Resting State Electroencephalogram Oscillatory Abnormalities in Schizophrenia and Psychotic Bipolar Patients and Their Relatives from the Bipolar and Schizophrenia Network on Intermediate Phenotypes Study

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Background: Abnormal resting state electroencephalogram (EEG) oscillations are reported in schizophrenia (SZ) and bipolar disorder, illnesses with overlapping symptoms and genetic risk. However, less evidence exists on whether similar EEG spectral abnormalities are present in individuals with both disorders or whether these abnormalities are present in first-degree relatives, possibly representing genetic predisposition for these disorders.

Methods: Investigators examined 64-channel resting state EEGs of 225 SZ probands and 201 first-degree relatives (SZR), 234 psychotic bipolar (PBP) probands and 231 first-degree relatives (PBPR), and 200 healthy control subjects. Eight independent resting state EEG spectral components and associated spatial weights were derived using group independent component analysis. Analysis of covariance was conducted on spatial weights to evaluate group differences. Relative risk estimates and familiality were evaluated on abnormal spectral profiles in probands and relatives.

Results: Both SZ and PBP probands exhibited increased delta, theta, and slow and fast alpha activity. Post-hoc pair-wise comparison revealed increased frontocentral slow beta activity in SZ and PBP probands as well as SZR and PBPR. Augmented frontal delta activity was exhibited by SZ probands and SZR, whereas PBP probands and PBPR showed augmented fast alpha activity.

Conclusions: Both SZ and PBP probands demonstrated aberrant low-frequency activity. Slow beta activity was abnormal in SZ and PBP probands as well as SZR and PBPR perhaps indicating a common endophenotype for both disorders. Delta and fast alpha activity were unique endophenotypes for SZ and PBP probands, respectively. The EEG spectral activity exhibited moderate relative risk and heritability estimates, serving as intermediate phenotypes in future genetic studies for examining biological mechanisms underlying the pathogenesis of the two disorders.

Key Words: Bipolar disorder, EEG, intermediate phenotypes, psychosis, resting state, schizophrenia

Schizophrenia (SZ) and bipolar disorder are two common psychiatric illnesses that share significant overlapping symptoms (1), brain structure and function (2), cognitive features (3), genetic risk (4), and medication response (5). The neurobiological underpinning of these disorders might provide a clearer basis for understanding their similarities and differences. Evidence suggests that SZ and psychotic bipolar disorder (PBP) are strongly heritable (6) and have similar genetic risk loci (7). Intermediate phenotypes, sometimes referred to as endophenotypes, are heritable quantitative biological measures presumably related to disease risk rather than overt clinical disorders, presumed to have simpler genetic architecture and to be closer to the causative genes than the clinical illness (8). Intermediate phenotypes are believed to be modulated by the disease-related genes influencing biological risk and may be expressed in unaffected relatives of probands.

Neural oscillations represent one type of candidate intermediate phenotype for SZ and PBP. Such oscillations normally play a vital role in defining temporal communication between circuits that represent various brain functions, such as information processing, memory, attention, perception, and consciousness. Basic fundamental building blocks defining these oscillations are the neuronal firing within cohorts of neurons, which are described by the frequency characteristics of electroencephalogram (EEG) recordings during a resting state. Disturbances in the spectral behavior of the oscillation patterns in probands could indicate aberrant brain function via neural dysfunction (9). Although several different frequency bands have been examined in previous resting state EEG studies of SZ (10), the results are inconsistent. Most prior investigations in SZ (11–13) show increased frontal slow wave activity, primarily assumed to reflect frontal lobe pathology (14). Augmented

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high-frequency beta (12) and gamma (12,15) abnormalities are also often noted. The main purpose of this study is to examine electrophysiologic phenotypes across psychotic disorders to dissect the common and distinct aspects of the psychosis dimension, an important clinical feature common to both SZ and PBP, and to test the hypothesis that endophenotype characteristics are homogeneous within phenomenologically derived DSM-IV diagnoses, rather than differentiating them (16). We assessed resting state EEG spectral activity in SZ and PBP (major psychoses) but not in nonpsychotic bipolar disorder. In general, published resting state EEG studies are less common in both PBP (17) and nonpsychotic bipolar disorder (12).

