INTRINSIC AND EVOKED OSCILLATORY BRAIN ACTIVITY AS POTENTIAL ENDOPHENOTYPES FOR SCHIZOPHRENIA AND PSYCHOTIC DISORDERS

by

LAUREN E. ETHRIDGE

(Under the Direction of Brett A. Clementz)

ABSTRACT

Evidence for a genetic component for schizophrenia has led to a search for potential endophenotypes that will aid in identifying genetic risk for schizophrenia as well as increase understanding of the etiology of the disorder. Endophenotypes by definition must be unique to the disorder of interest, so it is necessary to discriminate neural processing abnormalities between psychiatric groups. Utilizing electroencephalography (EEG) to measure time-frequency characteristics of the neural response to a steady-state stimulus and two modalities of oddball stimuli, the present work contributes a number of important advances to the current literature on the use of intrinsic and evoked neural activity to develop endophenotypes for schizophrenia, psychotic bipolar disorder (BPP), and general psychosis. Abnormalities in prestimulus intrinsic activity are characteristic of schizophrenia and these abnormalities may interact with subsequent task-related processing, producing commonly observed deficits in steady-state and event-related potential (ERP) responses. Commonly observed deficits in oscillatory response to the auditory oddball task are not unique to schizophrenia, but may be indicative of risk for psychosis in general. However, the late beta/gamma accentuation to auditory oddball stimuli discriminates schizophrenia, BPP, and healthy subjects, being unique to BPP. Late beta single trial power to

both targets and standards is also heritable in healthy twins, suggesting that this variable may provide an interesting avenue for further examination as an endophenotype for BPP.

INDEX WORDS: Schizophrenia, EEG, intrinsic activity, steady state, ssVEP, oddball

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DEDICATION

I would like to dedicate this work to my wonderful, loving, and supportive parents and husband; my parents for always encouraging me to do my best, to succeed, and constantly asking when my dissertation will be finished; my husband for knowing that it's not really a good idea to ask that question.

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CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

Schizophrenia is a chronic and disabling disorder that affects approximately 1% of the population in the United States alone (Regier et al., 1993) and in a report by the World Health Organization (The Global Burden of Disease: 2004 update) was rated as the fifth leading cause of years lost due to disability worldwide. Schizophrenia as a syndrome, or constellation of clinical symptoms as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM – IV-tr), is a surprisingly heterogeneous disorder, further complicated by instability in symptom count across time within a single individual. This heterogeneity in clinical definition has led some researchers to investigate whether schizophrenia is one disorder or whether it exists on a spectrum of psychotic disorders which include schizoaffective disorder, schizotypal personality disorder, and psychotic bipolar disorder (Fischer et al., 2009; Berrettini, 2000a, Ritsner, 2011). In order to more fully define schizophrenia and understand its etiology, it is necessary to determine biological characteristics present across all affected individuals, regardless of behavioral symptomotology.

Evidence for a genetic component for schizophrenia has been largely supported by family, twin, and adoption studies, leading to some promising research in the molecular genetics of schizophrenia pointing to genes linked to clinical presentation of the disorder (Baron, 2001; Berrettini, 2000b; Ripke et al., 2011). The variation in clinical symptoms of schizophrenia across individuals, however, greatly increases the difficulty in defining gene products contributing to neural processes characteristic of all persons with the disorder. Endophenotypes, which can serve as an intermediate step between genetic risk and symptomology, provide a useful tool for implementing this process. Endophenotype studies utilize tasks for which the supporting neural architecture is relatively well understood in order to decompose genetic contributions to neural abnormalities associated with risk for disease, providing a simpler biological profile in which to begin the search for candidate genes for both healthy and abnormal brain function. Because an endophenotype by definition must be specific to a certain disorder and those at risk for that disorder (Gottesman and Gould, 2003), this avenue of research interacts heavily with work on neurophysiological discriminators of psychotic disorders. In order to develop reliable endophenotypes for schizophrenia and eventually to understand its etiology and genetic basis, brain activity patterns characteristic of this brain-based disorder must be fully explored. Once characteristic activity patterns are defined, heritability can be assessed for these specific responses through twin and family studies. Heritability is a necessary component to separating endophenotypes, which have a strong genetic component and presumably a simpler genetic profile, from biological markers, which may have environmental, epigenetic, or multifactorial causes, and overt phenotypes, which have complex genetic underpinnings (Gottesman and Gould, 2003).

Schizophrenia patients (SZ) have early visual processing deficits under some, but not all, stimulus conditions (Butler et al., 2008; Clementz et al., 2008; Kieffaber et al., 2007; Luck and Gold, 2008; Wang et al., 2010). SZ show deficits in gain control as measured with contrast gratings and steady-state techniques (Butler and Javitt, 2005; Butler et al., 2007). They also show integration impairments in contour, form and motion processing, indicating deficits in M-pathway and its integration with lower-level P-pathway (Butler et al., 2005; 2008; Kim et al., 2006). Motion processing deficits most likely do not occur early in the M-pathway, as evidenced

by intact early (90 ms post-stimulus) and impaired late (400 ms post-stimulus) motion-related neural activity (Wang et al., 2010). Sustained attentional selectivity to spatial locations and visual stimulus features is relatively unimpaired in SZ, although target detection processes are disrupted (Clementz et al., 2008). SZ can also exhibit normal attentional set switch latency costs in certain tasks if task switches are explicitly cued, however they show deficits in response accuracy (Kieffaber et al., 2007). In addition, Luck and Gold (2008) found that while initial implementation of attentional selection is intact, SZ patients show deficits in maintaining rules for controlling attentional selection, as required for successful performance in antisaccade and Stroop tasks. These diverse findings suggest that SZ visual processing abnormalities are a function of complex interactions between brain regions (Kemner et al., 2009) that are supported by oscillatory activities within cortical neural networks (Uhlhaas & Singer, 2006). In order to disentangle the neural basis for early visual processing deficits in particular, it may be useful to develop a better understanding of the oscillatory capability of visual cortical neurons among SZ.

SZ also show auditory processing deficits that indicate a need to further investigate the oscillatory capability of neuronal populations in SZ auditory cortex. In auditory oddball tasks, reduced amplitude of the P300 component of the auditory event-related potential (ERP) relative to healthy subjects has been a robust finding in schizophrenia (Roth and Cannon, 1972; Bramon et al., 2004; Ford, 1994; McCarley et al., 1993; O'Donnell et al., 2004; Salisbury et al., 1998; Mathalon et al., 2010). In auditory sensory gating or "paired click" tasks, SZ show an abnormal ratio between P50 amplitude to the first and second stimuli, with initial findings pointing to a lack of amplitude suppression to the second, repetitive stimulus as compared to healthy controls (Patterson et al., 2008). However, utilization of appropriate baseline and consideration of potential intrinsic baseline "noise" differences between schizophrenia patients and healthy

subjects have shown that the "suppression effect" ratio is primarily driven by decreased amplitude to the first stimulus (Blumenfeld and Clementz, 2001; Clementz and Blumenfeld, 2001; Hamm et al., 2012). Additionally, gamma and beta band oscillatory power deficits in schizophrenia have been observed during baseline corrected auditory gating tasks (Hall et al., 2010; Brenner et al., 2009; Johannesen et al., 2008). Difference in baseline between groups were not addressed, therefore it is unclear whether these observed deficits are absolute power differences between groups or relative to a heightened baseline in SZ. Together these findings indicate the importance of considering intrinsic oscillatory activity in any study with SZ.

SZ often differ from healthy subjects on background neural activity across many frequency bands (Clementz et al., 2008; Wang et al., 2010; Winterer et al., 2000; 2004; 2006). Background noise in SZ is most frequently defined using a ratio of single trials to average trial power (Winterer et al., 2000; 2004) or by measuring evoked power in bands other than the driving frequency (Butler et al., 2001; Krishnan et al., 2005; Kim et al., 2005; 2006; Wang et al., 2010). SZ differ in resting, or baseline, power (Clementz et al., 1994), but this measure is rarely considered and adjustments for baseline activity are routinely employed in studies of oscillatory activity (Krishnan et al., 2005; 2009; Riecansky et al., 2010; Spencer et al., 2008). The common finding with the aforementioned baseline corrected data, noise corrected data or data measured as SNR is either no difference between groups (Wang et al., 2010) or a reduced ssVEP response in SZ relative to healthy subjects (Butler et al., 2001; Kim et al., 2005; 2006; Krishnan et al., 2005; 2009; Riecansky et al., 2010; Spencer et al., 2006; Krishnan et al., 2005;

In light of clear differences in intrinsic neural activity between schizophrenia patients and healthy subjects, it seems critical to further examine oscillatory properties of SZ in any task that is to be assessed as an endophenotype or discriminating factor for this disorder. For

endophenotype status, it is important to define a pattern of oscillatory activity that is a unique identifier for SZ and is also heritable.

Neuronal oscillations can be quantified in a number of ways, one of the most common being the Morlet wavelet (Goupillaud et al., 1984). The wavelet transform is computed as the original EEG time series convolved with a scaled mother wavelet function. The mother wavelet function is an enveloped sinusoidal waveform with a zero mean that has a specific location in both time and frequency space. This localization provides time resolution, crucial for analyzing nonstationary events such as EEG data. The mother wavelet can consist of many cycles at a particular frequency, which allows for better frequency resolution because more data is sampled, however a trade-off exists in that the wavelet covers more time in one measurement and thus decreases temporal resolution. The width of the wavelet function can be adjusted at different frequencies to obtain the best combination of time and frequency resolution for the needs of the experiment. Convolving the EEG time series with the mother wavelet creates a series of coefficients that quantify the similarity of the original data to the mother wavelet. The Morlet wavelet function is complex, and the coefficients for its real part denote amplitude of the frequency sinusoid at any given time, while the coefficients for the imaginary part denote phase angle, or relation of any given datapoint to the peak in the sinusoid (Herrmann et al., 2005).

Complex Morlet wavelets can be computed on either single-trial data or grand averaged data. Amplitude of the signal at each time-frequency point is computed, then averaged over trials, to give an estimate of induced single-trial power (STP). Phase angle can also be averaged over trials, to give an estimate of similarity of phase of an evoked signal over many repetitions, or inter-trial coherence (ITC). On data that is grand-averaged prior to wavelet analysis, information about induced activity is generally lost in the grand-averaging process because it is

not phase locked to stimulus onset (see Figure 1.1 for an example). Instead, evoked power, or phase-locked activity than varies in amplitude, is captured as an aggregate measure of amplitude and phase-locking. This method has benefits in that it is most equivalent to the way in which ERPs are traditionally measured, since single-trial ERPs suffer from poor signal-to-noise ratio. Therefore, evoked power is simpler to relate to ERP correlates; indeed, time-frequency plots of evoked power show evidence of a shape that is generally similar to that of an ERP, with clear peaks across time. Single-trial power and inter-trial phase locking time-frequency plots are not always as clearly indicative of the original event-related data, but may provide additional information about the nature of the underlying signal.

Utilization of steady-state stimuli, or stimulus trains that are presented in rapid succession at a constant rate over time, can provide additional information about oscillatory capability of a sensory processing stream. Neuronal pools that are processing the stimulus train will begin to oscillate in frequency with the rate of presentation, providing a strongly phase-locked signal that may give some indication of the integrity of the system (Regan, 1989). Neuronal pools that can "keep up" with the barrage of stimuli, for example in healthy subjects, will have stronger ITC than those of subjects with sensory processing deficits. Steady-state paradigms provide one advantage in that a target frequency with high signal-to-noise is created (Mast and Victor, 1991), and that frequency can be tracked across different brain areas that are actively processing the stimulus at any given time. In the visual modality, multiple stimuli flickering at different frequencies at different spatial locations can provide an elegant way to measure both covert and overt shifts in spatial and object-based attention (Wang et al., 2007). Additionally, there is some evidence that driving neurons at certain frequencies can partially alleviate processing deficits by potentially normalizing oscillatory patterns over time (Williams et al., 2006).

The following body of work utilizes complex Morlet wavelets in three ways: i) to capture with accurate time resolution of the oscillatory response of SZ to a visual steady-state stimulus, ii) to compare evoked power of the oscillatory response of SZ and BPP to an auditory oddball stimulus, and iii) to further breakdown the oddball task, this time a visual oddball, into STP and ITC responses in order to determine heritable oscillatory brain activity patterns to this task in healthy twins.

The purpose of this body of work is to further elucidate the underlying oscillatory capability of cortical neuronal populations in schizophrenia in both visual and auditory domains, as well as intrinsic differences in cortical oscillatory dynamics associated with the disorder. Twin data will also provide information about heritable aspects of oscillatory activity to one of these tasks (oddball). The ultimate goal of this work is to link characteristic, heritable, and discriminating oscillatory patterns of brain activity in order to better understand the etiology of schizophrenia, its biological and genetic relationship to other psychotic disorders (such as BPP), and to identify potential candidate endophenotypes for SZ, BPP, and/or psychosis broadly defined.



Figure 1.1: Evoked power, with data averaged over trials prior to wavelets analysis, more closely resembles ITC, which is phase locked over time, and fails to capture many aspects of amplitude changes that are not phase-locked (single trial power).

