UNDERSTANDING PSYCHOTIC PATHOPHYSIOLOGY WITH TRANSIENT, SUSTAINED, AND OSCILLATORY AUDITORY NEURAL RESPONSE ABNORMALITIES

by

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(Under the direction of Brett A Clementz)

ABSTRACT

Auditory processing abnormalities are a core feature of psychosis and may underlie perceptual distortions and cognitive deficits characteristic of major psychotic disorders such as schizophrenia (SZ) and psychotic bipolar disorder (BDP). Attempts at linking experimentally quantified auditory processing abnormalities to underlying biological disease mechanisms and genetic causes have thus far been inconclusive. Such investigations might benefit from i) characterizing abnormalities with respect to underlying psychopathological domains (psychotic, affective) as they cut across DSM-IV diagnostic categories, and ii) appreciating the complexity of the auditory neural response through the use of powerful electrophysiological and analytic tools. Indeed auditory stimulus evoked cortical potentials (measured with scalp electroencephalography) involve spatiotemporally distinct transients (n100 and p200 peaks), sustained slow-potentials, and brief oscillatory events in low (theta), mid (alpha/beta), and high (gamma) frequency bandwidths. Each of these oscillations index unique aspects of local and distributed auditory cortical circuitry. The present set of investigations sought to examine each of these components in the context of interacting psychopathological domains (psychotic versus affective). Measurements were also taken from unaffected family members of persons with SZ or

BDP and analysed in the context of both protective and risk factors. The manifold of results indicate that low frequency (delta-theta band) and widely distributed (P300) cortical events show little specificity toward psychotic and affect domains of psychopathology, display general heritability, and are present regardless of context. Early occurring mid-frequency (alpha) and transient events (n100, p200) display psychotic and affective domain specificity, complex heritability patterns (enhanced in non-psychotic first-degree relatives), and are partially ameliorated when auditory stimuli are attended. Finally, high-frequency response abnormalities show the least heritability and are substantially influenced by physical stimulation properties (but not attention). Altogether, this pattern of low versus high frequency and early versus late cortical potentials provides a series of specific hypotheses for future genetic research with regard to neurochemical (gaba/glutamate versus cholinergic/adrenergic) and neuroanatomical (large versus small scale connectivity) pathological processes underlying psychosis and their heterogeneous co-presentations.

INDEX WORDS: Schizophrenia, Bipolar, Psychosis, auditory, gamma, heritability, ERP

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BS, University of Georgia, 2008

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A Dissertation Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment of the Requirements for the Degree

DOCTOR OF PHILOSOPHY

ATHENS, GEORGIA

2013

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December 2013

DEDICATION

I dedicate this work to my supportive parents Paul and Deborah and to my loving wife Amy.

ACKNOWLEDGEMENTS

Funding for these studies was provided by NIH Grants MH077945, MH077862, MH077851, MH078113, MH094172, and MH085485 as well as the support of the Franklin Foundation Neuroimaging Training Program. Dr. Clementz served as an excellent mentor and, along with Drs. McDowell and Sabatinelli, provided invaluable input and support in the conceptualization, planning, and realization of this document and the associated research. Current and past graduate students and research assistants, including Dr. Lauren Ethridge, Dr. Kara Dyckman, William Oliver, Matthew Hudgens-Haney, Lauren Hayrynen Schaeffer, Anastasia Bobilev, David Parker, Sophie Arkin, Emily Parker, John Shapiro, Mackenzie Davis, Abby Weinberger, Greg Spillers, and Assaf Hod, provided critical support in data collection, processing, and interpretation. Dr. Buckley and individuals responsible for planning and coordination of the Bipolar and Schizophrenia Network on Intermediate Phenotype consortium (BSNIP; Drs. Keshavan, Tamminga, Sweeney, Thaker, Pearlson) provided important logistical support in the research projects presented herein.

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CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

Psychosis is a serious medical condition requiring urgent attention. Psychosis involves sensory hallucinations and persistent delusional beliefs, experienced oftentimes without insight from the person afflicted (David, 1990). The syndrome can have a multitude of causes, both organic and iatrogenic, but when symptoms are determined to be associated with a psychiatric disorder such as schizophrenia or bipolar I disorder, they are associated with chronic and significant occupational and psychosocial impairment. Schizophrenia (SZ), in particular, is characterized by psychotic symptomology in the absence of major mood instability and is often accompanied by significant affective flattening and thought disturbance as defined by the Diagnostic and Statistical Manual of Mental Disorders version IV text-revision (DSM-IV-TR). Conversely, Bipolar Disorder (BD) is characterized specifically by mood instability in the form of a major manic and depressive episodes (although only one manic episode is necessary to warrant a DSM-IV diagnosis) which are accompanied with psychotic symptoms about 60% of the time (Keck et al., 2003). While the phenomenological distinction between SZ and BD is clear, the two psychotic disorders do not 'breed-true'; that is, persons with SZ have an increased prevalence of both SZ and BD in their families, and the same is true for persons with BD (Potash, 2006) and especially persons with BD with psychosis (Goes, Sanders, & Potash, 2008; Potash et al., 2001; Potash et al., 2007). The two disorders also show overlapping deficits in neural (De Peri et al., 2012; Meda et al., 2012) and cognitive (Chan et al., 2012; Hill et al., 2009) functioning compared to the psychiatrically healthy population. Further complicating the SZ/BD

dichotomy is the existence of an ostensibly intermediate syndrome termed schizoaffective disorder, which, like BD, involves the presence of major manic and/or depressive episodes, but with intermittent, non-affective psychotic episodes. Schizoaffective disorder also does not breed true, but displays shared heritability, neuro-biological abnormalities, and cognitive impairment with both SZ and BD (Goes et al., 2008). Current knowledge about the biological substrates and causes of major psychotic disorders, as well as how and why they give rise to psychotic symptomology, can be considered incomplete at best. The fact that psychotic disorders, irrespective of other clinical phenomena, have overlapping genetics and functional characteristics may hint at a shared etiology and neural mechanisms underlying the clinical syndrome (Lichtenstein et al., 2009; Thaker, 2008). Therefore, by studying psychotic disturbance as a psychopathological domain and including patient samples which cut across DSM-IV categories, researchers could achieve new insight into psychotic eitopathophysiology while parsing it from other comorbid psychiatric symptom domains including affective and cognitive dysfunction (Craddock, O'Donovan, & Owen, 2009).

Disruptions in auditory perception are a hallmark symptom of psychosis and may thus provide a useful window into the complicated neuropathology of psychotic disorders. For example, although hallucinations in all sensory modalities are reported in BD with psychosis (BD-P) and SZ, hallucinations in the auditory domain are by far the most common (Baethge et al., 2005). Further, people with SZ have impaired auditory tone discrimination which is not due to attentional impairments (Rabinowicz et al., 2000), implying that abnormalities are present in SZ patients' basic auditory neural circuitry (Javitt, 2009). Auditory perceptual (Bredgaard & Glenthøj, 2000) and electrophysiological (Perez et al., 2012; Shin et al., 2009) abnormalities are

also present prior to the full onset of psychotic disorders, indicating that they are not likely simply a consequence of medications or secondary disease processes.

The human auditory system is comprised of a dense circuit of direct relay and dynamical feedback of neural impulses from the basilar membrane in the inner ear to distinct pontine and midbrain nuclei, where position and pitch information is sharpened, to the medial geniculate nucleus in the thalamus (MGN) relaying auditory information to primary and secondary sensory cortices in the superior temporal lobe (Schofield, Motts, & Mellott, 2011). In psychotic disorders, abnormalities in brainstem auditory circuits have been reported (Källstrand, Nehlstedt, Sköld, & Nielzén, 2012; Kang et al., 2008) but are not consistently found (for a discussion see Leavitt, Molholm, Ritter, Shpaner, & Foxe, 2007) and could result from more caudally based abnormalities via disrupted cholinergically mediated cortical feedback (Schofield et al., 2011). Abnormalities in thalamocortical (Ferrarelli & Tononi, 2011) and corticocortical (Chance, Casanova, Switala, & Crow, 2008; Sweet et al., 2007) auditory circuits are clearly present in psychotic disorders and can be studied with high temporal precision and great reliability (Rentzsch et al., 2008; Tervaniemi et al., 1999; Tlumak et al., 2011) with electroencephalography (EEG) and magnetoencephalography (MEG). The spatial accuracy achievable in EEG and MEG studies (i.e. knowing which auditory brain region is contributing to which aspects of the measured data) is attenuated by volume conduction (EEG only), the inverse problem, and relative oversensitivity to more superficial cortical sources (Michel et al., 2004; Pascual-Marqui, 2002). Still, when limited cortical populations with known orientations and temporal activation patterns are the subject of study (as is the case when studying basic auditory processing), the spatial resolution of EEG/MEG studies is acceptable (Yvert et al, 2001; Yvert et al, 2005).

Abnormalities of auditory neurophysiology in psychosis: classic paradigms and measures

One of the most well studied EEG/MEG indices of thalamocortical auditory neural abnormalities in psychosis is the "P50-gating" or "sensory gating" response (Light & Braff, 1999). Typically, a pair of "click" stimuli separated by 500ms is presented every 8-10 seconds while a subject passively listens and EEG is recorded. The P50 event-related potential (ERP) is a positive deflection maximal at fronto-central EEG electrodes, occurring at 25 to 75ms post-stimulus onset and reflecting early stimulus registration in primary auditory cortices in lateral Heschyl's gyrus and superior temporal gyrus (Yvert et al., 2001). In paired-stimulus studies, the P50 amplitude to the first stimulus (S1) is compared to that of the second stimulus in the pair (S2) as an index of suppression of the auditory neural response to predictable and/or repetitive stimulation. Psychotic individuals generally show a smaller S1-S2 difference or S1/S2 ratio score than healthy comparison subjects (Sánchez-Morla et al., 2008) which has been demonstrated to result from reduced P50 responses to S1 (Clementz & Blumenfeld, 2001), as well as enhanced responses to S2 (Hamm, et al., 2012) in patients (for a review see Chang et al., 2011). This effect has been theorized to indicate impaired thalamic inhibitory "gating" mechanisms related to nicotinic receptor alpha-7 subunit abnormalities (Martin & Freedman, 2007) and/or reduced noradrenergic tone (Adler et al., 1994) and their underlying genetic promoters (Martin & Freedman, 2007), providing promising links between the auditory paired-stimulus markers and biological mechanisms. Such impairments in inhibiting input to the cortex could underlie auditory hallucinations (Adler et al., 1998), but evidence pointing also to a failure to 'gate-in' S1 (properly enhance processing of S1) and other salient stimuli (Brenner et al., 2009) suggests a more general deficit in maintaining a healthy signal-to-noise ratio in thalamocortical circuits (Ferrarelli & Tononi, 2011).

Another index of impairment in psychotic patients' cortical auditory processing is the P300 potential, which is typically elicited in an "oddball" paradigm involving the presentation of repeated tones (standard stimuli) serially interspersed with deviant "target" stimuli (e.g. at 80/20% frequencies, respectively). The P300 is a large positive voltage event peaking from 300 to 400ms post-targets with a fronto-centrally maximal "P3a" component experimentally associated with novelty detection and a parietally distributed "P3b" component associated with context updating and planning of a motor response to "target" stimuli (Linden, 2005). Both P3a and P3b components show consistent reductions in persons with psychosis (Bramon, 2004) and likely relate to a failure to process acute events in an ongoing temporal context (Ford et al., 2010), frequent lapses of auditory attention (Ford et al., 1994), and impairments in distributed cortical synchronization in high frequency bands (Melloni et al., 2007) as reflected in lower frequency bands (Wang & Ding, 2011). Importantly, the P300 has a late latency and a widely distributed set of cortical generators (Mulert et al., 2004), and thereby may simultaneously index a number of separate, partially unrelated sensory neural abnormalities, potentially accounting for its relative lack of specificity to psychosis or to any one psychiatric disorder (Bruder, 1992; Johannesen et al., 2012; Linden, 2005).

Abnormalities of auditory neurophysiology in psychosis: beyond the P50 and P300

Informative measurements in paired-stimulus and oddball paradigms are not limited to P50 and P300 potentials. The N1 peak reflects early stimulus registration within and synchronization between primary and secondary auditory cortices in the superior lateral temporal lobe (Yvert et al., 2005) and is maximal at fronto-central leads at 80-120ms post stimulus onset when recorded with EEG. The fact that attentional context (Hillyard et al, 1973) and inter-stimulus interval (Rosburg, Boutros, & Ford, 2008) strongly modulate the N1 amplitude suggest

that it may index the earliest cognitively influenced auditory neural event reliably measureable with EEG. The P2 peak occurs between 180 – 250ms and may reflect independent neural processes and additional, more tertiary-auditory and associative cortical substructures than the N1 (for a review see Crowley & Colrain, 2004). In the paired-stimulus paradigm, N1 and P2 components to S1 are both reduced in psychosis patients while showing larger effect sizes than P50 measures (Hamm et al., 2012). In the oddball paradigm, N1 peaks to both targets and standards and P2 amplitudes to standards are reduced in psychotic patients with either SZ or BD-P (Ethridge et al., 2012). Further, N1 deficits show specificity to psychosis due to a psychiatric disorder (i.e. SZ), while the P300 is also reduced in individuals with epilepsy (Ford et al., 2001).

Of further importance is a late frontal-negative drift seen to paired-stimuli peaking just before the presentation of S2 about 450ms after S1. This drift appears to be absent in SZ (SZ return to baseline EEG levels before S2) but not in BD-P, showing specificity not to psychosis but to schizophrenia in particular. The properties of this ERP component show similarities to the "stimulus preceding negativity," a classically studied readiness potential in EEG research which relies on intact circuits between frontal cortices, sensory cortices, and the thalamic reticular nucleus (Brunia & van Boxtel, 2001). Overall, this effect could explain and mediate traditionally reported P50 gating measures (Hamm, Ethridge, et al., 2012) while undergirding the importance of pre-stimulation brain state on evoked neural activity (Hamm et al., 2010; Matsuzaki et al., 2012).

Analysis of EEG data in the time-frequency domain (e.g. using modified Morlet wavelet convolutions or moving window Fast Fourier Transformations) provides complementary information to peak/waveform measures on cortical processing of auditory stimuli. For instance, evoked gamma band oscillations peaking early in stimulus processing (approx. 75-ms post

stimulus) reflect sensory integration (Uhlhaas & Singer, 2010); lower frequency oscillations (<25 Hz) peak later (150 to 300-ms) and may reflect widespread network involvement and novelty detection (Kopell et al., 2000). Some reports suggest that early gamma-band oscillations to the onset of stimuli (S1 in gating; standards and targets in oddball) are reduced in psychosis (Uhlhaas & Singer, 2010), yet these reports are balanced by null (Ethridge et al., 2012; Hamm, Ethridge, et al., 2012) and opposing findings (Hamm, Gilmore, & Clementz, 2012). Disrupted evoked low frequency oscillations to both paired-stimulus and oddball stimuli is a much more consistent finding in and heritable marker of psychosis (Moran & Hong, 2011), implying a closer relationship to core etiology. Beta band (mid-range) oscillations occurring soon after S1 have been suggested to fully mediate traditional P50 "gating" measurements (Hong et al., 2008), and are reduced in both SZ and BD-P (Ivleva et al, in 2013). Importantly, augmentations and deficits in background (Ethridge et al., 2012; Hamm, Ethridge, et al., 2012), prestimulus (Hamm, Ethridge, et al., 2012), and resting (Venables, Bernat, & Sponheim, 2009) gamma, beta, and low frequency oscillations all indicate disruptions in intrinsic auditory neural oscillator activity which are relevant to psychosis related paired-stimulus or oddball effects. Overall, the N1, P2, and oscillatory measures all display greater reliability than the P50 potential (Rentzsch et al., 2008) and more specificity to psychosis and psychiatric disorders than the P300 potential (Bruder, 1992; Johannesen et al., 2012; Linden, 2005).

Auditory steady-state responses: probing gamma-band entrainment

The auditory steady-state response (aSSR) reflects a basic neural entrainment response to stimulation at a constant frequency (e.g., 20 Hz is a stimulus every 50 msec; 40 Hz is a stimulus every 25 msec; Picton et al., 2003) and is relatively newer, yet equally promising, index of impaired auditory neurophysiology in psychosis relative to measurements of paired-stimulus and

oddball paradigms. For 40hz, when measured with EEG or MEG, aSSR cortical generators lie mainly in Heschl's gyrus and are believed to arise from interactions between thalamocortical glutamatergic stimulation and intrinsic local network oscillations (Gutschalk et al., 1999; Ross, Picton, & Pantev, 2002) driven by gamma-aminobutyric acid (GABA)ergic modulation of pyramidal cells (Bartos, Vida, & Jonas, 2007; Plourde, Baribeau, & Bonhomme, 1997; Plourde et al., 2008). Gamma band (but not lower than gamma) aSSR reductions have been reported in BD-P and SZ in nearly all studies (Brenner et al., 2009; Oda et al., 2012). Further aSSR reductions are present in psychiatrically healthy first degree relatives of SZ patients, indicating that gamma band entrainment may be closely related to the heritable, perhaps genetic, substrate of psychosis (Hong et al., 2004; Rass et al., 2012; effects in BD-P relatives have not been examined). Taken together, disrupted aSSRs in psychosis and pharmacological studies of aSSR properties (Plourde et al., 1997; 2008) strongly support a combination of NMDA and GABA-a receptor related pathology underlying psychosis (Hamm, Gilmore, et al., 2012), potentially uniting it with NMDA based explanations of N1 (Javitt, 2009) and evoked low-frequency disruptions (Hong et al., 2010).

Remaining issues to be addressed

Preliminary studies from the University of Georgia group and the Bipolar and Schizophrenia Network on Intermediate Phenotypes (BSNIP) consortium (Ethridge et al., 2012; Hamm, Ethridge, et al., 2012; Hamm, Gilmore, & Clementz, 2012; Hamm et al., 2011) introduce several exciting issues concerning paired-stimulus, oddball, and aSSR paradigms. Firstly, regardless of the imaging modality (EEG versus MEG), cortical analytical focus (auditory cortex versus wide-spread potentials), analytical method (peak versus time/frequency measurements), attentional context (active versus passive listening), and stimulus bandwidth (broadband

repetition, brief click, or tone), the N1/P2 wave complex to the onset of auditory stimuli is reduced in SZ patients (Ethridge et al., 2012; Hamm, Gilmore, et al., 2012; Hamm et al., 2011; Hamm, Ethridge, et al., 2012). When studied as distinct phenomena, the N1 and P2 waves show slightly differential deviations between SZ and BD-P (Hamm et al., 2012). During active listening (oddball paradigm), reductions in the N1 peak are equivalent between SZ and BD (Ethridge et al., 2012). During passive listening (e.g. paired-stimulus paradigm) the N1 peak is more severely reduced in SZ than in BD-P (Hamm et al, 2012), confirming its viability as a SZ specific biomarker (Turetsky et al., 2008). Conversely, the P2 is reduced at nearly identical levels in BD-P and SZ populations regardless of the attentional context (Hamm et al, 2012; Ethridge et al, 2012). This consistency begins to suggest that the P2 peak is a marker of psychotic psychopathology and, therefore, may constitute an important target for future etiological research. Yet given the currently available data, the P2 reductions could mark general psychopathology or even both affective and psychotic domains at once. Examining its properties in psychotic versus non-psychotic BD (**Chapter 2**) would address this remaining uncertainty. It may be the case that persons with non-psychotic BD do not display reduced P2 amplitudes relative to healthy individuals, suggesting i) that P2 amplitudes are a candidate for genetic research into more elemental neurophysiological disruptions in psychosis and ii) that neural communication and synchronization in extended (rather than focal) auditory and associative cortical circuits is specifically disrupted in psychotic pathology, suggesting roles for white matter integrity and neurochemical systems coordinating mediating long scale neural communication.

Second, reports from Hamm et al (Hamm et al, 2012; Ethridge et al, 2012) establish two important findings which suggest differential auditory neural abnormalities in SZ psychosis versus BD-P psychosis: late S1 negative drift absence in SZ (paired-stimuli) and the late

beta/gamma enhancement in BD-P (paired-stimuli and oddball paradigms). These two effects were previously not seen, and the report in **Chapter 3** will seek to i) replicate them in a larger sample (200+ SZ, BDP, and healthy comparison subjects), ii) examine the presence of these effects in psychiatrically healthy family members, and iii) estimate the heritability of these effects. Further, **Chapter 3** will achieve these three goals for the DSM-disorder non-specific effects seen in Hamm et al (2012) and Ethridge et al (2012) such as the P2 and low frequency evoked responses. Establishing heritability and diagnostic specificity is a necessary step to position the field of psychiatry for future effective genetic and/or etiological studies. For instance, if the late S1 drift effect in SZ is heritable, SZ specific in the large sample, and present in some unaffected family members, it may represent a more basic phenotype (endophenotype) which could relate more closely to (and enhance scientists' ability to find) risk genes for psychopathology (Thaker, 2008). Such a finding could imply that stimulus expectation and anticipatory modulation of thalamocortical inputs (perhaps via the reticular nucleus; Ferrarelli & Tononi, 2011) underlie traditionally studied P50 gating impairments in SZ rather than simple inhibitory dysfunction in stimulus registration. Further, results of **Chapter 3** may further the establishment of late-beta band augmentations as an endophenotype for bipolar disorder, implicating its utility for finding related genetic risk variants and emphasizing the need for future research into its neurophysiological and neurochemical mechanisms.

Third, while most reports concerning gamma-band entrainment in psychosis have shown reductions in patients relative to healthy subjects, two reports add important nuance. First, Hamm et al (2011) demonstrated that 40Hz aSSR reductions in SZ auditory cortices are limited to right hemisphere when stimuli i) have extended duration (1500ms as opposed to previous durations of 500ms) and ii) are actively attended to by the participant (as opposed to all 15 previous studies

with subjects passively listening to stimuli). Second, Hamm, Gilmore, and Clementz (2012) showed that SZ gamma band aSSRs measured with EEG are, in fact, larger than healthy comparison subjects during passive listening if the stimuli are long enough (again, 1500ms). Together, these advances begin to suggest that previous interpretations of impaired basic GABAa mediated inhibition in local cortical circuitry based on SZ and BD patients' inability to generate aSSRs are incomplete; indeed, persons with psychosis are capable of generating entrained, coherent gamma band oscillations under certain conditions (and even generate them in excess). The study presented in **Chapter 4** will specifically compare short to long duration aSSR responses in SZ during both active and passive listening contexts (2X2 design in SZ and healthy comparisons subjects), addressing whether aSSR reductions in psychosis reflect impaired basic gamma-band entrainment mechanisms (impaired in all conditions in SZ), impairments in default brain responsivity (SZ impaired only in passive listening conditions), or deficits in thalamocortical or GABA-b related (Hamm, Gilmore, et al., 2012) gain control in stimulus duration expectation (SZ reduced for short duration and enhanced for long duration). Finally, the study presented in **Chapter 4** serves to promote a better understanding of how transiently evoked auditory response abnormalities (i.e. low frequency evoked responses) relate to intrinsic and entrained gamma oscillatory abnormalities, providing an important stepping stone towards an integrated theory of auditory neurophysiological disruptions in psychosis. So while **Chapter 3** will establish the heritability of intrinsic (baseline) gamma abnormalities in psychosis, **Chapter 4** will examine and compare both pre- and during-stimulation gamma entrainment directly to establish whether these abnormalities reflect impaired contextual modulation of gamma or a more general gamma generation/control deficit.

In sum, the psychosis specificity (**Chapter 2**), heritability, and/or diagnostic specificity (**Chapter 3**) of both N1/P2 reductions, late-S1 drift (**Chapters 2-3**) and intrinsic and reactionary gamma-band oscillatory control (**Chapters 3-4**) will be addressed in the following text.

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CHAPTER 2

FAMILY HISTORY OF PSYCHOSIS MODERATES EARLY AUDITORY CORTICAL RESPONSE ABNORMALITIES IN NON-PSYCHOTIC BIPOLAR DISORDER[1]

[1]Hamm, J.P., Ethridge, L.E., Shapiro, J.R., Pearlson, G.D., Tamminga, C.A., Sweeney, J.A., Keshavan, M.S., Thaker, G.K., Clementz, B.A. 2013. *Bipolar Disorders*. 15: 774-786. Reprinted here with permission of the publisher.

Abstract

Objectives: Bipolar-I disorder is a disabling illness affecting 1% of people worldwide. Family and twin studies suggest that psychotic bipolar disorder (BDP) represents a homogenous subgroup with an etiology distinct from non-psychotic bipolar disorder (BDNP) and partially shared with schizophrenia. Studies of auditory electrophysiology (e.g. paired-stimulus and oddball measured with electroencephalography [EEG]) consistently report deviations in psychotic groups (schizophrenia, BDP), yet such studies comparing BDP and BDNP are sparse and, in some cases, conflicting. Auditory EEG responses are significantly reduced in unaffected relatives of psychosis patients, suggesting that they may relate to both psychosis liability and expression.

Methods: While 64-sensor EEGs were recorded, age and gender matched samples of 70 BDP, 35 BDNP (20 with a family history of psychosis [BDNP(+)]), and 70 psychiatrically healthy subjects were presented typical auditory paired-stimuli and auditory oddball paradigms.

Results: Oddball P3b reductions were present and indistinguishable across all patient groups. P2s to paired-stimuli were abnormal only in BDP and BDNP(+). Conversely, N1 reductions to stimuli in both paradigms and P3a reductions were present in both BDP and BDNP(-) groups but were absent in BDNP(+).

Conclusions: While nearly all auditory neural response components studied were abnormal in BDP, BDNP abnormalities at early and mid latencies were moderated by family psychosis history. The relationship between psychosis expression, heritable psychosis risk, and neurophysiology within bipolar disorder, therefore, may be complex. Consideration of such clinical disease heterogeneity may be important for future investigations of the pathophysiology of major psychiatric disturbance.

Introduction

Persons with Bipolar I disorder experience distressing and disabling affective instability including both manic and depressive symptomology. Approximately 60% of bipolar I disorder (BD) patients experience concurrent psychosis, which carries additional devastating clinical and psychosocial consequences (Goodwin & Jamison, 2007; Keck et al., 2003). Psychosis breeds true within BD families (Goes, Sanders, & Potash, 2008). BD patients with psychosis (BDP) are 2-3 times more likely to have relatives with BDP than BD without psychosis (Potash et al., 2007), and quantitative psychotic symptomology is significantly familial (spearman's rho=.33) among BD siblings (5; for a detailed review of its heritability see Goes et al 2008). Across DSM-IV diagnoses, psychosis carries a similar neurophysiological signature (Pearlson et al., 1995; Thaker, 2008) and displays shared heritability and genetics (Goes et al., 2008). Individuals with schizophrenia have increased rates of psychotic versus non-psychotic BD (BDNP) in their family (Kendler, Gruenberg, & Tsuang, 1985), and twin studies indicate a strong genetic basis for this association (Cardno, Rijsdijk, Sham, Murray, & McGuffin, 2002). Psychosis may capture unique pathophysiological substrates with implications for how BD is characterized, studied, and treated.

If BDP and BDNP represent distinct pathophysiological entities, then evidence supporting this distinction should be present in independent biological or cognitive measurements. Most investigations into the biological or cognitive correlates of BD have commingled BDP and BDNP (Emsell & McDonald, 2009). Studies separating these groups demonstrate that BDP tend to have more severe disturbances of some, but not all, cognitive functions (Glahn et al., 2007; Weiser et al., 2008). Ventricular enlargement may be present only in BDP (Byne, Tatusov, Yiannoulos, Vong, & Marcus, 2008; Strasser et al., 2005), but other

neuroanatomical deviations reliably associated with psychotic psychopathology, including gray matter thickness reductions (Gur, Keshavan, & Lawrie, 2007), may not differentiate BDP from BDNP (Emsell & McDonald, 2009; Javadapour et al., 2010; Takahashi et al., 2010).

Studies of auditory neurophysiology are informative for identifying psychosis-related biological deviations. Hallucinations are commonly auditory in psychosis, and auditory neurophysiological deviations are state-invariant and appear in unaffected relatives of individuals with psychotic disorders (Mei-Hua Hall, Taylor, Salisbury, & Levy, 2010; M-H Hall et al., 2009; Schulze et al., 2007). The presentation of auditory stimuli elicits a series of event-related potentials (ERPs, measured with electroencephalography), including the P1 (25-75ms post-stimulus onset) reflecting stimulus registration in primary auditory cortices (B Yvert, Crouzeix, Bertrand, Seither-Preisler, & Pantev, 2001), the N1 (75-125ms) reflecting early synchronization between primary and secondary auditory cortices in the superior lateral temporal lobes (Blaise Yvert, Fischer, Bertrand, & Pernier, 2005), and the P2 (175-250ms) reflecting further processing and more widespread integration as auditory cortices are synchronized with tertiary and associative cortical regions (for a review see 22). Attentional context (Hillyard, Hink, Schwent, & Picton, 1973) and inter-stimulus interval (Rosburg, Boutros, & Ford, 2008) strongly modulate N1 amplitude implying that it indexes the earliest cognitively influenced auditory neural event reliably measureable with EEG.

Classic auditory paired-stimuli paradigms involve presentation of clicks (S1 and S2 separated by 500ms with long interval between pairs) while ERPs (P1, N1, and P2) to the stimuli are quantified and compared(Schulze et al., 2007). Many studies show smaller differences between ERPs to S1 and S2 from individuals with psychosis compared to healthy subjects, an effect determined by smaller responses to S1 (Brett A Clementz, Dzau, Blumenfeld, Matthews,

& Kissler, 2003; Hamm et al., 2012) and/or larger responses to S2 (Hamm et al., 2012; Sánchez-Morla et al., 2008). The few studies directly comparing BDP and BDNP ERPs have reported abnormalities either i) limited to BDP and their relatives (Olincy & Martin, 2005; Schulze et al., 2007), ii) limited only to BDNP (Carroll et al., 2008), or iii) present in both groups (Cabranes et al., 2012; Patterson, Sandman, Ring, Jin, & Bunney, 2009). Therefore, the degree to which paired-stimuli ERPs mark psychosis in bipolar disorder is unresolved.

Auditory oddball paradigms involve presenting repeated tones (standard stimuli) interspersed with deviant "target" stimuli (e.g. at 80/20% frequencies, respectively). The auditory P3 ERP, an event occurring about 300ms post-targets, is associated with novelty detection (P3a) and/or context updating (p3b; 32), reflects widespread cortical synchronization and temporal orienting (Linden, 2005; Mulert et al., 2004), and is reliably reduced in schizophrenia and BDP. Earlier ERPs, including N1, P2, and N2 to standard and target stimuli, also show promise as psychosis markers (Ethridge et al., 2012), indicating that fundamental disruption in auditory target differentiation might contribute to P3 reductions in psychosis. Again, comparisons between BDP and BDNP are inconclusive regarding auditory neurophysiological heterogeneity in BD (Fridberg et al., 2009).

Inconsistency across auditory processing studies fails to support a "difference-in-kind" taxonomy of BDP versus BDNP as suggested by other data. Of particular importance for addressing this issue may be consideration of psychosis risk rather than just psychosis expression. Auditory electrophysiological responses are significantly heritable (estimated proportion of variance explained by genetic factors equal to 0.4 to 0.7; 37,38,39) and may index factors predisposing an individual to psychosis. If so, then one might expect different ERP presentations in BDNP with a family history of psychosis (+) compared to those without such a

history (-) regardless of equivalent clinical presentation. For instance, if an auditory ERP component purely marks risk for developing psychosis, BDNP(+) would be expected to deviate from healthy and BDNP(-) but be similar to BDP. Conversely, some ERPs marking affective disturbance could index resilience to psychosis (Frangou, 2011) and thus be at least normal in BDNP(+) while being deviant in BDNP(-) and BDP, capturing important etiological variance and predictive power (Jonsson et al., 2012). The likely commingling of BDNP (+) and (-) in previous studies could account for inconsistent findings; an effect of family history of psychosis on auditory neurophysiology would implicate previously unrecognized etiological factors.

In contrast to other reports of auditory ERPs that assessed only peak estimates from 1-3 EEG scalp sensors, the present study quantified ERPs across the entire scalp using spatial principal components analysis (PCA) and compared waveforms across the entire recording epoch in temporal bins, making maximal use of the available information. Previous work from the current group and others has established these methods as reliable and sensitive quantifiers of auditory neurophysiology in auditory ERP paradigms (Carroll et al., 2008; B A Clementz & Blumenfeld, 2001; Ethridge et al., 2012; Hamm et al., 2012). In addition to the use of robust methods and a sizable, well-matched sample (n=175), the current study examined whether family history of psychosis moderated BDNP deviations from BDP and from healthy subjects.

Materials and Methods

Subjects

As part of a large, multi-site data collection project (B-SNIP), 175 subjects were recruited, interviewed, and tested at five sites: University of Illinois-Chicago, Yale University/IOL (Hartford, CT), University of Texas Southwestern (Dallas, TX), Harvard University (Boston, MA), and University of Maryland (Baltimore, MD). Clinically stable

participants outside of an acute episode of illness were recruited via community advertisements, linked community facilities and programs, and local NAMI-type organizations. Three age- and gender-matched groups were constructed based on DSM-IV diagnosis and clinical history and blind to brain activity measurements: 70 BDP, 35 BDNP, and 70 healthy persons. Groups were matched on age, gender, and proportion of subjects from each recruitment site (**Table 1 and S1**). All subjects provided written informed consent prior to participation. All procedures were approved by IRBs at each recruitment and analysis site and are in accordance with the Helsinki Declaration of 1975. No EEG data in this manuscript have been used in a previous publication.

Medical and family history, structured clinical interview for DSM-IV diagnosis (SCID patient or nonpatient version as appropriate), Positive and Negative Symptom Scale (PANSS; 35), Young Mania Rating Scale (YMRS; 44), Montgomery-Asberg Depression Rating Scale (MADRS; 45), and Global Assessment of Functioning scale (GAF; axis V of Diagnostic and Statistical Manual of Mental Disorders IV [DSM-IV]) were acquired by trained and experienced clinicians. 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 (8 panel screen for amphetamines, barbiturates, cocaine, methadone, opiates, cannabinoids, propoxyphene and TCAs), 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 DSM diagnosis themselves and of any psychosis in a first-degree relatives. The family history of psychotic illnesses was assessed for all participants using Family History Research Diagnostic Criteria (Andreasen, Endicott, Spitzer, & Winokur, 1977). Twenty BDNP had first-degree relatives with BDP (n=17), schizophrenia (n=7), and/or

schizoaffective disorder (n=8). The remaining 15 BDNP had no first or second-degree relatives with any psychotic disorder. Additionally, all healthy persons (H) had no first or second-degree relatives with major affective or psychotic diagnoses. All analyses in this manuscript were therefore completed using 4 groups: H, BDP, BDNP with no 1st or 2nd degree relative with psychosis (BDNP(-)), and BDNP with at least one 1st degree relative with a psychotic disorder (BDNP(+)).

All clinical information (including study diagnosis) for each subject were reviewed and confirmed in a best estimate diagnostic meeting including at least one senior psychiatrist/psychologist and the clinician who conducted the structured interview and completed the clinical ratings. Instructions for rating on the SCID diagnostic scale, PANSS, YMRS and MADRS were carried out at the beginning and updated at 6-month intervals during the study, while inter-rater reliability was kept at >.85 (ICC or Kappa) across all sites (Tamminga et al., 2013).

Stimuli

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. For the paired-stimuli task, subjects passively listened to 150 binaural broadband auditory stimuli pairs (4 ms duration at 75dB) separated by an average of 9.5 sec (9-10 sec inter-pair interval; rectangular distribution), with 500 ms between stimuli in a pair. For the oddball task, subjects listened to 567 standard (1500-Hz) and 100 target (1000-Hz) tones presented in pseudorandom order (1300 ms inter-trial interval). Subjects were asked to press a button when a target was detected, and the percentage of targets detected was compared

between subject groups with a one-way ANOVA. Button press data were unavailable for subjects at the Dallas site. Participants refrained from smoking 1 hour prior to testing.

Recording

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

Data 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). Data were then converted to an average reference montage and digitally bandpass filtered from 0.5–55 Hz (zero phase filter; rolloff: 6 and 48 dB/octave, respectively). Blink and cardiac artifacts were removed using Independent Components Analysis (EEGLAB 9.0; Delorme & Makeig, 2004). Data were segmented into epochs from 100 ms before to either 550 ms (oddball standards), 750 ms (oddball targets), or 800 ms after stimulus onset (paired-stimuli S1) based on waveform stabilization and return to baseline (Figures **S1-S3**). The 100 ms pre-stimulus period was used for baseline adjustment (S1 only for paired-stimuli). Epochs containing activity greater than 75 μV at any sensor were eliminated. The total number of trials used did not differ between groups for any stimulus type (**Table 1**). Data from good trials were averaged across trial-types within a subject to create 64-sensor ERPs (Butterfly plots available in Figures **S1**-**S3**).

PCA data reduction

In order 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) was completed on grand average waveforms acquired from 64-sensor scalp EEG using BESA (MEGIS Software, Grafelfing, Germany) and Matlab (The Mathworks, Matick, MA). This resulted in component scores that were analyzed instead of single sensors (i.e. as 1-2 "virtual sensors"), minimizing the number of comparisons and maximizing the signal/noise ratio of the ERP data (Dien, Khoe, & Mangun, 2007).

For each stimulus type (paired-stimuli, oddball-standard, oddball-target), a PCA with promax (oblique) vector rotation and Kaiser normalization (Dien et al., 2007) was calculated on the 64X64 sensor covariance matrix (time-points as observations). Scree tests were used in each case to determine the optimal number of components (Cattell, 1966). PCA completed on averaged epochs for the paired-stimuli paradigm revealed a sole component with a frontal-central maximum (FCz) that accounted for 87.9% of the variance in waveforms across sensors (Figure **S1**). PCA completed on epochs for the oddball paradigm revealed 1 component with a frontal-central maximum (FCz) for standards accounting for 88.3% of the variance (Figure **S3)** and 2 components for target stimuli including a central parietally-distributed component accounting for 85.4% of the variance (Pz maximum; with an equivalent timecourse and distribution to the P3b) and one with a frontal-central maximum accounting for 12.2% of the variance (FCz; equivalent to the P3a; Figure **S2**). No additional components in any PCA accounted for more than 5% of the variance. When these steps were completed within analysis groups (see figures **S4-S7**), the PCA factor weights for both oddball and paired-stimulus did not differ between any analysis group result (all r's > .90) or between any group and the overall average (all r's > .95). These

factor solutions, along with the substantial equivalence of the results across divergent subject groups, are highly consistent and nearly identical with previous reports from separate (Ethridge et al., 2012; Hamm et al., 2012) and independent samples (Carroll et al., 2008).

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, reducing waveforms from one for each sensor to one waveform per component for each subject for paired-stimuli, oddball standards, and oddball targets (4 total).

ERP waveform analysis

For each subject waveform data from the entire epoch were grouped into 65-90 separate 10 ms bins and averaged within each bin. For each bin, a one-way ANOVA ($F(3,171)$) was calculated to determine group differences in waveform amplitude. To control for aberrant significant effects due to a small number of large voltage values within a bin, 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). Non-parametric probability estimates (p) of observed F values were then calculated as the proportion of randomly generated F values greater than the actual estimate. To control for family-wise error due to multiple comparisons, a clustering method was implemented using Monte Carlo simulations calculated across time-bins using AlphaSim (Cox, 1996; Forman et al., 1995). In order to maintain a family-wise alpha of .05, three sequential time-bins were required to be significant at $p<.025$.

Post-hoc discriminant analyses

To efficiently summarize variables that uniquely differentiated groups, values from significant time-bin clusters were averaged within clusters for each subject and submitted to a

linear discriminant analysis with group as the dependent variable (H, BDP, BDNP(-), BDNP(+)). