC. 2c) Sample characteristics by Biotype constructs.

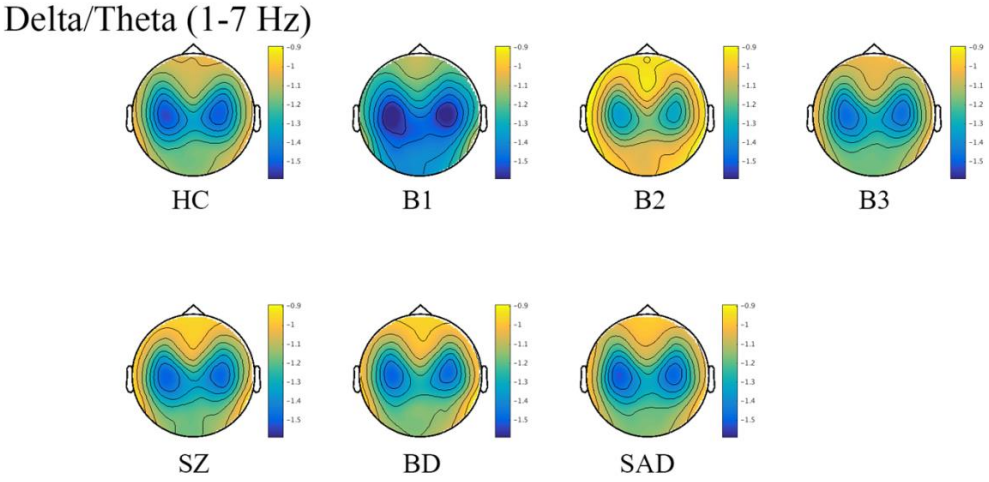
Supplemental Table 2c	**Sample Characteristics by Biotype Relative Constructs**					
	HC (*n*=218)	**B1R (*n*=139)**	**B2R (*n*=195)**	**B3R (*n*=255)**	**Test Statistic**	***P* Value**
Concomitant Medications, *n*(%)						
Off Psychotropic Medications	207 (95.8)	95 (69.3)	132 (68.0)	179 (71.6)	-	-
Antipsychotics	0 (0)	10 (14.6)	19 (9.8)	16 (6.4)	-	-
CPZ-equivalents, Mean (SD)	-	306.57 (471.25)	578.99 (512.71)	216.77 (219.56)	$F_{5,361}$=2.058	0.07
Mood Stabilizers	0 (0)	12 (8.8)	17 (8.8)	17 (6.8)	-	-
Lithium	0 (0)	9 (0.70)	5 (2.6)	4 (1.6)	-	-
Anticonvulsant	0 (0)	11 (8.0)	12 (6.2)	13 (5.2)	-	-
Antidepressants	3 (1.4)	26 (19.0)	44 (22.7)	52 (20.8)	-	-
Anxiolytics/Hypnotics	6 (2.8)	10 (7.3)	21 (10.8)	23 (9.2)	-	-
Anticholinergics	0 (0)	2 (1.5)	3 (1.5)	1 (0.4)	-	-
Stimulants	1 (0.5)	5 (3.6)	5 (2.6)	6 (2.4)	-	-

Supplemental Table 2(a-d): Concomitant Medications of Relatives and HC. 2d) Sample characteristics by conventional diagnoses.