CHAPTER 2

SUSTAINED VERSUS TRANSIENT BRAIN RESPONSES IN SCHIZOPHRENIA: THE ROLE OF INTRINSIC NEURAL ACTIVITY¹

¹Ethridge, L.E., Moratti, S., Gao, Y., McDowell, J.E., Clementz, B.A. 2011. *Schizophrenia Research*. 133: 106-111. Reprinted here with permission of the publisher.

Abstract

Schizophrenia patients (SZ) show early visual processing deficits in many, but not all, tasks. These deficits may be associated with dysregulation of intrinsic oscillatory activity that compromises signal-to-noise in the SZ brain. This question was studied using visual steady-state stimulation and post-steady-state presentation of transient visual stimuli. SZ had higher intrinsic oscillatory activity at the steady-state stimulation frequency (12.5 Hz) and at the 6.25 Hz subharmonic, showed a significant decrease in visual steady-state magnitude over 2 sec of stimulation, and were unable to promptly terminate the steady-state response following stimulation offset. If adjustment for levels of intrinsic brain activity were made, however, it would have appeared that SZ had activity of similar magnitude as healthy subjects following steady-state stimulus termination, indicating that such adjustments could substantially alter theoretical interpretations. Visual evoked potential abnormalities (N1/P2 amplitudes) present among SZ at the initiation of steady-state stimulation were less apparent in the 750 ms immediately following steady-state stimulation offset. Higher intrinsic oscillatory brain activity may be a fundamental characteristic of SZ that merits further evaluation for understanding this disorder's neuropathological correlates and associated symptomatology.

Introduction

Schizophrenia patients (SZ) have early visual processing deficits under some, but not all, stimulus conditions (Butler et al., 2008; Clementz et al., 2008; Kieffaber et al., 2007; Luck and Gold, 2008; Wang et al., 2010). For instance, lower-tier (primary and extrastriate) visual electrocortical facilitation and attentional selectivity are relatively unimpaired in SZ when visual attention and target detection processes are differentiated (Clementz et al., 2008; Kieffaber et al., 2007). SZ also may have difficulty modulating gain (response amplitude relative to intrinsic neural activity) in the visual system (Clementz et al., 2008; Butler & Javitt, 2005). These diverse findings suggest that SZ visual processing abnormalities are a function of complex interactions between brain regions (Kemner et al., 2009) that are supported by oscillatory activities within cortical neural networks (Uhlhaas & Singer, 2006). To develop a better understanding of the neural basis for early visual processing deficits in SZ, it may be useful to study the oscillatory capability of their visual cortical neurons.

Oscillatory activity in visual cortex can be effectively evaluated by measuring the steadystate visual evoked potential (ssVEP) with electroencephalography (EEG). The ssVEP is brain activity that evolves to equal the stimulus flicker rate (Regan, 1989). In contrast to visual evoked potentials (VEPs) where changes occur at many frequencies, ssVEPs occur predominantly at known frequencies of interest, and are characterized by high signal-to-noise ratios (Mast and Victor, 1991), even among SZ (Clementz et al., 2008). At steady-state stimulus onset there is still a VEP (Clementz et al., 2004; Moratti et al., 2007), but after a few hundred ms, the neural response is primarily at the flicker frequency with neural sources in, or close to, lower-tier visual cortex (Di Russo et al., 2006; Clementz et al., 2008).

Few studies have evaluated the ssVEP in SZ (e.g., Clementz et al., 2004; Jin et al., 1990; Krishnan et al., 2005; Riečanský et al., 2010; see Brenner et al., 2009, for recent review). Patients have shown reduced amplitude ssVEPs in response to flickering stimuli in the theta, high alpha, beta, and gamma frequency ranges (Brenner et al., 2009). In response to extended steady-state stimulation (2 sec), however, Riečanský et al. (2010) found enhanced initial ssVEP in the gamma range among SZ that appeared to settle to more normal levels over time; SZ also had accentuated high alpha-to-low beta range oscillations following steady-state offset (a lingering oscillation effect reminiscent of Clementz et al., 2004). Interestingly, intrinsic prestimulus neural activity (see, e.g., Fox et al., 2007) among SZ also tends to be enhanced in lower (theta to alpha) frequencies. Most of the above studies (save Riečanský et al., 2010) considered the ssVEP to be a stable event (one that is stationary from beginning to end), even though this response evolves over the stimulation period (Moratti et al., 2007).

The present report addressed three issues. First, SZ often differ from healthy subjects on intrinsic prestimulus neural activity across many frequency bands (Clementz et al., 2008; Wang et al., 2010; Winterer et al., 2004). SZ also differ from other groups on instrinsic low frequency neural activity at rest (Clementz et al., 1994), but this difference is rarely considered and adjustments for baseline activity are routinely employed in studies of neural oscillations (see Brenner et al., 2009, for a discussion). It is important to consider, therefore, whether baseline adjustments contribute to group effects on visual oscillatory activity. Second, given that the ssVEP develops over stimulation time, differences in its evolution should be investigated to evaluate the stability of this visual sensory response among SZ. Third, Clementz et al. (2004) showed that the SZ visual system recovers sluggishly from stimulus processing. If so, subsequent stimulus registration may be affected. Presenting transient visual stimuli in the period

immediately after steady-state offset provides a novel means for addressing this issue (Moratti et al., 2007).

Materials and Methods

Twelve right-handed chronic outpatient SZ (4 females; mean age = 36.4 years; Global Assessment of Functioning score M=34, SD=4) and twelve right-handed healthy (6 females; mean age = 35.2 years) participants were recruited from the community. SZ were clinically stable on atypical antipsychotic medications for >8 weeks prior to participation. Subjects were interviewed with the SCID (First et al., 1995) by two psychologists to either verify their clinical diagnosis (SZ) or rule out Axis I disorders (healthy subjects). Participants were absent of neurological hard signs, possibly confounding treatments for electrophysiological measurements (such as ECT or benzodiazepines), history of head trauma and current psychoactive substance use disorders. The study was approved by the Institutional Review Board at the University of Georgia; participants provided written informed consent prior to study involvement and were paid \$10 US.

Subjects viewed steady-state stimuli on a 19-inch computer monitor (refresh rate 100 Hz) positioned 80 cm from their eyes. Stimuli were two red 8 x 8 checkerboards (four 1.2 cm square red and black boxes in alternating sequence), one each in left and right visual fields (same as Moratti et al., 2007). Checkerboards were positioned so their inner borders were 6.8 degrees from central fixation, and were luminance-modulated (40 ms on, 40 ms off) at a fixed rate of 12.5 Hz for 2000 ms. This oscillation frequency allowed for evaluation of both ssVEP development and lingering oscillatory effects following steady-state offset (Clementz et al., 2004; Moratti et al., 2007; Riečanský et al., 2010). Transient stimuli were presented at three times relative to steady-state offset: +240 (T240 condition), +480 (T480 condition), and +720 ms

(T720 condition), and consisted of 9.6 cm square solid red blocks presented at central fixation for 240 ms. All trials were presented in one block of randomly interleaved trials, with 66 trials of each condition. Six trials of each condition were targets (the transient stimulus was pink instead of red). Subjects were to simultaneously press buttons on a response pad with their left and right index fingers upon target appearance; these trials were not included in analyses (their purpose was encourage attention to the task). Trials were followed by a random 6 to 10 sec interval. Participants briefly practiced the task to ensure their ability to discriminate pink and red boxes. Both groups performed at 100% target detection accuracy, and there was no between-groups difference on latency (based on F-tests).

EEG data were continuously recorded using a 257 sensor Electrical Geodesics net, digitized at 250 Hz, analog filtered from .01 - 100 Hz, and referenced to Cz. Sensor impedances were kept below 50 k Ω . Sensors at the outer canthi and above and below the eyes recorded eye movements and blinks. Sensors on the neck and cheeks were excluded, leaving 216 for further analyses. Blink and heart-rate artifacts were corrected using BESA (Berg and Scherg, 1994). Data were average-referenced, and filtered (zero phase) from .5 - 75 Hz. Epochs of 4000 ms including a 500 ms baseline were scored using BESA and Matlab 7.7 (Mathworks, Natick, MA). *ssVEP scoring*

Grand averages during steady-state stimulation at the driving frequency (across all conditions because subjects did not know the transient condition at this point, so ssVEP was unaffected by condition) were analyzed using a Morlet wavelet with 3 cycles at 6.25 Hz (1/2f), 4 cycles at 12.5 Hz (1f), and 5 cycles at 25 Hz (2f), with wavelets centered on every time point, in order to balance time resolution at the lower frequencies with stability at the higher frequencies (Busch & VanRullen, 2010). The resulting power values from 29 sensors that captured the peak

ssVEP activity (from the grand average topography across groups over the entire steady state stimulation period; see Figure 2.1) were analyzed both before and after baseline correction starting 500 ms after steady-state onset (to ensure establishment of ssVEP) in 500 ms bins (midpoints of 750, 1250, and 1750 ms; see Figure 2.1).

VEP scoring

Data were filtered (zero phase) from 2 - 30 Hz with a 12.5 Hz notch (1 Hz width) to reduce ssVEP contribution to VEPs (although results were the same without the notch filter). EEG data were averaged across trials using 750 ms windows (including a 250 ms baseline). To integrate data recorded from every sensor, spatial principal components analysis (PCA) was implemented. For each group average and condition, a 216x216 covariance matrix was calculated (using time points as observations) and PCA was calculated with promax vector rotation and Kaiser normalization (Dien, 2006). Scree plots for each group and condition always identified 2 components, with the spatial distributions of these components and amount of variance accounted for (always close to 90%) being nearly identical between groups and within condition.

There was remarkable between-groups similarity in spatial distribution and factors loadings of (i) VEPs to onset of peripheral steady-state stimuli and (ii) across VEPs to all three central transient (post steady-state) conditions. Therefore, a grand average was created (i) across groups for VEPs to steady-state onset and (ii) across groups and conditions for VEPs to central post steady-state transients. This allowed for creation of spatial PCA components that were directly comparable between-groups and across conditions (post steady-state transients). For steady-state onset, the first two components accounted for 72.9% and 18.8% of the VEP variance; for post steady-state transients, the first two components accounted for 68.4% and 20.4% of the VEP variance.

For both PCAs, factor weights were multiplied by each subject's VEP data, summed across the sensors, and divided by the sum of the factor weights. For steady-state onset, eigenvalue-weighted averages of the two PCA factor waveforms were computed for each subject yielding a single waveform (Figure 2.2). For post steady-state transients, eigenvalue-weighted averages of the two PCA factor waveforms were computed for each subject and transient condition (T240, T480, and T720) yielding three different waveforms (Figure 2.2). N1 and P2 VEPs could be identified in these waveforms for all subjects and conditions; P1 was not similarly identifiable for all subjects and conditions so it was not scored. For every subject and condition, VEP peak amplitudes and latencies were quantified at the peaks closest in time to the grand average responses.

Results

ssVEP analyses

At 6.25 Hz (1/2f), SZ had higher baseline activity (M=20.0 μ V²/Hz, SD=3.6) than healthy subjects (M=16.7 μ V²/Hz, SD=3.6), t(22)=2.3, p=.03; the same was true at 12.5 Hz (1f), t(22)=2.6, p=.018 (Figures 2.1 and 2.3). Only the 12.5 Hz driving frequency, however, showed a significant ssVEP, or increase from baseline, following steady-state onset, F(1,22)= 60.5, p<.001, so subsequent statistical analyses were restricted to this frequency. There were significant Group by Time Bin interactions both with and without baseline adjustment, F(2,44)=6.9, p=.008, ε =.24 (see Figures 2.1 and 2.3). Simple main effects analyses showed an effect of bin for SZ, F(2,22)= 14.2, p=.001, ε =.56, but not for healthy subjects, F(2,22)=1.2, p=.315, ε =.09. For SZ; the 750 ms time bin had significantly stronger magnitude than the 1750 ms time bin, t(1,11)=3.89, p=.003.

Clementz et al. (2004) showed that SZ had prolonged ssVEP activity, so linear contrasts were performed on three 100 ms bins (prior to VEP activity associated with the first transient) after steady-state stimulation offset. Healthy subjects, F(1,11)=12.5, p=.005, but not SZ, F(1,11)=1.4, p=.262, had a significant linear decrease in 12.5 Hz power during this interval (Figure 2.3). This effect was evident in a Time Bin by Group interaction, F(1,22)=3.6, p=.04, for both baseline corrected and non-baseline corrected data. For non-baseline corrected data, however, there was also a main effect of Group, F(1,22)=4.5, p=.045, indicating that SZ power at the driving frequency remained higher than that of healthy subjects.

VEP analyses

At steady-state onset, there was a main effect of group on VEP amplitudes, F(1,22)=5.1, p=.034, with healthy subjects having larger N1s (M=-1.6 μ V, SD=0.7) than SZ (M=-1.3 μ V, SD=0.6), and smaller P2s (M=0.9 μ V, SD=0.6) than SZ (M=1.2 μ V, SD=0.5). There were no significant differences between-groups on VEP amplitudes to the transients (Figure 2.2). There were also no group differences on VEP latencies at either steady-state onset or to the post-steady-state transients (Figure 2.2).

