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

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ABSTRACT

BACKGROUND: The investigators compared event-related potential (ERP) amplitudes and event-related oscillations across a broad frequency range during an auditory oddball task using a comprehensive analysis approach to describe shared and unique neural auditory processing characteristics among healthy subjects (HP), schizophrenia probands (SZ) and their first-degree relatives, and bipolar disorder I with psychosis probands (BDP) and their first-degree relatives.

METHODS: This Bipolar-Schizophrenia Network on Intermediate Phenotypes sample consisted of clinically stable SZ ($n = 229$) and BDP ($n = 188$), HP ($n = 284$), first-degree relatives of schizophrenia probands ($n = 264$), and first-degree relatives of bipolar disorder I with psychosis probands ($n = 239$). They were administered an auditory oddball task in the electroencephalography environment. Principal components analysis derived data-driven frequency bands evoked power. Spatial principal components analysis reduced ERP and frequency data to component waveforms for each subject. Clusters of time bins with significant group differences on response magnitude were assessed for proband/relative differences from HP and familiality.

RESULTS: Nine variables survived a linear discriminant analysis between HP, SZ, and BDP. Of those, two showed evidence (deficit in relatives and familiality) as genetic risk markers more specific to SZ (N1, P3b), one was specific to BDP (P2) and one for psychosis in general (N2).

CONCLUSIONS: This study supports for both shared and unique deficits in early sensory and late cognitive processing across psychotic diagnostic groups. Additional ERP and time-frequency component alterations (frontal N2/P2, late high, early, mid, and low frequency) may provide insight into deficits in underlying neural architecture and potential protective/compensatory mechanisms in unaffected relatives.

Keywords: Auditory Oddball, ERP, P300, PCA, Psychosis, Time-Frequency

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Neurophysiological methods such as event-related potentials (ERPs) provide unique, state-independent, and heritable measures of psychosis risk. Abnormalities are often present before the development of clinically significant symptoms; however, the specificity of individual measures to subtypes of psychosis, such as schizophrenia (SZ) and bipolar disorder with psychosis (BDP), is still uncertain (1). The current study investigates such measures in the auditory oddball paradigm.

The P300 ERP is a robustly replicated, multisource brain-generated physiologic response associated with novelty/salience detection, working memory, context updating, and target recognition during visual and auditory oddball tasks (2). Reduced P3b (P300 subcomponent centered at parietal scalp locations) amplitude is frequently reported in schizophrenia (3–8) and bipolar disorder (6,7,9–11). P300 abnormalities may be useful for understanding disease risk, as reductions in this component have been reported among clinically healthy first-degree relatives of probands with (SZrel) (12–16) and bipolar disorder (17). P3b amplitude reductions among family members of affected probands suggest auditory oddball processing is associated with constitutional liability for illness. A twin study meta-analysis of P300 indicated high aggregate heritability estimates among healthy participants (50% to 60%) (18), consistent with the possibility that P300 may be a liability indicator for psychosis (1,19). Although P300 is the most commonly studied ERP in oddball paradigms, other ERPs to both target and standard stimuli may provide important information about psychosis as well (20). Reductions in N1 and P2 amplitude have been reported in both first-episode and chronic SZ (21). N1 reductions also have been reported in first-degree relatives of SZ but not first-degree relatives of probands with bipolar disorder I with psychosis (BDPrel) (22). Similarly, SZ and BDP both show N2 abnormalities, but usefulness of N2 as an endophenotype is currently unknown (22–25). In this article, we evaluate multiple ERP responses during auditory oddball processing that are associated with disease effects and those that are candidates for further genetic modeling.

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Inherited biomarkers (endophenotypes) should be relatively specific to persons with a disease and those at increased genetic risk for that disease (26). Most endophenotype studies of ERPs target a single diagnostic group. However, multiple lines of evidence indicate that P300 abnormalities may be liability markers for psychotic disorders generally rather than for a specific diagnostic group (11,17,27,28). Indeed, P300 abnormalities have been described for multiple neurobehavioral diagnostic categories (29).