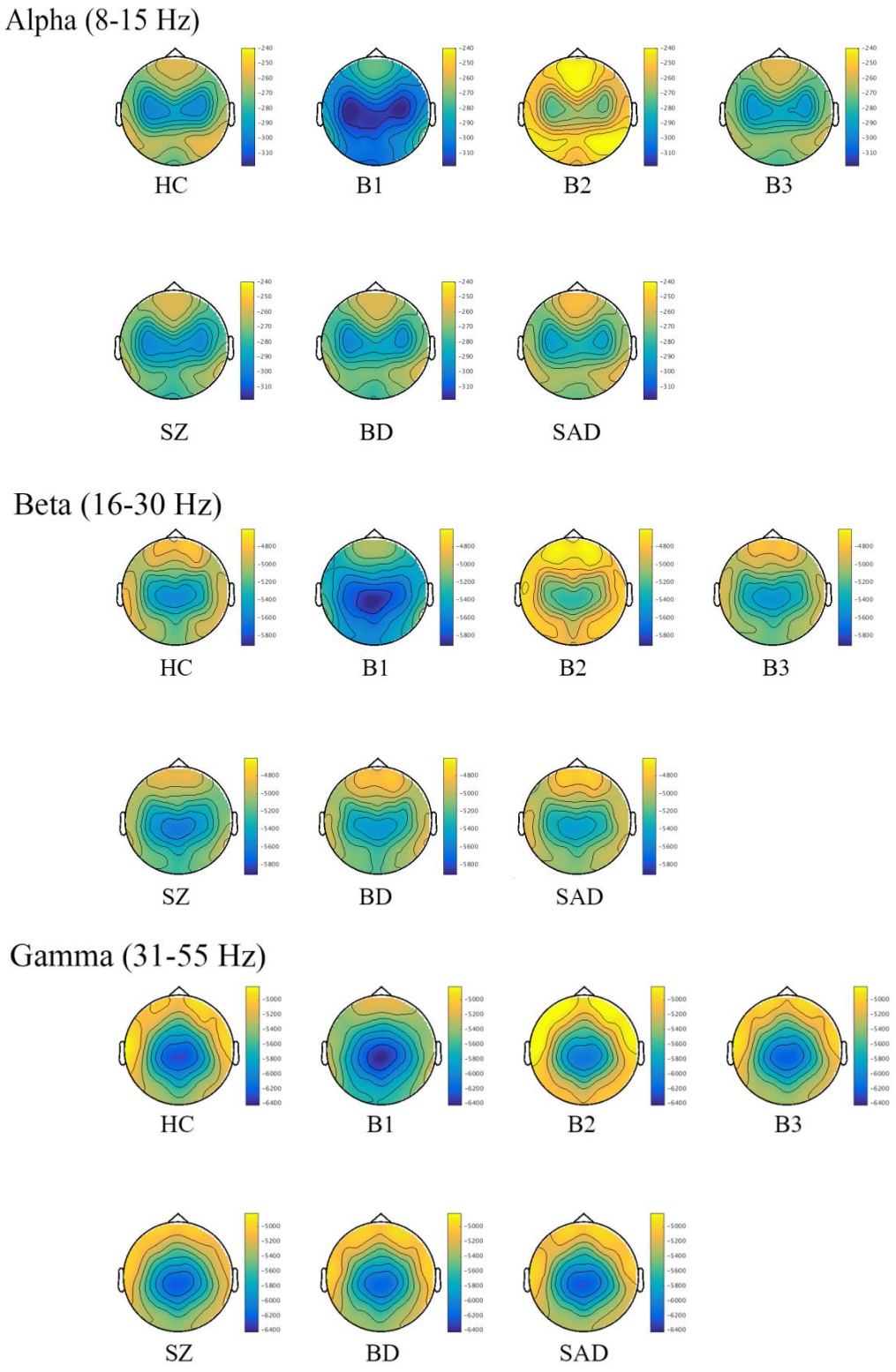
Supplemental Table 2d		Sample Characteristics by Conventional Diagnoses Relatives				
	HC (*n*=218)	**SZR (*n*=236)**	**SADR (*n*=152)**	**BDR (*n*=201)**	**Test Statistic**	***P* Value**
Concomitant Medications, *n*(%)						
Off Psychotropic Medications	207 (95.8)	173 (74.9)	101 (67.3)	132 (66.0)	-	-
Antipsychotics	0 (0)	23 (10.0)	18 (12.0)	17 (7.0)	-	-
CPZ-equivalents, Mean (SD)	-	450.54 (527.43)	373.15 (497.64)	282.50 (257.67)	$F_{5,361}$=4.051	<.005
Mood Stabilizers	0 (0)	8 (3.5)	15 (10.0)	23 (11.5)	-	-
Lithium	0 (0)	2 (0.9)	4 (2.7)	4 (2.0)	-	-
Anticonvulsant	0 (0)	6 (2.6)	11 (7.3)	19 (9.45)	-	-
Antidepressants	3 (1.4)	39 (16.9)	36 (24.0)	47 (23.5)	-	-
Anxiolytics/Hypnotics	6 (2.8)	23 (10.0)	12 (8.0)	19 (9.5)	-	-
Anticholinergics	0 (0)	4 (1.7)	1 (0.70)	1 (0.5)	-	-
Stimulants	1 (0.5)	1 (0.40)	4 (2.7)	11 (5.5)	-	-

5.3 EEG Recording/ Preprocessing

Electroencephalogram (EEG) data was continuously recorded and inspected for artifacts/bad sensors as described in Chapter 2.



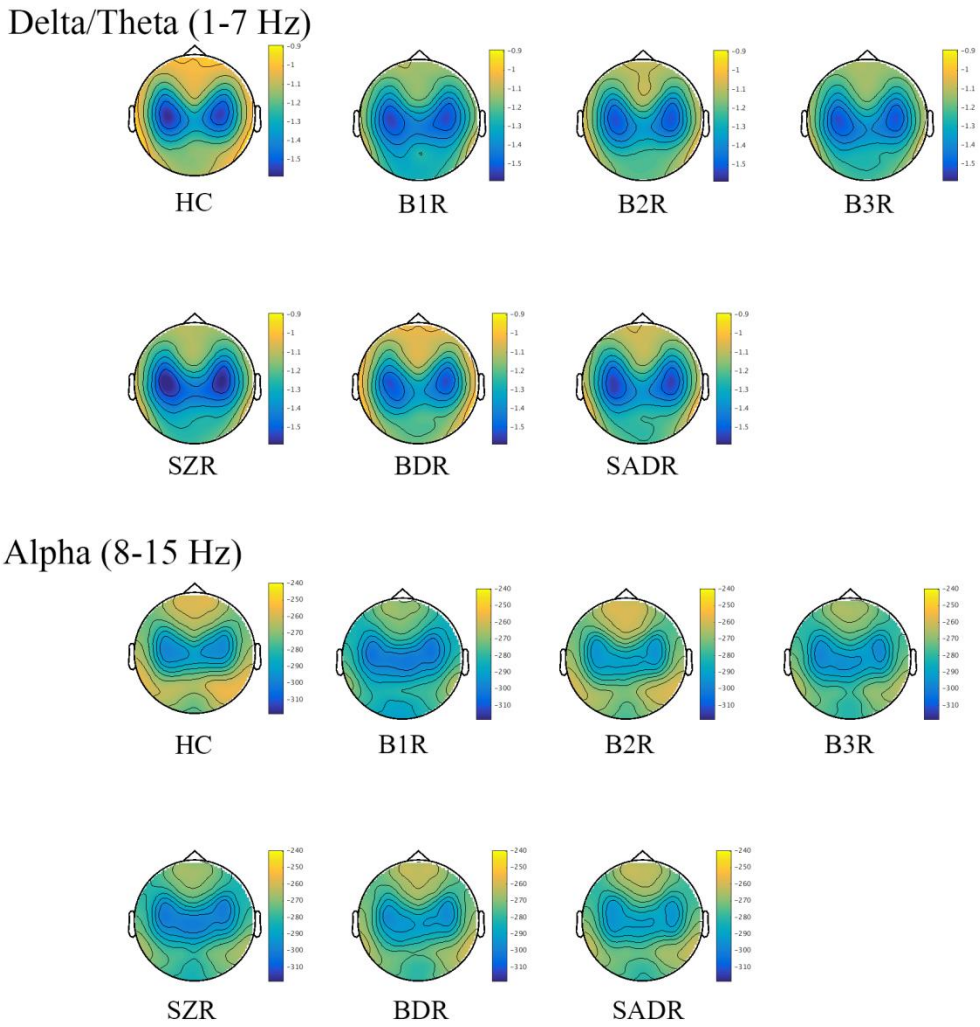
Supplemental Figure 1_a: Topographical Depictions of IA. Visual representations of IA data with frequency-wise PCA weights applied for each frequency band, by Biotypes and by conventional diagnoses.



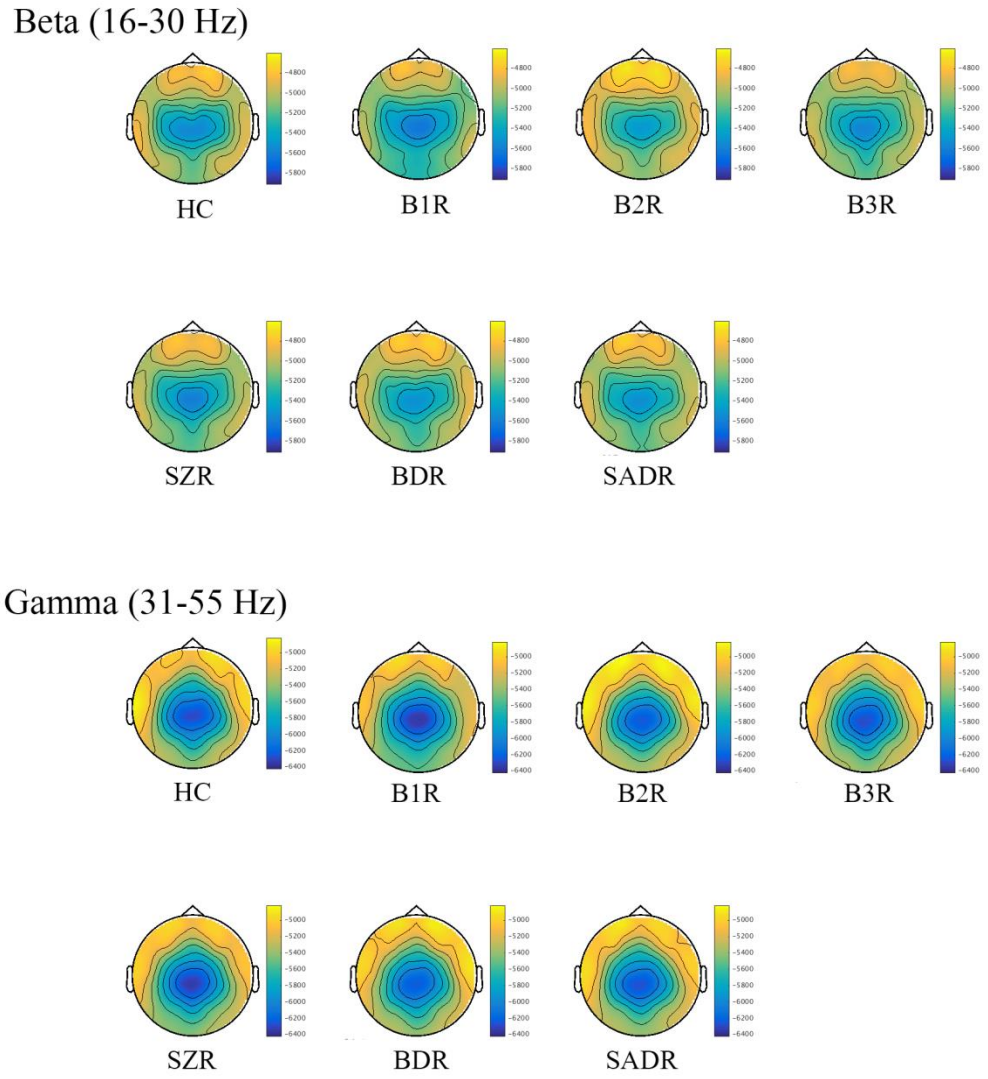
Supplemental Figures $1_{b\text{-}d}$: Topographical Depictions of IA. Visual representations of IA data with frequency-wise PCA weights applied for each frequency band, by Biotypes and by conventional diagnoses.