Because resting state EEG exhibits heritable characteristics (18,19), several studies have examined resting state EEG abnormalities in unaffected relatives of SZ (12,15,17,20) and PBP (17) probands to determine whether risk for each disorder is genetically determined. Some limitations with these studies include the use of few scalp leads, small study samples, and uncertainty in identifying reliable intermediate phenotypes. To address the lack of spatial recording leads, Venables *et al.* (12) conducted a study with 28 channels in both eyes open and closed conditions and demonstrated that augmented gamma activity was expressed in SZ relatives (SZR) and nonpsychotic bipolar disorder relatives, whereas increased beta activity was specific to SZR. Similar findings were reported in SZ siblings (20,21). Another study (15) identified abnormal low-frequency theta-alpha as a specific SZ risk marker. No resting state EEG abnormalities were present in relatives in the study by Clementz *et al.* (17), which used only three central electrodes and may have lacked the ability to detect frontotemporal-parietal differences. Although the Clementz *et al.* (17) study clearly differentiated probands from nonpsychiatric control subjects, it did not distinguish between SZ and bipolar disorder probands. Because of the heterogeneity of these illnesses and the variable findings in establishing neural oscillations as potential intermediate phenotypes for SZ and bipolar disorder separately, we conducted a large-scale multisite study to test directly the hypotheses that resting state EEG frequency abnormalities are unique to SZ and PBP probands and to examine whether these abnormalities are expressed in their first-degree relatives, to confirm genetic liability for these disorders.

The objectives of this study were to 1) determine whether resting state EEG spectral profiles were unique to SZ and PBP or common to both illnesses, 2) examine whether abnormal spectral composition was present in SZR and PBPR to detect any genetic link to these disorders, 3) estimate heritability of frequency abnormalities present in probands and relatives, 4) compare SZ and PBP probands with relatives with DSM-IV cluster A (schizotypal, schizoid, paranoid) and cluster B personality disorders diagnoses regarded as formes frustes of the illnesses or psychosis spectrum personality disorders (PSPD) versus relatives with nonpsychotic DSM-IV Axis I disorders and relatives with neither Axis I nor cluster A or B diagnoses, and 5) correlate oscillatory activity in probands with symptom scores including the Schizophrenia-Bipolar Scale (SBS) (1) and Positive and Negative Syndrome Scale (PANSS) (22).

We predicted that frontal slow wave (delta, theta, slow alpha) oscillations would be disrupted in both SZ and PBP probands confirming prior studies, with similar abnormalities likely manifesting in SZR and PBPR. From prior work, we expected augmented fast beta abnormalities in both SZ probands and SZR and gamma abnormality in both SZR and PBPR.

Methods and Materials

Participant Recruitment

Probands were recruited from inpatient and outpatient units at the five centers (Supplement 1) comprising the collaborative Bipolar and Schizophrenia Network on Intermediate Phenotypes study (16). Inclusion criteria for probands were age 15–65 years, meeting Structured Clinical Interview for DSM-IV (23) criteria for SZ or bipolar disorder I disorder with psychosis (24), and having one or more eligible first-degree relatives participating in the study. There were 225 SZ probands and 234 PBP probands. Other groups comprised 201 SZR, 231 PBPR, and 200 healthy control (HC) subjects. Table 1 presents demographic information and characteristics for subjects. All subjects had the study explained to them, and written informed consent approved separately by institutional review boards of individual sites was obtained. Probands with schizoaffective disorder depressed and manic subtype diagnoses were classified as SZ and PBP, respectively (1,25,26). Relatives of probands with schizoaffective disorder depressed and manic subtypes were classified as SZR and PBPR, respectively. Relatives with lifetime Axis I psychoses who met the Structured Clinical Interview for DSM-IV criteria for SZ or PBP were assigned to the respective probands, but relatives with nonpsychotic Axis I disorders (e.g., major depression or anxiety disorder) were included in the SZR or PBPR category. Probands and relatives with psychotic psychiatric disorders were on stable doses of medication $\geq$4 weeks; nonpsychotic and unaffected relatives and HC subjects took no psychoactive medications (Table S1 in Supplement 1). The HC group included subjects not meeting DSM-IV criteria for any Axis I disorder.

EEG Data Collection and Processing

The EEG recordings were collected (Supplement 1) in electrically shielded booths with electrodes placed in accordance with the International 10–10 system using a 66-electrode cap with ground electrodes at the mid forehead and nose as references (Figure S1 in Supplement 1). The EEG data were preprocessed (Supplement 1) for generating artifact free epochs.

EEG Frequency Analysis

Frequency data for all subjects were estimated by applying spectral transformation (Supplement 1) to clean epochs. We included subjects with epochs ranging between 20 and 281 in the analysis.

Group Independent Component Analysis

Independent component analysis is a data-driven multivariate tool that employs higher order statistics for separating maximally independent sources from linear mixture, based on presumed EEG source independence, to provide better signal-to-noise ratio by identifying and eliminating unstructured noise sources from the data (27). Group independent component analysis (GICA) examines independent spatial-spectral components by treating spectral activity as a single effect across the entire group (probands, relatives, and HC subjects) data. Prior imaging studies have employed GICA (28); we extended this approach to resting state EEG (29) to identify spectral sources common to SZ probands, PBP probands, SZR, PBPR, and HC subjects. The data organization for the GICA procedure is detailed in Supplement 1 (Figure S2 in Supplement 1). The spectral data were decomposed into eight (>95% reliability) independent frequency components, estimated using Infomax independent component analysis in Infomax independent component analysis in EEGIFT (http://icatb.sourceforge.com). To facilitate the interpretability of GICA results,