Discussion

This investigation yielded four noteworthy outcomes. First, SZ had higher intrinsic neural activity at both the 12.5 Hz steady-state frequency and its 6.25 Hz subharmonic than healthy persons; adjusting for this difference had implications for SZ ssVEP characteristics (see below). Second, SZ showed a significant decrease in ssVEP magnitude over the course of steady-state stimulation. Third, after termination of the steady-state stimulus, healthy persons returned to near

baseline 12.5 Hz magnitude within 300 ms, but SZ had continued oscillatory activity that did not decrement over this same interval (Clementz et al., 2004). Fourth, group differences in stimulus registration (N1/P2 amplitudes) at steady state onset were attenuated to transients occurring after steady-state offset. The implications of these findings for understanding SZ neuropathology are briefly discussed below.

High levels of intrinsic neural activity characterize SZ (Clementz et al., 2004; Clementz et al, 2008; Krishnan et al. 2005; Rolls et al., 2008; Winterer et al., 2004), and might reveal a constitutionally mediated core deficit in SZ cortical functioning (Rolls et al., 2008). Intrinsic (not stimulus evoked, although perhaps stimulus-related) neural activity can be measured in multiple ways; nevertheless, studies in which such data are reported agree that SZ are elevated on this parameter compared to healthy subjects. This effect may be particularly evident in the theta to high-alpha range, although a systematic evaluation of this phenomenon across multiple frequencies has not appeared in the archival literature. Like in this report, which quantified activity in lower frequency ranges, high intrinsic neural oscillations can masquerade as accentuated responding in sensory cortices (Clementz et al., 2008; Spencer et al., 2004; Wang et al., 2010), but ultimately deleteriously affects signal-to-noise ratios. For instance, although SZ had modestly enhanced early ssVEP magnitudes (similar to that observed by Riečanský et al., 2010, in the gamma range), their percentage increase over baseline was sub-normal (38% for SZ versus 49% for healthy subjects); by the end of the steady-state stimulation period, the apparent difference in these values was more remarkable (19% for SZ versus 45% for healthy subjects). Diminished signal-to-noise could affect stimulus processing fidelity and perceptual experience, an issue that could be fruitfully addressed in subsequent investigations.

SZ did not maintain ssVEP at their initial magnitudes over the stimulation period.

Without adjusting for baseline differences at 12.5 Hz, Figure 1 illustrates that SZ had modestly accentuated initial oscillatory responses that significantly diminished over time to equal those observed among healthy subjects (albeit with lower signal-to-noise). After baseline adjustment, however, SZ initial ssVEP appeared to be more similar to healthy persons but then significantly diminished over time to appear lower than healthy subjects. Use of baseline adjustment may depend on questions of interest; however, for understanding the nature of SZ ssVEP, baseline adjustments may be of limited value. Appreciating group differences on signal-to-noise may require separate quantification of baseline and ssVEP activity. For instance, it seems inaccurate to infer SZ had healthy-level initial ssVEP magnitudes (given signal-to-noise differences) even though this would be the conclusion when only analyzing baseline-adjusted data.

Consistent with other research, at steady-state onset SZ had smaller N1 (e.g., Clementz et al., 2004) and larger P2 (e.g., Krieger et al., 2001; Nagasawa et al., 1999) VEPs than healthy persons. In response to the post-steady-state transients, however, these effects were attenuated. The visual N1 is more closely related to sensory registration than the P2, which may be associated with stimulus classification processes (Garcia-Larrea et al., 1992). With increased attention, the N1 is typically enhanced but the P2 may be diminished in amplitude (Crowley and Colrain, 2004). The pattern observed here may be a consequence of a relative between-groups equalization of intrinsic brain activity in neurons tuned for the (central) transient stimuli location. Although SZ VEPs to the transient stimuli were still modestly different from those observed among healthy subjects, the groups did not differ significantly on transient VEP magnitudes, in contrast to what was observed for VEPs at steady-state onset. This phenomenon could be more completely investigated by manipulating the locations of transient stimuli in relation to steady-

state stimulus location and timing (e.g., at the same or different location and during or following steady-state stimulation; see, e.g., Rockstroh et al., 1996). Future work will be needed to address whether there are differences in transient response amplitudes secondary to such manipulations.

One issue to consider is that after steady-state offset oscillatory activity among neurons tuned to the flickering stimuli locations was still not equal between-groups. With the present paradigm, we were unable to quantify intrinsic activity for neurons tuned specifically to the transient location. Perhaps enhancing neuronal investment at peripheral locations by steady-state stimulation modifies between-groups differences in intrinsic activity in neuronal pools tuned for other spatial locations. For instance, intrinsic activity is enhanced for neurons tuned to a spatial location requiring enhanced neural investment like the steady-state location in the present study (Ress et al., 2000), and the level of this enhancement correlates with task difficulty (Howard et al., 2003), with the same task perhaps requiring greater cognitive control for successful performance among SZ. Increasing cognitive control requirements may produce abnormally elevated intrinsic activity in specific neuronal pools among SZ, a maladaptive effort which may leave other neuronal pools unaffected. (see, e.g., Kapur, 2003). If so, transient stimuli may have been presented to SZ and healthy neuronal ensembles in more similar states of sensory processing readiness, which could reduce between-groups differences in neural responses to stimulus events.

Knowledge of SZ neuropathology may yield a partial explanation for the present findings. Low NMDA receptor function, perhaps a primary pathology in SZ (Kantrowitz & Javitt, 2010), prompts a secondary decrease of GABAergic interneuron activity, causing both disinhibition of pyramidal cells (Belforte et al., 2010; Gordon, 2010) and an inability to generate high signal-to-noise excitatory drive in cortical networks supporting specific stimulus processing requirements (Rolls et al., 2008; Tanaka, 2008; Yoon et al., 2010). Evidence for this ultimately maladaptive effort to restore homeostatic balance in local cortical circuits has been reported in multiple SZ brain regions, including visual cortex (Hashimoto et al., 2007). These cellular deviations are most evident in more superficial cortical layers where neurons support feature integration, communication with other cortical locations (Lewis, 2009), and are the most likely generators of N1/P2 VEPs. This neuropathology could account for both accentuated early visual processing in SZ (Clementz et al., 2008; Spencer et al., 2004; Wang et al., 2010) and lingering of the ssVEP after stimulus termination because such a system would be unable to efficiently recover from a bout of prolonged sensory processing (Clementz et al., 2004; Rolls et al., 2008).

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Contributors

SM, AK, and BAC designed the study and wrote the protocol. SM and YG collected the data and performed preliminary analyses. LEE performed all final analyses and wrote the manuscript in collaboration with all authors, who have seen and approved the final version.

Conflicts of Interest

The authors report no conflicts of interest.

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Figure 2.1: Steady-state VEP from a sensor in the middle of the activated region over dorsal visual cortex. A.) Topography of baseline power at the driving frequency for healthy and SZ participants. B.) Baseline corrected grand average power topographies for healthy and SZ participants in 500 ms bins centered as indicated. B.) Same topographies without baseline correction.



Figure 2.2: ERPs to steady-state stimulus onset and transient stimuli. ERPs represent the weighted average of the sensor weights for the first two PCA components for that condition applied to each individual's data and then averaged over the entire head. Topographies illustrate the weighted average of the first two PCA components for the steady-state onset and the averaged transient stimuli at the N1 and P2 peaks. Transient ERPs are differentially scaled from steady-state onset ERP in order to best show the peaks of interest, therefore absolute differences in peak amplitude between groups should be noted according to the scale.



Figure 2.3: Dynamics of non-baseline-corrected power at the driving frequency across time for healthy and SZ participants. Time labels on the X axis represent the baseline period (-324 to -50 ms pre-stimulus), centers of 500 ms windows during steady-state stimulation, and 100 ms windows for the period following steady-state stimulation offset.

Supplementary Materials – Spatial PCA

The data reduction method of spatial PCA has been utilized by many groups to improve the manageability of large datasets with many observations per subject (Arzy et al., 2010; Clementz & Blumenfeld, 2001; Clementz et al., 2007; Pourtois et al., 2008; Spencer et al., 1999; Smit et al., 2007; Zanotelli et al., 2010. EEG data, which can consist of hundreds of sensors and thousands of time-points for an individual, can be usefully reduced in complexity using methods like spatial PCA.

Spatial PCA can decompose data into factors (or components). In the case of EEG data, this means creating linear combinations of sensors with invariable spatial distributions (topographies) and variable time-courses (essentially creating a single 'virtual sensor' that has a time course and spatial distribution). In the present study, the inputs to a spatial PCA are sensors (216 sensors or variables) and time-points (750 time-points or observations), and such data are transformed to a sensors by sensors covariance matrix, where patterns of shared spatial variance between sensors can be quantified.

The first principle component (which accounts for the highest proportion of the spatial variance) is a linear combination of sensors that minimizes the sum of squared distances from the mean value of all sensors. After variance accounting for the first component has been removed, the process is repeated again to obtain the second principle component. The components then can be further adjusted to account for a higher proportion of variance by rotating their linear solutions around their mean value. This can be done either using a procedure that maintains spatial independence of the solutions or allows for some degree of correlation between components, the latter typically called an oblique solution. The oblique solution is more akin to theories concerning physiological data, i.e. the brain is not orthogonal (Dien, 2006). In the

present report, Promax rotation with Kaiser normalization was used, which is a common and well-tested oblique rotation (Dien, 2005).

This procedure of creating spatial components is halted when a significant proportion of variance is not captured by the next component. Rotated factors are presented in terms of percent variance accounted for, which can help the experimenter determine which factors should be retained and which do not contribute significantly to the data. The simplest method for determining the number of factors to retain is to examine the scree, a line plot of the percent variance accounted for by each factor is descending order. Factors above the bend in this typically exponential-appearing function (the "elbow" of the plot) are retained in the solution.

Spatial PCA produces time courses that represent the variation in voltage across time for a specific spatial component (see Figure 2 in the main text). Note that while the voltage switches from positive to negative, and the waveform changes in amplitude over time, the spatial topography does not differ within components. An eigenvalue, or scaled weight vector, for each sensor representing how much that sensor contributes to the spatial distribution of the factor is also obtained. Factor weights are multiplied by each individual's data, then summed across sensors resulting in a single waveform (sometimes called a 'virtual sensor'), representing the weighted average of all sensors across time. In this study, weighted waveforms for the first and second components were combined into a weighted average based on the proportion variance accounted for, to obtain a single average waveform across both retained components. The data for each subject was then reduced to this single virtual sensor and the waveform scored in the same way as a standard single sensor VEP.

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CHAPTER 3

NEURAL ACTIVATIONS DURING AUDITORY ODDBALL PROCESSING DISCRIMINATING SCHIZOPHRENIA AND PSYCHOTIC BIPOLAR DISORDER¹

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Abstract

Background: Reduced amplitude of the P300 event-related potential in auditory oddball tasks may characterize schizophrenia (SZ), but is also reported in bipolar disorder. Similarity of auditory processing abnormalities between these diagnoses is uncertain given the frequent combination of both psychotic and nonpsychotic patients in bipolar samples; abnormalities may be restricted to psychosis. In addition, typically only latency and amplitude of brain responses at selected sensors and singular time points are used to characterize neural responses. Comprehensive quantification of brain activations involving both spatio-temporal and timefrequency analyses could better identify unique auditory oddball responses among patients with different psychotic disorders.

<u>Methods:</u> Sixty SZ, 60 bipolar I with psychosis (BPP), and 60 healthy subjects (H) were compared on neural responses during an auditory oddball task using multi-sensor electroencephalography. Principal components analysis was used to reduce multi-sensor data prior to evaluating group differences on voltage and frequency of neural responses over time. <u>Results:</u> Linear discriminant analysis revealed five variables that best differentiated groups: (i) late beta activity to standard stimuli and (ii) late beta/gamma activity to targets discriminated BPP from other groups; (iii) mid-latency theta/alpha activity to standards and (iv) target-related voltage at the late N2 response discriminated both psychosis groups from H; and (v) targetrelated voltage during early N2 discriminated BPP from H.

<u>**Conclusions:**</u> Although the P300 significantly differentiated psychotic groups from H, it did not uniquely discriminate groups beyond the above variables. No variable uniquely discriminated SZ, perhaps indicating utility of this task for studying psychosis-associated neurophysiology generally and BPP specifically.

Introduction

During auditory oddball processing, reduced amplitude of the P300 auditory eventrelated potential (ERP) has been a robust finding in the schizophrenia literature¹⁻⁷. A similar deviation from normal has been reported among bipolar disorder patients, although this is a less frequently investigated phenomenon^{5,8-11}. Supplementing its possible usefulness for understanding disease risk are reports of P300 abnormalities among clinically normal firstdegree relatives of schizophrenia patients¹²⁻¹⁶ and the unaffected first-degree relatives of bipolar disorder patients¹⁷.

P300 deviations among clinically normal family members of affected probands suggest that auditory oddball processing is associated with constitutional liability for illness. A metaanalysis of twin studies on P300 responses indicated relatively high aggregate heritability estimates among healthy participants (60% for amplitude, 51% for latency¹⁸), although high heritability among healthy samples can compromise the utility of possible risk indicators for uncommon illnesses¹⁹. Nevertheless, evidence of genetic contribution to P300 variance further supports proposals of endophenotype status for these variables²⁰⁻²¹.

Endophenotypes should be relatively specific to persons with a disease and those at increased genetic risk for that disease²². One study reported differences in P300 topographies between schizophrenia versus bipolar patients¹⁰, but most investigations focus on only one of the two patient groups, making direct comparison of P300 abnormalities difficult. P300 abnormalities may be endophenotypes for psychotic disorders generally rather than risk indicators for a specific diagnostic group^{11,17,23-25}. Study groups comprising only psychotic bipolar disorder patients are uncommon¹¹, however, so the comparative uniqueness of specific P300 abnormalities to a particular psychotic group is unknown. In addition, P300 abnormalities

when quantified using traditional ERP latency and peak amplitude measurements have been described for multiple behavioral deviations (e.g., Carlson et al., 2004²⁶; Carlson et al., 2007²⁷). The frequent association of traditional P300 measurements with diverse patho-physiological conditions may indicate the importance of developing alternative quantification schemes that may capture this etio-pathological diversity.

A complement to traditional ERP voltage measurements is quantification of frequency variations in neural oscillations as a function of time. Indeed, ERP peak voltage measurements may not capture the complexity of neural responding that is evident in time-frequency representations²⁸. Such an integrated analysis approach allows for quantification of both the evoked and oscillatory components of neural responses to stimulus events (e.g., Lakatos et al., 2009²⁹), perhaps not obvious in the traditional ERP waveforms, to be evaluated simultaneously. Studying neural responses during auditory oddball processing using both voltage and frequency domain approaches may help elucidate differences between even nosologically similar diagnostic groups.

Frequency domain measures have already shown possible usefulness for clarifying psychosis-related neural deviations during auditory processing³⁰⁻³². For instance, Hamm et al.³¹ found an accentuation of late (250 ms post-stimulus) beta-range activity that was peculiar to BPP among psychosis patients (see also Lee et al., 2010³³; Ozerdem et al., 2008³⁴). This effect hints at differences in stimulus processing between SZ and BPP that could reveal critical variations in neuropathology. Synchronized beta-range activity is required for distant cortico-cortical communication³⁵, and is supported by the very cortical circuitry that is purportedly hypo-functional in SZ³⁶. This difference also may reveal a neurophysiological correlate of the enhanced sustained attention/vigilance that at least partially characterizes BPP³⁷.

The present investigation of the Bipolar and Schizophrenia Network on Intermediate Phenotypes (B-SNIP²¹) sample compared ERP amplitude measurements and event related oscillations across a broad frequency range during an auditory oddball task. Neural activations from whole head EEG recordings during stimulus processing were compared between healthy (H), schizophenia (SZ), and bipolar disorder with psychosis (BPP) participants. A comprehensive analysis approach was used to describe these groups' shared and unique neural auditory processing characteristics. The aim of the present study was to utilize large matched samples of SZ and BPP using an analysis approach that can identify neural processing deviations that are either shared between or unique to each psychotic disorder.

Methods and Materials

Participants

As part of the large, multi-site data collection project Bipolar and Schizophrenia Network on Intermediate Phenotypes (B-SNIP), subjects were recruited, interviewed, and tested at four sites: University of Illinois in Chicago, Illinois, Yale University/IOL in Hartford, Connecticut, University of Texas Southwestern in Dallas, Texas, and University of Maryland in Baltimore, Maryland. Stable participants were recruited via community advertisements, linked community facilities and programs, and local NAMI-type organizations.

Three age- and gender-matched groups were constructed blind to brain activity measurements: 60 SZ (30 female; mean age = 36.3; range 19-55); 60 BPP (30 female; mean age = 36.3; range 18-53); and 60 healthy persons (30 female; mean age = 36.2; range 18-54; recruited via random digit dialing or community advertisements). Data from a different paradigm for these same participants were also used in a previous manuscript³¹. All but five SZ and nine BPP were taking psychotropic medications. Detailed information regarding medications is presented in Supplementary Table S3.1.

Medical history, structured clinical interview for DSM-IV diagnosis (SCID patient or nonpatient version as appropriate³⁸), Positive and Negative Symptom Scale (PANSS³⁹), Young Mania Rating Scale³⁹, Montgomery Asberg Depression Rating Scale (MADRS⁴⁰), and Global Assessment of Functioning scale (GAF; axis V of Diagnostic and Statistical Manual of Mental Disorders IV [DSM-IV]) were acquired by trained Masters or Doctoral-level clinicians. The presence of serious medical, neuro-opthalmological, or neurological illness (e.g., cancer, seizure disorders, coarse brain-disease), mental retardation, head trauma with >30 minutes unconsciousness, current substance use ascertained by history as well as urine drug screens on the day of testing, abuse in the past three 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 a family history of psychotic or BP disorders in their first-degree relatives according to Family History Research Diagnostic Criteria⁴¹. All clinical information and diagnoses for each subject were reviewed and confirmed in a best estimate diagnostic meeting including a senior psychiatrist/psychologist and the clinician who conducted the structured interviews.

Stimuli and Procedures

Recording conditions were equivalent and stimulus presentation and recording equipment identical across sites. Seated in a sound and electrically shielded booth (ambient sound = 61-63 dB; luminance = 0.11-0.12 foot-candles) subjects listened to tones delivered by two 8-ohm speakers located 50 cm in front of them. Stimuli were 567 standard (1500Hz) and 100 target (1000Hz) tones presented in pseudorandom order (1300 ms inter-trial interval). Subjects were asked to press a button when a target was detected. Subjects refrained from smoking 1 hour prior to testing.

EEG recording

EEG was continuously recorded from 64 Ag/AgCl sensors (impedance <5 K Ω ; Quik-Cap, Compumedrics Neuroscan, El Paso, TX), positioned according to the standard 10-10 EEG system plus mastoids and CP1/2 locations to provide for greater sampling below the canthomeatal line, with nose reference and forehead ground. Recordings were amplified (12,500x) and digitized (1000 Hz) using Neuroscan Acquire and Synamps2 recording systems (Compumedrics Neuroscan, El Paso, TX).

EEG processing

Raw EEG data were inspected for bad sensors and artifacts. Bad sensors were interpolated (<5% for any subject) using spherical spline interpolation (BESA 5.3; MEGIS Software, Grafelfing, Germany). Blink and cardiac artifacts were removed using Independent Components Analysis (EEGLAB 6.0^{42}). EEG data were segmented into 1000 ms epochs from 250 ms before to 750 ms after stimulus onset and digitally bandpass filtered from 0.5 - 55 Hz (zero phase filter; rolloff: 6 and 48 dB/octave, respectively). The 250 ms pre-stimulus period was used for baseline adjustment. Epochs containing activity greater than 75 µV at any sensor were not included; at least 60% of trials were accepted for all subjects.

PCA data reduction

To use EEG data recorded from every sensor and, thus, to most accurately and comprehensively capture the spatial topography of evoked brain responses across time, spatial principal components analysis (PCA) on grand average data⁴³⁻⁴⁴ was implemented using BESA (MEGIS Software, Grafelfing, Germany) and Matlab (The Mathworks, Matick, MA) to identify spatial patterns in the EEG topography. Target and standard conditions were averaged separately across groups. For each condition, a PCA with promax (oblique) vector rotation and Kaiser normalization⁴⁵ was calculated on a 64X64 sensor covariance matrix (using 1000 time points as observations). Scree tests⁴⁶ identified 2 components for the target condition (accounting for 55.9 and 39.0 percent of the variance) and 1 component (87.5 percent of the variance) for the standard condition (Figure 3.1). The spatial distributions of these components and amount of variance accounted for in the grand average were nearly identical across groups (see Supplementary Figure S3.1, all correlations between groups greater than r=.975). Each set of component weights was multiplied by each subject's grand average data, summed across sensors, and divided by the plus sum of the component weights. This reduced waveforms from one for each sensor to one waveform per component for each subject for targets and standards (Figure 3.2).

ERP time course analyses

For each condition and subject, component waveforms from -200 ms to 600 ms were grouped into 80 separate 10 ms bins and averaged within each bin. For each bin, a one-way ANOVA was calculated to determine group differences in waveform amplitude. To control for family-wise error due to multiple comparisons, a clustering method was implemented using Monte Carlo simulations calculated using AlphaSim⁴⁷. In order to maintain a family-wise alpha of .01, three sequential time bins were required to be significant at alpha<.05 (Figure 3.2). *Time frequency analyses*

For each subject, separately for each component waveform, oscillatory power for frequencies from 3-52 Hz was calculated with 1 Hz frequency resolution using a modified Morlet wavelet transformation every 4 ms on the grand averaged ERPs. In order to balance the tradeoff between temporal resolution at low frequencies and stability of measurement at higher frequencies⁴⁸, wavelet length increased linearly from 1 cycle at 3 Hz to 8 cycles at 52 Hz (Figure 3.3). Group comparisons for each condition and component were calculated using point-by-point one-way ANOVAs across the time-frequency matrix. Again, a clustering method was implemented to control for family-wise error. Utilizing the same procedure as for the ERP analyses, family-wise alpha at .01 was maintained with clusters of 5 or more sequential time-points significant at p<.01. To control for aberrant significant effects due to a small number of large power values, F-value distributions were created using a bootstrap procedure. For each condition and factor, the same one-way ANOVAs were run 5000 times with group membership randomly shuffled at each step (sampling with replacement). Probability estimates of the observed F-values were then calculated as the proportion of randomly generated F-values greater than the actual estimate. There were no significant site by group interactions on any of the variables that significantly distinguished groups (Supplementary Figures S3.2 and S3.3). *Post-hoc discriminant analyses*

To efficiently summarize EEG variables that uniquely differentiated groups, values from significant time bin and time-frequency clusters were averaged within adjacent clusters for each subject and submitted to a linear discriminant analysis with group as the dependent variable (H, SZ, BPP). Variables that minimized the overall Wilks' lambda and had individual multiple F-statistics significant at p<.05 were entered in a stepwise fashion⁴⁹, leaving a parsimonious selection of neurophysiological measures. This additional statistical analysis was included specifically to describe the variables most important to group separations rather than as an attempt to classify observations. The latter approach will be more appropriate when we can add additional tasks and observations to our data collection efforts.

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Results

ERP time bins

One-way ANOVAs for each condition and spatial factor revealed 7 clusters that differentiated groups (Figure 3.2). Given a bimodal distribution in F-values for the P300 cluster (see Figure 3.2), it was split into early and late sections at the point of rarity (410ms). For the following comparisons, the patient groups did not significantly differ from each other.

- (i) For target component 1, from 150 to 210 ms (early N2 time range), peaking at 190 ms, F(2,177)=7.95, p<.001, BPP showed significantly less voltage change from baseline than H, t(118)=2.09, p<.05.
- (ii) For target component 1, from 320 to 400 ms (early P3b time range), peaking at 370 ms, F(2,177)=6.39, p=.002, both BPP, t(118)=2.23, p=.03, and SZ, t(118)=2.77, p=.006, showed less voltage change from baseline than H.
- (iii) For target component 1, from 410 to 580 ms (late P3b time range), peaking at 540 ms, F(2,177)=7.34, p<.001, both BPP, t(118)=2.19, p=.03, and SZ, t(118)=3.17, p=.002, showed less voltage change from baseline than H.
- (iv) For targets component, 2 from 50 to 110 ms (N1 time range), peaking at 60 ms,
 F(2,177)=7.08, p=.001, both BPP, t(118)=2.43, p=.02, and SZ, t(118)=3.95, p<.001, showed less voltage change from baseline than did H.
- (v) For targets component 2, from 200 to 220 ms (late N2 time range), peaking at 210 ms, F(2,177)=4.69, p=.01, both BPP, t(118)=2.89, p<.01, and SZ, t(118)=3.5, p<.001, showed less change from baseline than did H.

- (vi) For standards from 60 to 110 ms (N1 time range), peaking at 100 ms, F(2,177)=5.61, p=.004, both BPP, t(118)=3.14, p=.002, and SZ, t(118)=2.78, p=.006, showed less change from baseline than did H.
- (vii)For standards from 210 to 230 ms (P2 time range), peaking at 210 ms F(2,177)=3.73, p<.05, both BPP, t(118)=2.27, p=.03, and SZ, t(118)=2.39, p=.02, showed less change from baseline than did H.</p>

Time-frequency

Point-by-point one-way ANOVAs on averaged time-frequency plots revealed 7 clusters which significantly differentiated groups (red outlines in Figure 3.3). For the purposes of statistical and post-hoc analyses, clusters that spanned large amounts of time and showed evidence for multiple centers of convergence were split at the time-point with the lowest F-value.

- (i) For targets, component 1, from 165 to 195 ms, peaking at 180 ms and 15 Hz,
 F(2,177)=7.76, p<.001, both SZ, t(118)=3.68, p<.001, and BPP, t(118)=2.89, p=.005, showed less power than H.
- (ii) For targets, component 1, from 165 to 265 ms, peaking at 220 ms and 3 Hz,
 F(2,177)=12.34, p<.001, both SZ, t(118)=3.83, p<.001, and BPP, t(118)=3.82,
 p<.001, showed less power than H.
- (iii) For targets, component 1, from 265 to 400 ms, peaking at 275 ms and 3 Hz,
 F(2,177)=9.41, p<.001, both SZ, t(118)=3.95, p<.001, and BPP, t(118)=3.27, p=.001, showed less power than H.
- (iv) For targets, component 1, from 530-560 ms, peaking at 535 ms and 37 Hz,
 F(2,177)=5.84, p=.003, BPP showed more power than both SZ, t(118)=2.72, p<.01, and H, t(118)=3.73, p<.001.

- (v) For standards, from 20 to 150 ms, peaking at 60 ms and 3 Hz, F(2,177)=7.79,
 p<.001, both SZ, t(118)=2.98, p=.004, and BPP, t(118)=3.51, p<.001, showed less power than H.
- (vi) For standards, from 150 to 305 ms, peaking at 230 ms and 4 Hz, F(2,177)=9.18,
 p<.001, both SZ, t(118) =3.58, p<.001, and BPP, t(118)=3.74, p<.001, showed less power than H.
- (vii) For standards, from 440 to 490 ms, peaking at 470 ms and 27 Hz, F(2,177)=7.78, p<.001, BPP showed more power than both SZ, t(118)=3.45, p<.001, and H, t(118)=3.51, p<.001.

Discriminant Analyses

All 14 variables that differentiated groups were used in a linear discriminant analysis, which resulted in five variables that best discriminated groups, 2 ERP time bins and 3 time-frequency clusters (Table 3.2):

- (i) The target late N2 (component 2) significantly discriminated patient groups from H.
- (ii) The target early N2 (component 1) significantly discriminated BPP, but not SZ, from H.
- (iii) Late beta power to standards significantly discriminated BPP from both SZ and H.
- (iv) Late beta-gamma power to targets significantly discriminated BPP from both SZ and H.
- (v) Mid-range theta-alpha power to standards significantly discriminated patient groups from H.

Clinical Correlations

Separately for both patient groups, all available clinical variables (Table 3.1) were submitted to Pearson correlations with the 5 discriminating EEG variables. The only significant correlation was late beta/gamma power in the target condition with MADRS (Montgomery-Asberg Depression Rating Scale) scores for the BPP group (r=.276, p<.05).

Discussion

The purpose of this study was to use ERP and time-frequency quantifications of auditory oddball processing to characterize neurophysiologically distinct measures of similarities and differences among SZ and BPP. Out of 14 variables showing between-groups effects, five efficiently summarized group discrimination variance, with all of these measures providing important information for understanding the neurophysiological correlates of psychosis generally and (perhaps) BPP specifically. Variables that best differentiated psychosis from healthy subjects were mid-latency theta/alpha activity during standard stimuli processing and the target-specific late N2 ERP. Late beta/gamma activity during standard and target stimuli processing best differentiated BPP from SZ and H. The target-specific early N2 ERP, with a topography covarying with the P3b, discriminated BPP from H. No variable specifically discriminated SZ from the other two groups. The significance of these findings for understanding shared and unique neurophysiological characteristics of SZ and BPP is discussed below.

Two variables, theta/alpha band activity to standards and the late N2 to targets, differentiated psychosis groups from healthy subjects. Reduced low-frequency power to both targets and standards has been shown for SZ^{50-53} ; this effect had not been previously described for BPP, perhaps because such large samples of bipolar patients with psychosis are uncommonly included in such reports. Abnormalities in low frequency response may serve as a good indicator of psychosis; indeed, reduced delta and theta synchrony may be a better discriminator of SZ and H than P3b amplitude³⁰. Task-related theta and alpha abnormalities have been reported for SZ and their healthy first-degree relatives, suggesting that low frequency processing deficits may be indicative of genetic risk for psychosis⁵⁴.

Amplitude reductions of the target-related N2 ERP, associated with initial stimulus categorization, have been shown for SZ⁵⁵⁻⁵⁶, but have not been extensively studied in BPP. Using a passive oddball paradigm, Kaur et al.⁵⁷ reported amplitude reductions of N2 and P3 among both BPP and SZ, but no difference between patient groups. Distinct early and late components in the N2 range were found in the present study, with the earlier N2 ERP (differentiating BPP and H) topographically associated with the P3b and the later N2 ERP (differentiating psychosis groups from H) topographically associated with the N1 and P3a (see Figure 3.2). Similar to the findings of Kaur and colleagues⁵⁷, neither of these N2 ERPs discriminated between SZ and BPP, suggesting that neurophysiological processing deviations captured by the target-specific N2 (e.g., Kaur et al., 2011⁵⁷; Naatanen, 1990⁵⁸) are shared between psychotic disorders.

Augmented late responses in higher frequencies (beta and gamma) discriminated BPP from both SZ and H. Increased beta-band response in a visual oddball task, an abnormality that is somewhat normalized by valproate³⁴, is associated with bipolar I disorder. Hamm et al.³¹ reported this same increased beta-band response following auditory paired stimuli processing in this sample. Beta oscillations are critical for long-range cortico-cortical communication³⁵ and rely on GABAergic NMDA networks⁵⁹⁻⁶¹. Widespread loss of GABAergic NMDA neurons has been associated with both SZ and bipolar disorder⁶². GABAergic activity is modulated by dopamine, and increased dopamine activity is associated with both psychosis in general and with mania⁶³⁻⁶⁵, which may facilitate cyclical down-regulation of dopamine receptors during depressive phases⁶⁶. Perhaps interactions between cyclic dopamine levels and disrupted GABAergic neurotransmission lead to heightened beta and gamma band response when an interaction between long-range communication and local processing is required (e.g. following stimulus evaluation and response selection during target detection tasks). In the current study, accentuated late beta/gamma activity correlated with MADRS scores, indicating that this response may be linked to the emotion regulation abnormalities more endemic to BPP. In addition, due to its uniqueness to BPP, augmented beta/gamma band response to the oddball task may afford an interesting avenue as a potential endophenotype for BPP, although further work incorporating familial risk factors will be necessary to support this assertion.

Consistent with previous work^{11,17,23-25}, the P3b did not differentiate SZ and BPP. Earlier target-related ERPs (the early and late N2s) share the same component topographies and may capture some of the variance associated with the P3b and P3a, respectively; both of these ERPs were smaller in amplitude among SZ and BPP when compared to H. Indeed, SZ and BPP had similar decreases in P3b amplitude (see Figure 3.2), suggesting that this target-specific response captured psychosis variance in the present report (see also Bestelmeyer et al., 2009²³). Indeed, a recent meta-analysis of structural MRI studies on SZ and bipolar I disorder found overlapping areas of grey matter volume loss for both groups in the cingulate cortex, a structure that likely contributes nontrivial variance to P3 generation⁶⁷⁻⁶⁸. It is also clear, however, that P3b amplitude reductions are associated with multiple other pathologies^{26-27,69}, so this ERP measure's utility for capturing disease-specific variance is at present uncertain.

A genetic basis for reduced P3 amplitude as an endophenotype for psychosis risk is supported by shared variation between P3 abnormalities and DISC1, a gene that has been associated with psychosis risk (both SZ and bipolar I disorder) and memory impairments⁷⁰⁻⁷².

DISC1 is translated into a protein that primarily localizes to mitochondria in neurons and glial cells⁷² and has functional consequences for glutamatergic activity⁷³, neurite outgrowth⁷⁴, and early development of the major dopamine systems which have been associated with both schizophrenia and P3 generation⁷⁵⁻⁷⁶.

This study differs in a number of ways from previous literature on auditory oddball response in clinical populations. Rather than selecting a single sensor as representative of the ERP response, we used the spatial PCA approach to derive a data-driven integrated neural response incorporating information from all sensors across the head. In addition, rather than comparing data only at waveform peaks or time-frequency intensities, a binning and clustering approach was used in order to identify areas of maximal variance across the entire time range of neural response generation to stimulus events. The present results suggest that time-frequency measures complement ERP voltages for characterizing neural abnormalities in psychosis groups. It was also clear that incorporating information from the entire neural processing range can illuminate neural processing deviations not readily apparent from studying specific, predefined frequency bands or time ranges. The utility of the auditory oddball task for identifying BPPspecific neural processing deviations in particular is a significant new revelation for this research domain. Our more comprehensive analysis strategy was critical for yielding a series of new discoveries. Future work implementing this approach to investigate neural correlates and genetic/familial risk factors associated with auditory processing deviations in psychosis will open particularly exciting new avenues for research.

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| | Bipolar I Psychosis | Schizophrenia | Healthy | Significance Test |
|------------------|---------------------|---------------|---------------|-------------------|
| Subjects | 60 | 60 | 60 | |
| From each site | | | | |
| UIC ^a | 22 | 21 | 21 | |
| YU | 16 | 14 | 17 | _ |
| UTS | 12 | 13 | 14 | _ |
| UM | 10 | 12 | 8 | $X^{2}(6)=1.28$ |
| Percent female | 50% | 50% | 50% | |
| Age | 36.3 (18-53) | 36.6 (19-55) | 36.2 (18-54) | F(2,177)=.026 |
| Trials accepted | | | | |
| Standards | 525 (374-567) | 530 (406-567) | 540 (342-567) | F(2,177)=1.53 |
| Targets | 93 (69-100) | 94 (79-100) | 96 (64-100) | F(2,177)=2.26 |
| Clinical Scales | | | | |
| GAF | 59.1 (30-82) | 47.8 (30-90) | - | t(112)=4.73*** |
| PANSS-pos | 13.6 (7-24) | 17.4 (8-29) | - | t(112)=4.47*** |
| PANSS-neg | 11.9 (7-30) | 17.2 (7-32) | _ | t(112)=5.45*** |
| PANSS-gen | 29.1 (18-56) | 33.3 (17-52) | _ | t(112)=2.65** |
| MADRS | 11.3 (0-43) | 10.7 (0-30) | _ | t(112)=.327 |
| YMS | 5.15 (0-21) | 4.47 (0-19) | _ | t(112)=.714 |

Table 3.1: Demographic and clinical statistics.

^a UIC, University of Illinois, Chicago; YU, Yale University/IOL; UTS, University of Texas Southwestern; UM, University of Maryland; GAF, Global Assessment of Functioning; PANSS,

Measure	Wilk's Lambda	F-value *	H vs. SZ	H vs. BPP	SZ vs. BPP
Standard Late Beta	0.821	9.13	t(118)=.08	t(118)=3.51	t(118)=3.45
			p=.94	p<.001	p<.001
Target Late Gamma	0.775	7.94	t(118)=1.14	t(118)=3.73	t(118)=2.72
			p=.26	p<.001	p<.01
Standard Mid Alpha/Theta	0.741	7.03	t(118)=3.58	t(118)=3.74	t(118)=.47
			p<.001	p<.001	p=.63
Target Late N2	0.704	6.63	t(118)=3.50	t(118)=2.89	t(118)=.59
			p<.001	p<.01	p=.56
Target Early N2	0.667	6.43	t(118)=1.62	t(118)=2.09	t(118)=.47
			p=.11	p<.05	p=.64

 Table 3.2. Results from linear discriminant analysis

* All F values are significant at p<.001



Figure 3.1: Grand averaged butterfly plots and PCA component waveforms and topographies for target and standard conditions.



Figure 3.2: PCA weighted waveforms for each group for targets and standards. The lower plots display F values for one-way ANOVAs for each 10ms time bin. Time bin clusters were significant at p<.01 if three consecutive time bins were significant at p<.05 (F=3.05, indicated by the horizontal gray line).



Figure 3.3: Time-frequency plots by group and point-by-point F value plots with significant clusters (indicated by red boxes) for each factor and condition. For display purposes, group time-frequency plots are rescaled by each frequency's mean across all groups and time-points



Figure 3.4: Group averages and standard errors for five main group discriminators determined in the linear discriminant analysis. P-values are based on two-tailed independent samples t-tests (df=118).

Medication	SZ	BPP
Antidepressants		
Bupropion	5	6
Buspirone	3	5
Citalopram	3	3
Duloxetine	3	3
Escitalopram	1	2
Fluoxetine	4	4
Fluvoxamine	1	1
Mirtazapine	0	1
Paroxetine	3	0
Sertraline	3	0
Trazodone	8	11
Venlafaxine	1	1
Subjects on at least 1		
medication	22	27
Anticholinergics		
Benzatropine	9	4
Anticonvulsants/Mood stabilizers		
Carbamazepine	1	1
Gabapentin	1	0
Lamotrigine	2	12
Lithium	3	13
Oxcarbazepine	1	6
Topiramate	0	1
Valproate	4	7
Zolpidem	3	2
Subjects on at least 1 med	8	25
First Generation Antipsychotics		
Chlorpromazine	1	2
Fluphenazine	3	1
Haloperidol	7	1
Loxapine	1	0
Perphenazine	0	1
Thiothixene	1	1
Subjects on at least 1 med	11	6
Second Generation Antipsychotics		
Aripiprazole	13	6
Clozapine	6	2
Olanzapine	3	4
Paliperidone	3	1
Quetiapine	11	17
Risperidone	15	11
Ziprasidone	5	4

Subjects on at least 1 med	43	38
Sedatives		
Alprazolam	2	2
Chlordiazepoxide	0	1
Clonazepam	5	9
Diazepam	2	0
Lorazepam	4	4
Temazepam	1	1
Zaleplon	1	0
Subjects on at least 1 med	17	16
Stimulants		
Atomoxetine	1	2
Dexmethylphenidate	1	0
Dextro-a-amphetamine	1	2
Lisdexamphetamine	0	1
Methylphenidate	2	1

Supplementary table S3.1: Medication information for each patient group, with the total number of subjects taking at least one medication in each drug class.



Figure S3.1: PCA component topographies by group, with percent variance accounted for by each component.



Figure S3.2: F value plots for ERP time bins by condition and factor. Solid lines indicate F values for main effects, while dotted lines indicate the interaction, or site effects. Horizontal gray line marks the F value at which p<.05. Note that no site effects reached significance.



Figure S3.3: F value plots for time-frequency clusters by condition and factor. Left column indicates main effects of group, with significant clusters outlined in red. Right column indicates site effects, scaled to accentuate significant time-points (p<.01). Note that significant site effect time-points do not overlap with any significant main effect clusters.

CHAPTER 4

GENETIC INFLUENCES ON COMPOSITE NEURAL ACTIVATIONS SUPPORTING VISUAL TARGET IDENTIFICATION¹

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Abstract

Behavior genetic studies of the brain activity associated with complex cognitive operations are surprisingly uncommon. In the present project, monozygotic (N=51 pairs) and dizygotic (N=48 pairs) twins performed a visual oddball task while EEG was collected from a 61channel montage. Using spatial PCA, two principle components were retained for each condition and wavelets were used to obtain time-frequency maps of the eigenvalue weighted event related oscillations for each individual. Distribution of inter-trial phase coherence (ITC) and single trial power (STP) over time indicated that early components were primarily associated with ITC while later components were more associated with a mixture of ITC and STP. Point-by-point heritability revealed clusters of heritability that were then tested using Cholesky decomposition. Clusters of heritability were not entirely dependent on peaks of brain activity, suggesting that this method provides a new approach to identifying potential endophenotypes for neuro-psychiatric disorders.

Introduction

Studying genetic influences on complex cognitive operations and their neural correlates is a relatively new field of interest, and developing reliable measures for assessing heritability of complex neural activity is an important step in the process of gene identification. Monozygotic (MZ or identical) twins share all of their genes, while dizygotic (DZ or fraternal) twins share 50% of their genes on average. In the simplest formulation, an increased similarity between MZ compared to DZ twins for a particular trait is theorized to result from shared genes rather than environment. Numerous twin studies show that genes play a large role in determining a number of important human characteristics (Carlson & Iacono, 2006; Frederick & Iacono, 2006).

Comprehensive evaluations of genetic influences on brain activity in normal cognitive neuroscience studies could be important for many reasons. First, brain activity measures are closer to the primary gene products than are molar-level behaviors (Iacono & Clementz, 1993), so they may have simpler genetic profiles. Second, activity in particular brain regions, rather than molar-level behaviors, may provide more specific information about the genetic variance in specific neural circuitries that support complex cognitive operations. Third, studying genetic variation at the level of neural activity may provide useful information about the genetics of cognitive control that is independent of particular task demands. Most studies of genetic influence on human behavior have focused on personality and/or characteristics associated with psychopathologies (Frederick & Iacono, 2006; Lykken, 2006). Neuroimaging studies (fMRI and EEG/MEG) investigating the genetic variance of the neural architecture supporting cognition in normal twins are surprisingly uncommon, with many imaging genetic studies focusing on twins discordant for certain pathologies in an effort to identify endophenotypes (Gottesman & Gould, 2003) for those disorders.

The present study used a classical twin design to evaluate genetic influences on spectral components of brain responses that are associated with both simple and complex cognitive operations elicited by a visual oddball task (Katsanis et al., 1997; Steinhauer et al., 1987; Simson et al., 1977). Multiple brain regions are activated during such tasks, including visual, parietal, inferior temporal, anterior cingulate, and prefrontal cortices (Linden, 2005). A prominent brain response, called the P300, has been the focus of most twin studies using similar target detection tasks (e.g., van Baal et al., 1998; van Beijsterveldt et al., 1998; 2001; Begleiter et al., 1998; Almasy et al., 1999; Anohkin et al., 2001; Carlson & Iacono, 2006;). The P300 is generally associated with context updating in working memory and target evaluation (Linden, 2005). Meta-analytic studies show that about 60% of the variance in P300 amplitude and 50% of the variance in latency is attributable to genes (van Beijsterveldt & van Baal, 2002). These analyses, however, were mostly limited to evaluations of voltage at single sensors (Pz) so they may have incompletely described the genetic and environmental variance constituents of this neurophysiologically complex trait.

Considerable effort has been devoted to studying genetic influences on P300, including its endophenotype characteristics (e.g., Bestelmeyer et al., 2009; Hall et al., 2009; Schulze et al., 2008; Yoon et al., 2006; Bramon et al., 2005; Carlson, Iacono, & McGue, 2004), but other brain responses elicited during the same tasks have received considerably less attention. Indeed, the degree of genetic influence on earlier brain responses in visual oddball paradigms is, at best, uncertain (e.g., Katsanis et al., 1997; Almasy et al., 1999; Smit et al., 2007). The standard N100 appears to be moderately heritable (Almasy et al., 1999; Smit et al., 2007), while, surprisingly, the target N100 seems to possess limited genetic variance (Katsanis et al., 1997). Katsanis and colleagues (1997) also reported significant genetic variance for P200 and N200 neural responses.

Like most P300 investigations, these studies also used few sensors, and measured neural activity at a single time point, limiting their ability to completely describe genetic contributions to these complex neural responses.

Brain processes can be measured in many ways. Investigations of genetic influences on amplitude and latency of individual ERP peaks (at individual and limited time points) have been useful. ERP peak measurements, even for brain responses to simple stimuli, however, most likely fail to capture the complexity of neural responding that is evident in time-frequency representations, a quantification approach which is also more consistent with the actual functional characteristics of the brain (e.g. Privman et al., 2011; Samar et al., 1995; Gray & Singer, 1989).

There are few investigations of event related oscillations (EROs) in twins (Gilmore et al., 2010a; 2010b). Most studies reporting heritability statistics on frequency spectra come from resting state paradigms with no external stimulus. In the resting state, heritability has been established for delta, theta, alpha, and beta bands (Smit et al., 2005; 2010; Posthuma et al., 2001; van Beijsterveldt et al., 1998; Zietsch et al., 2007). Genetic influences on oscillations occurring in response to an external stimulus or task have been useful in studies of twin pairs discordant for specific pathologies (Hall et al., 2011; Smit et al., 2009), but are infrequenct in the normal cognitive neuroscience literature. Reports on oddball task EROs often focus entirely on the P300, and many use ERP-related methods for quantification, such as grand-averaging and/or restricted time ranges (Basar-Eroglu at al., 2001; Devrim et al., 1999; Ergen et al., 2008; Gilmore et al., 2010a; Ucles, Mendez, & Garay, 2009; but see Demiralp et al., 1999), despite evidence that alternative approaches may be useful (Andrew & Fein, 2010). For instance, single trial analyses, a method uncommonly used in ERP studies can be used to parse neural contributions to multiple

ERP components (Mouraux & Iannetti, 2008; Hu et al., 2010). Because neural oscillatory activity changes over the course of stimulus processing, quantifying heritability changes in frequency space over time would be useful. This paper quantifies genetic influences on neural oscillatory activity during complex cognitive processing over time using point-by-point broad spectrum heritability of whole head neural activity.

The purpose of the present investigation was to investigate the utility of a novel approach for studying genetic variance on brain activations during complex cognitive processing. Two specific modifications to the typical approach used in twin studies were implemented here. First, spatial PCA was used to reduce whole head EEG data to components that efficiently captured neural activation variance in response to task stimuli. These components were then subjected to frequency decomposition over time using Morlet wavelets. Significant time-frequency regions of heritable neural activity were submitted to Cholesky decomposition to evaluate sources of genetic and environmental variance for brain oscillatory behavior during complex cognitive processing. This approach (i) used minimal data processing adjustments to impose the fewest restrictions possible on data analyses, (ii) integrated information across a large number (61) of EEG sensors, allowing for maximal use of available data, (iii) rather than arbitrarily selecting sensors for analyses, used spatial PCA to empirically derive a multi-sensor neural response that could be quantified with enhanced signal-to-noise ratio and improved reliability of measurement (Braboszcz & Delorme, 2011) and (iv) evaluated neural responses over the entire time range of stimulus processing to perhaps provide a closer approximation to the actual functional characteristics of brain activations supporting complex cognitive operations.

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Materials and Methods

Participants

The Minnesota Twin Family Study, begun in 1990, is an epidemiological study of all same sex twin pairs born in the state of Minnesota during selected birth years. For the present study, 51 MZ (24 female) and 48 DZ (22 female) twin pairs from this project were used, all 29 yrs of age (see Iacono et al., 1999 for a description). Twin pairs were randomly selected from a subgroup of subjects with relatively artifact-free EEG data.

Procedure

In the EEG environment, participants performed the rotated heads task developed by Begleiter and colleagues (1984; see also Carlson & Iacono, 2006). Subjects viewed a sequence of 240 stimuli. The stimuli were presented for 98 ms with an inter-stimulus interval of 3-4 sec (rectangular distribution). One third of the stimuli (targets) showed a top-down view of a schematic head, with nose and one ear depicted by a triangle and a small oval, respectively. The remaining 160 trials (standards) showed a simple oval with no corresponding head features. Participants were asked to respond to targets and indicate whether they saw a left or right ear by pressing a corresponding left or right response button. For half of the targets, the nose pointed upward and the task was relatively straightforward. For the other half of the targets, the head was rotated 180 degrees to make the nose point downward, making the task of indicating left or right subjects failed to respond were re-presented at the end of the run, preceded by two standards to maintain the ratio of target to standard responses (Gilmore et al., 2009).

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ERP Recording

EEG was continuously recorded and digitized at 1024 Hz, with a 5th-order Bessel antialiasing filter at 205 Hz, using a 61-channel BioSemi system with electrodes placed according to the International 10/10 system (Chatrian et al., 1985). Recording included two mastoid electrodes, two electrodes on the outer canthus of each eye, and one electrode each above and below the right eye to record eye movements. All electrodes were referenced to a monopolar reference feedback loop (a feedback loop connecting a driven right leg passive electrode and common mode sense active electrode, both located on posterior scalp, which drives the subject's average.)

EEG Data Analysis

Raw data were visually inspected offline for bad sensor recordings. Bad sensors were interpolated using a spherical spline interpolation method as implemented in BESA 5.1 (MEGIS Software, Gräfelfing, Germany). Trials with sensor amplitudes exceeding 100 μ V were not used for data analysis. Data were transformed to an 81 sensor average reference montage in order to provide measurement for interpolated area in the lower occipital region between Oz and the lower CP1 and CP2 sensors on the original cap. Averages were digitally filtered from .5-100 Hz (6 and 12 db/octave rolloff, respectively; zero-phase) and baseline corrected using the 200 ms pre-stimulus interval. Grand averages were then calculated for each individual.

Grand averages over all individuals were computed separately for targets and standards (see Figure 4.1). Previous work with this paradigm has shown no significant differences in heritability estimates or P300 characteristics for the easy vs. hard target tasks (Katsanis et al., 1997), so data were collapsed over these two conditions to create one "target" condition. Errors are uncommon in this task, so all trials were included in the analysis.

To integrate data recorded from every sensor, spatial principal components analysis (PCA) was implemented. For each group average and condition, an 81x81 covariance matrix was calculated (using time points as observations) and PCA was calculated with promax vector rotation and Kaiser normalization (Dien, 2006). Scree plots (Cattell, 1966) for each condition always identified 2 components, with the spatial distributions of these components and amount of variance accounted for (always over 90%) being nearly identical between zygosities and within condition. For the target condition, the first and second components accounted for 67.7% and 25.8% of the variance, respectively. For the standard condition, the first and second components accounted for 88.7% and 7.2% of the variance, respectively.

For both target and standard PCA results, component weights were multiplied by each subject's VEP data, summed across the sensors, and divided by the sum of the component weights. Each set of component weights was multiplied by each subject's single trial data, summed across sensors, and divided by the plus sum of the component weights. This reduced waveforms from one for each sensor to one waveform per component for each subject for targets and standards (see Figure 4.1). PCA weighted waveforms for each subject were averaged into 20ms bins from -200 to 600 ms for biometrical analysis of ERP data.

Wavelet Analysis

PCA weighted waveforms for each subject were then analyzed trial by trial using Morlet wavelets with a frequency resolution of 1 Hz. To balance time resolution in the lower frequencies with stability in the higher frequencies (Busch & VanRullen, 2010), wavelets were calculated using a linearly increasing cycle length from 1 cycle at the lowest frequency (2 Hz) to 5 cycles at the highest (50 Hz). Wavelets provide a measure of single trial power (STP) and inter-trial coherence (ITC) which can be used to evaluate the relative amplitude of response at a particular frequency and how stable the response is in time across trials, respectively. STP and ITC values were averaged over trials for each individual and transformed into time-frequency plots (Hamm et al., 2012).

Biometrical Analysis

For time-frequency data, intraclass correlations were performed at each time point for each frequency for MZ and DZ twins. Intraclass correlations for a group of twins are calculated as the ratio of between-pair variance to the total variance (between-pair plus within-pair). Generally, genetic effects may be suspected if MZ intraclass correlations are higher than those of DZ twins, although other components such as shared environmental variance may contribute. Broad spectrum heritability (Falconer's h^2) was then calculated at each point as the doubled difference between MZ and DZ intraclass correlations, with h^2 bound between 0 and 100%.

To quantify significant heritability effects, at each time point 95% confidence intervals for each condition were bootstrapped by randomly shuffling the data by zygosity, maintaining twin pairs, and sampling with replacement for 1000 iterations. Data points in the time-frequency h² plots were considered to be significant at the .05 level if their value fell above 97.5% of the values in the bootstrapped distribution for that particular point. In order to account for increased Type 1 error due to multiple observations, a clustering technique was adopted. Clusters of significant data points that spanned at least 20ms in time and more than one consecutive frequency in frequency space were considered to be significant clusters of heritability (see Figures 4.2 and 4.3). Because some clusters spanned large amounts of time and overlapped both positive and negative power values, creating the potential for cluster averages to equal zero, an additional step was undertaken to determine the significant number of clusters and their boundaries. For each condition and component, data points from the grand average within all significantly heritable clusters, along with their time and frequency coordinates, were submitted to kmeans cluster analysis (MacQueen, 1967). Because kmeans is sensitive to the scale of variables, all input variables were standardized within variable prior to input (Norusis, 2011). The number of clusters to retain was determined by running the kmeans analysis 50 times, increasing at each step the number of retained clusters from 1 to 50. The minimum within-cluster sum of point-to-centroid distances at each step was plotted to form a type of scree plot, with the point at the elbow of the plot indicating the number of clusters to retain (Salvador and Chan, 2004).

Data points were averaged within each significant cluster for each individual, generating one value per individual per cluster. Cluster values were then analyzed for genetic and environmental effects using the standard univariate ACE and ADE twin models and their reduced models (AE, CE, DE, and E) as implemented in Mx (Neale et al., 2003). These models use Cholesky decomposition to partition genetic variance into additive (A, single-gene effects across multiple loci), non-additive or dominance (D, interactions between allele effects on a single locus) genetic effects, as well as shared (C) and unique (E) environmental variance. The E component also encompasses measurement error. Best fitting models were identified using the chi-square difference test and the Akaike information criterion (AIC). All best fitting models had a non-significant (p > .05) chi-square goodness of fit index, indicating that the model did not significantly differ from the observed variance structure. Nested models with non-significant chisquare indices were compared to the full (ACE or ADE) model using the chi-square difference test. If the difference was significant, the better fit was provided by the full model and so the full model was retained. If the difference was non-significant, the more parsimonious nested model was retained. In no case did the full model fit significantly better than the more parsimonious

nested models. Best fitting models were also those that minimized the AIC; small AIC indicates better model fit as well as parsimony, in that this criterion assesses the chi-square statistic as it relates to the degrees of freedom in the model.

Results

Wavelets

Figures 4.2 and 4.3 are consistent with the theory that early ERP peaks are more accounted for by phase locking within a neural mass than by recruitment of additional neurons/processing areas (Moratti et al., 2007; Sayers et al., 1974; Jansen et al., 2003; Klimesch et al., 2004; Gruber et al., 2005; Makeig et al., 2002). For both targets and standards, the 100-300ms time range was characterized by increased ITC and relatively lower STP. This time range is consistent with that of early sensory components such as the P1, N1, and P2 (targets only). The 300-600ms time range shows some ITC but is heavily dominated by an alpha/beta power decrease and accompanying low frequency power increase. This time range is consistent with the P300 ERP component in the target condition and the late slow wave in the standard condition. *Genetic Models*

No component best fit to the full ACE or ADE model; models estimating only one genetic source of variance appeared to be more parsimonious for this data. See Table 4.1 for variance parameter estimates and Figures 4.2 and 4.3 for clusters of heritability for STP and ITC, respectively.

Targets, Component 1: P300

ITC

Three significant clusters of heritability were found in the 100-400 ms range: 1) a cluster in the beta band and falling within the 100-250 ms time range, 2) a cluster spanning the theta to

alpha bands and falling within the 100-250 ms time range, and 3) a cluster spanning the delta to alpha bands and falling within the 200-500 ms time range. These time ranges are mostly consistent with the N1, P2 and P3 peaks visible in the Component 1 waveform. Genetic models showed a best fit for the dominance model (DE) for cluster 1 and the additive (AE) model for clusters 2 and 3.

STP

Three significant clusters of heritability were found for Component 1 STP: 1) a cluster spanning alpha to beta frequency bands and the 100-200 ms time range, 2) a late large cluster in the beta frequency band and the 400-600 ms time range, and 3) a late cluster in the alpha band and the 450-550 ms time range. Clusters 1 and 3 best fit with the dominance (DE) model of genetic effects, while cluster 2 best fit with the additive (AE) model.

Targets, Component 2: Sensory

ITC

Three significant clusters of heritability were found for Component 2 ITC: 1) an early cluster in the beta/gamma frequency bands in the 100-200 ms time range, 2) a cluster spanning the delta to low beta bands and the 0-300 ms time range, and 3) a later cluster spanning the delta to beta bands and the 250-350 ms time range. Clusters 1 and 3 best fit with the dominance (DE) model of genetic effects, while cluster 2 best fit with the additive (AE) model.

STP

Three significant clusters were found: 1) a cluster in the beta band and the 100-350 ms time range, 2) a cluster spanning the delta to alpha bands and the 100-350 ms time range, and 3) a late cluster in the beta band and the 500-600 ms time range. All of these clusters showed a best fit with the dominance model of genetic effects (DE).

ITC

Two significant clusters were found: 1) a cluster in the gamma frequency band and the 100-200ms time range, and 2) a cluster spanning the delta to low beta bands and the 200-400ms time range. These clusters best fit with the dominance (DE) and additive (AE) models, respectively.

STP

Two significant clusters were found: 1) a large cluster spanning the theta to low beta frequency bands and the 150-350 ms time range, and 2) a slightly later, smaller cluster spanning the theta to beta bands and the 200-450 ms time range. Both of these clusters best fit with the dominance (DE) model.

Standards, Component 2: Sensory

ITC

Four significant clusters were found: 1) a cluster in the beta band and the 100-200ms time range, 2) a cluster spanning beta to gamma bands and falling within the 100-200ms time range, 3) a cluster spanning the delta to alpha bands and the 250 to 350 ms time range, and 4) a late cluster in the alpha/beta bands and the 400-500 ms time range. Clusters 1,2 and 4 best fit with the dominance model (DE) while cluster 3 best fit with the additive model of genetic effects (AE). STP

No significant clusters were found for Component 2 STP.

Discussion

This study resulted in two notable findings. First, early and late components in the oddball evoked response differ in the composition of their frequency characteristics. Early

components are more characterized solely by ITC as compared to later components, which are more mixed. Second, heritable brain responses can be divorced from standard peaks of brain activity. The most obvious choice for measuring genetic effects based on time-frequency plots would be to average over area under the curve for each peak of STP or ITC. When assessed point-by-point, however, it becomes evident that clusters of highly heritable brain activity do not always overlap with the areas of highest brain activity.

The later components more associated with complex cognitive operations showed more increases in single trial power than did the earlier stimulus registration components (Figure 4.2). As previously shown, early ERP components such as the P1 and N1 are primarily accounted for by phase locking in lower frequencies (Moratti et al., 2007; Sayers et al., 1974; Jansen et al., 2003; Klimesch et al., 2004; Gruber et al., 2005; Makeig et al., 2002). Later components such as the P300 and late slow wave show a mixture of activity in the STP and ITC plots, with the late slow wave almost entirely associated with an increase in single trial power. Similar to Fell and colleagues (2004), the P300 to targets showed some phase locking and moderate power increases in the delta, theta, and alpha bands during the early part of the peak ERP response, but the latter half of the time range was primarily characterized by a large decrease in single trial power in the beta frequency band. The same time range for standards showed primarily a large decrease in single trial power in the alpha to beta bands. The late slow wave, present only in the standard condition, showed a large increase in single trial power in the delta and theta bands which was unaccompanied by similar increases in phase locking. Increases in phase locking may in part be attributed to more similar and precise timing of ERP components relative to stimulus onset (Fell et al., 2004). The relative decrease in phase locking for the later components in this study may simply be a product of more variability in inter-trial ERP latency as compared to earlier, more

automatic sensory components (Jung et al., 2001) or may represent real decreases in phase locking as more independently oscillating neural sources are recruited for more complex processing. Increases in single trial power for later components may support the latter hypothesis and indicate the addition of more neural resources and thus, greater amplitude (Fell et al., 2004; Lopes da Silva, 1993).

Interestingly, the peaks in the heritability plots do not entirely follow the peaks in the time-frequency plots, particularly for STP. This discrepancy suggests that although the primary mechanism behind early ERP peaks may be ITC, MZ twins still show more similarity than DZ twins in evoked power during these early time ranges. It stands to reason that evoked power during the early oscillatory response should not be ignored in the search for endophenotypes. Some of the ITC clusters follow this pattern as well, suggesting that the search for endophenotypes in the frequency domain perhaps should not be limited to restricted time ranges around ERP peaks or even restricted time or frequency ranges around peaks in time-frequency plots. Neurophysiological methods such as ERP have been heralded as being closer to the gene products than behavioral measures and thus a better candidate for endophenotype discovery (Meyer-Lindenberg & Weinberger, 2006). Characteristic differences in P300 response have been linked to several disorders with genetic components, including schizophrenia (Bestelmeyer et al., 2009; Hall et al., 2009; Bramon et al., 2005) and substance abuse (Begleiter et al., 1984; Iacono et al., 1999; 2000; 2003). The early and late components of the visual oddball task have been relatively neglected, but may provide complementary information about genetic influences on a variety of cognitive processes. By breaking down the entire ERP into its component frequency properties, more direct physiological mechanisms of ERP generation and their potential genetic influences can be studied.

The early clusters in the target condition show mixed results on best fit, with some clusters fitting to the DE model of genetic effects and others to the AE model. These results are somewhat in line with findings by Katsanis and colleagues (1997) on N1, P2 and N2 amplitude in a standard ERP voltage study using the same stimuli. For standards, early clusters showed dominance effects in the beta and gamma frequency bands and additive effects in the low frequency bands. ERP findings in the literature vary on heritability of standards early components. To the authors' knowledge, no studies have reported heritability for the visual oddball P1, so future studies will be necessary to corroborate the gamma cluster fit to the DE model. Additive genetic effects have been reported for standard N1 amplitude (Almasy et al., 1999; Smit et al., 2007). O'Connor and colleagues (1994) found a mixture of additive and dominant genetic effects for standard N1 latency, although this study utilized auditory oddball stimuli, and there is some suggestion that heritability may not translate across modalities (Katsanis et al., 1997). However, clusters of heritability within the N1 time window but with differing frequency and genetic profiles may shine some light on the mixed model findings of O'Connor and colleagues (1994) on ERP amplitude, which is a composite of all frequency bands. Indeed, these early clusters suggest that ERP heritability findings may be influenced by low-pass filtering. Filtering out high beta and gamma frequencies may remove valuable sources of genetic variation. In this report, additive and dominant effects in the standard early activity may show differences in genetic influence based on stimulus type and frequency band or may simply reflect a limited ability to distinguish the two genetic models due to sample size. The late clusters in the target condition also show mixed AE and DE model fits, showing support for genetic influences on the P300 component in both single trial power and ITC. Low frequency late components of the standard ERP, such as the late slow wave, do not show any heritable

components. This result may not necessarily mean that there is no genetic component to the late slow wave, but may be a function of the twin design and very little individual variability in this large amplitude component.

Much debate has occurred over whether nonadditive (dominance) effects should be seriously considered for psychophysiological data as additive effects are more in line with known gene interactions. However, on neuroimaging measures, evidence remains for nonadditive genetic effects (Tan et al., 2009). It has been suggested that more similar environments for MZ over DZ twins could mimic dominance, emergenic, or epistatic effects (Christian et al., 1975). Similar ICCs for MZs reared together and those reared apart (van Beijsterveldt & Boomsma, 1994) indicate that postnatal environments do not unduly influence variations in brain activity for MZ twins. Some evidence does imply that prenatal environment affects brain activity. For instance, MZ twins with monochorionic placentas are more alike for measures of type A behavior (Reed et al., 1991), personality scores (Sokol et al., 1995), IQ scores (Melnic et al., 1978), and may have higher concordance for schizophrenia (Davis et al., 1995). DZ twins are dichorionic, so it would seem that additional covariance between monochorionic MZs over dichorionic DZs may inflate heritability estimates and mimic dominance effects. Since approximately 66% of MZ twins are monochorionic, the total phenotypic variance of MZs across placental types may be greater than that of DZs, which may actually downwardly bias heritability estimates (Christian et al., 1996). If so, nonadditive genetic effects could be even higher than those estimated here.

Future studies could benefit from some methodological refinements. First, higher sensor densities with more recording locations below the cantho-meatal line would help fully capture visual cortex-related neural activities. Second, notwithstanding the heavy computational demands imposed by dense array ERP analysis, larger sample sizes would provide more power to evaluate the fit of different models as well as more precise heritability estimates.

Nevertheless, the present methodology and results illustrate the possible considerable advantages of related approaches over those typically encountered in studies addressing the genetics of brain activations. The present study illustrates the importance of considering multiple measures of brain activity, rather than voltage measurements from a single sensor alone, in the search for heritable and refined phenotypes for complex cognitive operations. Single peaks of brain activity do not occur in isolation. Moving beyond single peak amplitude measures with single sensors to more complex analysis of brain activity may better represent the complex organization of the neural response to a given stimulus and task. In turn, refining phenotypes using data reduction/integration techniques may more accurately characterize gene effects on certain complex cognitive operations.

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Figure 4.1: Grand average butterfly plots, PCA component waveforms and component topographies for each condition.



Figure 4.2: Significant clusters of heritability overlaid onto single trial power (STP) timefrequency plots for each condition and PCA component waveform. Areas outlined in the same color within a plot indicate a single cluster as determined by kmeans clustering analysis. Genetic modeling results are presented color-coded and in order of presentation in the text for each cluster in the upper left of each plot.



Figure 4.3: Significant clusters of heritability overlaid onto inter-trial coherence (ITC) timefrequency plots for each condition and PCA component waveform. Areas outlined in the same color within a plot indicate a single cluster as determined by kmeans clustering analysis. Genetic modeling results are presented color-coded and in order of presentation in the text for each cluster in the upper left of each plot.

		Genetic		Unshared		% Variance Accounted For		
	Best-	Goodnes	5					
Cluster	fitting	of Fit χ²						_
	Model	(df)*	V	SE	V	SE	h² (95%Cl)	e² (95%Cl)
Standard ITC Comp 1								
Cluster 1	DE	1.88(4)	044	.004	.032	.003	58(46-70)	42(34-51)
Cluster 2	AE	1.57(4)	.101	.010	078	.007	56(45-68)	44(35-52)
Standard ITC Comp 2								
Cluster 1	DE	3.35(4)	047	.009	064	.006	42(26-58)	58(47-68)
Cluster 2	DE	5.04(4)	.048	.004	032	.003	60(49-71)	40(33-49)
Cluster 3	AE	2.43(4)	.073	.013	101	.009	42(27-57)	58(48-68)
Cluster 4	DE	4.01(4)	059	.006	051	.005	54(43-65)	46(38-55)
Standard STP Comp 1								
Cluster 1	DE	4.01(4)	1.36	.154	1.16	.118	54(42-66)	46(37-55)
Cluster 2	DE	2.61(4)	1.53	.189	1.45	.144	51(39-64)	49(39-58)
Standard STP Comp 2								
No clusters								
Target ITC Comp 1								
Cluster 1	DE	5.35(4)	079	.007	054	.006	59(49-71)	41(32-49)
Cluster 2	AE	1.33(4)	.109	.011	082	.008	57(46-68)	43(35-51)
Cluster 3	AE	2.78(4)	.088	.015	114	.010	44(29-58)	56(47-67)
Target ITC Comp 2								
Cluster 1	DE	7.31(4)	051	.006	.044	.004	54(42-65)	46(37-55)
Cluster 2	AE	1.08(4)	.114	.014	102	.011	53(40-65)	47(38-56)
Cluster 3	DE	7.39 (4)	.083	.010	076	.008	52(40-65)	48(38-58)
Target STP Comp 1								
Cluster 1	DE	7.14 (4)	1.21	.130	1.06	.100	53(42-65)	47(38-55)
Cluster 2	AE	3.27 (4)	1.69	.157	1.17	.113	59(49-70)	41(33-49)
Cluster 3	DE	6.02 (4)	3.22	.347	2.89	.266	53(42-64)	47(39-56)
Target STP Comp 2								
Cluster 1	DE	7.54(4)	1.35	.123	.908	.092	60(49-70)	40(32-48)
Cluster 2	DE	.971 (4)	1.36	.129	.967	.973	58(48-70)	42(34-48)
Cluster 3	DE	5.04(4)	1.21	.152	1.23	.115	50(37-62)	50(41-59)

* Chi square goodness of fit indices are all non-significant at the α >.05 level, indicating a lack of divergence of observed values from model parameters.

Table 4.1: Best fitting m	odel results for clusters
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CHAPTER 5

DISCUSSION AND CONCLUSIONS

Schizophrenia is a multifaceted disorder with wide-ranging symptom constellations. Understanding the biological and genetic underpinnings of this syndrome will help in prediction of disease progression and treatment response, and may contribute to new treatment options, both biochemical and gene therapy-based. One method that contributes to this process is the definition of psychiatric endophenotypes (Gottesman and Gould, 2003). Endophenotypes must be specific to a disorder, present regardless of current symptoms (a trait variable), and be heritable (Gottesman and Gould, 2003). The work presented in this paper uses oscillatory characteristics of the brain in order to both better understand the etiology of schizophrenia and to develop new potential endophenotypes for this disorder.

In Chapter 2, we discussed the potential for intrinsic neural activity abnormalities to be a defining characteristic of schizophrenia. Schizophrenia patients exhibit increased background brain activity particularly in lower frequency bands both prior to stimulus onset (Clementz et al., 2008; Wang et al., 2010; Winterer et al., 2004) and at rest (Clementz et al., 1994). Utilizing a visual steady-state paradigm to measure the phase-locking capability of the visual system in schizophrenia, we discovered that schizophrenia patients show abnormalities in steady-state processing, perhaps caused by interactions between intrinsically heightened background activity and oscillations produced by processing the stimulus train. Increased background brain activity relative to task-related brain activation produces a reduced signal-to-noise ratio (Winterer et al., 2004), possibly making it more difficult for schizophrenia patients to process incoming signals

and correctly propagate these signals to higher-order processing centers. To support this theory, we also found no difference between groups in response to transient stimuli presented rapidly after the cessation of the steady state stimulus, as compared to the initial stimulus-onset response to the beginning of the steady state stimulus. The brains of schizophrenia patients tend to continue oscillating at the driving frequency longer than healthy subjects after the stimulus has been extinguished (Riečanský et al., 2010; Clementz et al., 2004). This increased oscillation may indicate a maladaptive effort on the part of SZ patients to enhance cognitive control through an increase in intrinsic neural activity. This enhanced activity in specific visual areas may include frequencies that contribute to the visual ERP and thus result in a more normalized ERP response to the transient stimuli.

Enhanced intrinsic activity clearly distinguishes schizophrenia patients from healthy subjects, but it is not clear from a two group experiment whether this oscillatory characteristic is unique to schizophrenia or may be exhibited in other groups with psychotic symptoms. In Chapter 3, we compared schizophrenia patients with matched samples of healthy subjects and patients with psychotic bipolar I disorder. In this study, we utilized the auditory oddball task, a task which produces a diminished auditory P300 response in both schizophrenia and BPP patients. Decreased amplitude of the P300 response is commonly cited as a potential endophenotype for either or both disorders (Thaker, 2008). With our large sample of psychotic subjects, we intended to determine whether abnormalities in any part of the evoked response to the auditory oddball could be considered specific to one group or whether these deficits were more likely to constitute a characteristic of psychosis in general. Using a time-frequency approach where we compared groups on all time-points and all frequencies, we were able to describe both ERP-related and more intrinsic oscillatory differences between groups.

Interestingly, no variable discriminated schizophrenia from both healthy and BPP.

Differences in oscillatory and ERP features were either characteristic of psychosis in general or specific to BPP. Also, no P300-related variables survived the discriminant analysis, indicating that other ERP and time-frequency measures best captured the differences between psychotic and healthy groups in this task. Together, these findings support research suggesting that task-related deficits noted in auditory oddball studies of schizophrenia patients may be more indicative of psychosis than schizophrenia specifically, and that while the P300 is clearly reduced in amplitude for schizophrenia patients, this reduction is not unique to the disorder (Bestelmeyer et al., 2009; Schulze et al., 2008; Picton, 1992; Hall et al., 2009; Simons et al., 2011).

Discriminating variables were found for BPP patients, however, particularly in timefrequency space. Accentuated late beta and gamma responses to both targets and standards were specific to BPP and discriminated them from both schizophrenia and healthy subjects. Late beta has been associated with motor system maintenance in some studies (Baker, 2007; Engel and Fries, 2010), however since this accentuation was also found in both conditions, which differed on whether a response was required, it is unlikely that the current results represent heightened motor activity in BPP. Beta has also been associated with increased top-down processing and cognitive control (Buschman and Miller, 2007; 2009; Engel and Fries, 2010), but enhanced cognitive control has not been a hallmark finding in BPP in any experimental condition (Bora et al., 2007; Martinez-Aran et al., 2008; Glahn et al., 2007; Selva et al., 2007), so it is also unlikely that this accentuation results from enhanced top-down processing. Increased gamma has been associated with visual change detection in monkeys (Gregoriou et al., 2009), which may be of interest here since BPP showed enhanced late gamma to targets. It is possible that beta and gamma abnormalities in BPP result from abnormalities in the dopamine system. Beta and gamma oscillations rely on GABAergic NMDA networks (Arai and Natsume, 2006; Traub et al., 2004; Yamawaki et al., 2008), which are modulated by dopamine. Dopaminergic abnormalities have been noted in BPP (Pearlson et al., 1995; Wong et al., 1997; Yatham et al., 2002). Interactions between cyclical dopamine and GABAergic networks may cause a heightened beta/gamma response in BPP in certain situations requiring long-range communication and local processing, such as context updating in memory, an aspect commonly associated with late processing in the oddball task (Lindin et al., 2004; Dien et al., 2003; Linden, 2005; Donchin and Coles, 1988; Katayama and Polich, 1998).

In Chapter 4, we further examine the oddball task using single trials and a twin population in order to model heritability of task-related oscillatory components. Early processing peaks show a clear association with inter-trial coherence (ITC) with very little increase in single trial power (STP), while later peaks of activity show a mix of ITC and STP or are mostly associated with changes in STP. This observation is consistent with the theory that early ERP peaks are more accounted for by phase locking within a neural mass (Moratti et al., 2007; Sayers et al., 1974; Jansen et al., 2003; Klimesch et al., 2004; Gruber et al., 2005; Makeig et al., 2002).

The early sensory processing components in the two oddball tasks are not directly comparable because they encompass different sensory modalities; presumably the early recorded responses have sources in or near primary auditory and visual cortices. Later complex cognitive processing, such as the P300 and later responses, have been shown to activate similar neural sources regardless of modality (Linden, 2005). Therefore it is interesting to note that the late beta response to both targets and standards, abnormally accentuated in BPP, shows a heritable component in healthy twins. This response is specific to single trial power, suggesting an overall

increase in induced amplitude of activity rather than a response phase-locked to stimulus onset. The late beta response begins to fulfill the requirements for endophenotype status: it is unique to one disorder (at least among the populations studied) and it is heritable.

There is some concern among scientists that a trait that is heritable in the general population, such as a trait studied in healthy twins, may not be a good indicator of risk in a disease population because of a high base rate in healthy subjects (Golden and Meehl, 1978; Meehl, 1989; Iacono and Clementz; 1993). In the current work, high beta/gamma power significantly differentiated BPP from healthy subjects, indicating that, at least in this healthy population, the rate of heightened power in this band was relatively low. Without established base rate statistics or actual genetic material, the base rate concern cannot be adequately addressed in the work presented here. It is possible that individual variation in beta/gamma power, as seen in Chapter 4, is genetically influenced in the general population. A specific, relatively rare, polymorphism in this same genetic structure may contribute to the heightened beta/gamma power in BPP that is above and beyond that of healthy individual variation. It is also possible that a particular epistasis or gene loading effect may interact with other risk factors for BPP and contribute to the abnormal variation in power characteristic of the disorder. Just as the P300 ERP amplitude is heritable in the general population but reduced amplitude is associated with various disorders (Frederick and Iacono, 2006; Thaker, 2008), heritability in the general population should not necessarily preclude beta/gamma power fluctuations from being a risk factor for BPP if extreme values are unique to that disorder.

Interesting to note are the locations in time and frequency space of some of the clusters of group differences in Chapter 3 and heritability in Chapter 4. Many of these clusters do not occur in concurrence with amplitude peaks in the data, underscoring the importance of consideration of

the entire data range rather than just areas of highest amplitude or power. In fact, some of the clusters of heritability in Chapter 4 overlap power gradients, or areas of rapid changes across time from positive to negative power values. It is possible that processing speed can be indexed by the amount of time necessary for an individual to switch from synchronization to desynchronization in a certain area of the brain as indicated by the slope of the power gradient.

ERP peak latency, particularly the P300 peak latency, has been studied with respect to discriminating psychiatric groups from healthy subjects and with respect to heritability (Thaker, 2008; van Beijsterveldt and van Baal, 2002). Both schizophrenia and BPP patients tend to show prolonged P300 latency (Shin et al., 2010; Schulze et al., 2008; Bramon et al., 2005) relative to healthy subjects. Results vary across studies on heritability of P300 latency; however in a meta-analysis of twin studies, P300 latency was found to moderately heritable at 51% (van Beijsterveldt et al., 2001). ERP peak latency is a potential indicator of processing speed; indeed, multivariate modeling has shown genetic factors associated with both P300 latency and behavioral measures of processing speed (Hansell et al., 2005). Given its highly significant heritability, if the slope of the power gradient can be utilized in a similar fashion to index neural processing speed, this variable may provide new information about genetic contribution to neural connectivity and efficiency in psychosis and health.

In conclusion, time-frequency analysis of neural oscillatory characteristics is a useful tool in further defining and perhaps discovering new endophenotypes for brain-based psychotic disorders such as schizophrenia and BPP. Abnormalities in prestimulus intrinsic activity are characteristic of schizophrenia and these abnormalities may interact with subsequent task-related processing, producing commonly observed deficits in steady-state and ERP responses. Commonly observed deficits in oscillatory response to the auditory oddball task are not unique to schizophrenia, but may be indicative of risk for psychosis in general. However, the late beta/gamma accentuation to auditory oddball stimuli discriminates schizophrenia, BPP, and healthy subjects, being unique to BPP. Late beta single trial power to both targets and standards is also heritable in healthy twins. Complementary research with first-degree relatives is necessary to fully support both intrinsic prestimulus activity in schizophrenia and late beta to auditory oddball stimuli in BPP as potential endophenotypes for these psychotic disorders.

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