5.4 Spatial PCA

A frequency-wise PCA of evoked power was first conducted in the interest of maximizing available spatial, temporal, and oscillatory information for each group (see Supplemental Figure 1). After, a spatial PCA was performed on each frequency band to reduce data to one virtual sensor for each band from 64 sensors (supplemental figure 2).



Supplemental Figures $2_{a\text{-}b}$: Topographical Depictions of Relatives' IA. Visual representations of the IA data of the first-degree relatives with frequency-wise PCA weights applied for each frequency band, by Biotypes and by conventional diagnoses.



Supplemental Figures $2_{c\text{-}d}$: Topographical Depictions of Relatives' IA. Visual representations of the IA data of the first-degree relatives with frequency-wise PCA weights applied for each frequency band, by Biotypes and by conventional diagnoses.

5.5 Canonical Discriminant Analysis (CDA)

A CDA was used to efficiently summarize variables responsible for efficiently and maximally differentiated groups from intrinsic neural responses by significant EEG Power/dbWPLI variables from group comparisons. Multivariate functions were conducted with a canonical discriminant analysis to identify the interrelation of descriptions of group differences

for EEG variables. While similar to PCA, CDA makes use of pooled, within-group covariance matrices and pit group means as variables and uses measurements as observations (Mardia and Kent, 1980; Kshirsagar, 1972; Lawley, 1959). Two, uncorrelated $n^{\wedge groups-1}$ functions maximizing group differences were extracted.

5.6 Canonical Correlation Analysis

In the interest of parsimoniously evaluating relationships between PCA neural components and clinical measures (GAF, SBS, PANSS Negative, PANSS Positive, PANSS General, Young Mania Rating Scale, Montgomery-Åsberg Depression Rating Scale), a canonical correlation analyses (CCA) across all proband groups was performed (Lambert et al., 1988). CCA is a data-driven, multivariate approach which identifies the relationship between two sets of variables (called variates) by maximizing correlations variable sets. CCA is particularly useful in the case of highly inter-correlated variables. CCA results in correlated pairs of latent variates with loadings of individual measures on the latent structure for each variate, and it can be interpreted in a similar manner as PCA (Parker et al., in press).

Supplemental Table 3: Canonical Correlation Coefficients for the Clinical Variate by clinical scale and the Neural Variate by frequency band.

Supplemental Table 3	**Clinical CCA Coefficients**	**Neural CCA Coefficients**	
Variable	***Coefficient***	***Variable***	***Coefficient***
GAF	-0.087	*Gamma STP*	-0.304
SFS	-0.056	*Beta STP*	-0.788
YMRS	-0.441	*Alpha STP*	-0.687
MADRS	-0.289	*Delta/Theta STP*	-0.625
PANSS Positive Total	-0.457	*Alpha dbWPLI*	-0.571
PANSS Negative Total	-0.4		
PANSS General Total	-0.808		
WRAT	-0.294		

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