P300 amplitude reduction may be a liability indicator for psychotic disorders generally. Alternatively, quantifying P3b amplitude, for instance using a single sensor (e.g., Pz) at a single time point (P3b peak), may fail to capture the richness and diversity of neural activations evoked by the oddball paradigm. More complete quantification schemes may be necessary to capture neuropathological response differences between diagnostic classes. Quantifying between-group differences on voltage over the entire ERP time range and frequency variations in neural oscillations as a function of time and integrating information over the whole head all may capture additional complexity of neural responding not evident in ERP peak voltage measurements (30) and may help elucidate differences between nosologically similar diagnostic groups (23,31). Quantifying event-related oscillations (EROs) has revealed early gamma band abnormalities during the auditory oddball task that are both heritable in twin studies (32) and present in first-episode (33) and chronic SZ (34). Early gamma responses have been relatively understudied in BDP but have been reported as heritable but not abnormal in one study of nonpsychotic bipolar patients (35), so this response may prove to be a candidate endophenotype of SZ. The current study provides direct comparison of SZ, BDP, and their first-degree relatives on ERP voltage and time-frequency measurements of the same responses and may help illuminate the most useful approach for discriminating between psychosis groups and identifying inherited biomarkers for these disorders.

The present investigation of the Bipolar-Schizophrenia Network on Intermediate Phenotypes (36) sample compared ERP amplitude measurements and EROs across a broad frequency range during an auditory oddball task using a comprehensive analysis approach to describe shared and unique neural processing characteristics among healthy subjects (HP), SZrel, and BDPrel. It was predicted that 1) time-frequency measures would provide useful information beyond that of traditional ERP measures, particularly in higher frequency bands; 2) P300 response would not discriminate psychosis groups; and 3) information from first-degree relatives would aid in identification of inherited biomarkers in components previously understudied in these groups, including the N2 ERP and mid-frequency EROs.

METHODS AND MATERIALS

Participants

As part of the large, multisite data collection project (Bipolar-Schizophrenia Network on Intermediate Phenotypes), participants were recruited, interviewed, and tested at five sites: University of Illinois-Chicago (Chicago, Illinois), Yale University/Institute of Living (Hartford, Connecticut), University of Texas Southwestern (Dallas, Texas), University of Maryland (Baltimore, Maryland), and Wayne State University (Detroit, Michigan)/Harvard University (Boston, Massachusetts). Participants with SZ (n = 229) or BDP (all subtype I, n = 188) who were clinically stable (not acutely ill and no changes in treatment for 1 month) and HP (n = 284) were recruited via community advertisements, linked community facilities and programs, and local National Alliance on Mental Illness type organizations. First-degree relatives of SZ (n = 264) and BDP (n = 239) were recruited through initial proband participation (Table 1 for demographics). Presence of SZ or BDP-type disorder was not an exclusion criterion for relatives, as these disorders tend to run in families, and a representative sample of the population was desired; however, analyses removing affected relatives were also performed (Table 2; Table S2 in Supplement 1). All participants provided written informed consent. This study was approved by Institutional Review Boards at each data collection and analysis site (36).

Medical history, Structured Clinical Interview for DSM-IV diagnosis (patient or nonpatient as appropriate) (37), Positive and Negative Syndrome Scale (38), Young Mania Rating Scale (38), Montgomery-Åsberg Depression Rating Scale (39), and Global Assessment of Functioning scale (Axis V of DSM-IV) were acquired by trained Masters- or Doctoral-level clinicians. Presence of serious medical, neuro-ophthalmologic, or neurological illness (e.g., cancer, seizure disorders, coarse brain disease); mental retardation; head trauma with >30 minutes unconsciousness; and current substance use ascertained by history plus urine drug screens on the day of testing (eight-panel screen for amphetamines, barbiturates, cocaine, methadone, opiates, cannabinoids, propoxyphene, and tricyclic antidepressants), abuse in the past 3 months, and dependence within 6 months or extensive history of drug dependence (DSM-IV) were criteria for exclusion. Healthy persons were free of any lifetime psychotic or mood disorder and family history of psychotic or bipolar disorders in first-degree relatives. All but 20 SZ and 14 BDP were taking psychotropic medications, while most first-degree relatives were free of psychotropic medications (Table 1).

Stimuli and Procedures

Recording conditions were equivalent and stimulus presentation and recording equipment were identical across sites. Seated in a sound and electrically shielded booth (ambient sound = 61–63 dB; luminance = .11–.12 foot-candle), subjects listened to tones delivered by two 8-Ω speakers located 50 cm in front of them. Stimuli were 567 standard (1000 Hz) and 100 target (1500 Hz) tones presented in pseudorandom order (1300 msec intertrial interval). Subjects were asked to press a button when a target was detected. Subjects refrained from smoking 1 hour before testing.

Electroencephalogram Recording

Electroencephalogram (EEG) was continuously recorded from 64 silver/silver chloride sensors (impedance <5 KΩ) (QuikCap; Compumedrics Neuroscan, El Paso, Texas), positioned according to the standard 10-10 EEG system plus mastoids and CP1/2 locations to provide sampling lower on the back of the head, with nose reference and forehead ground.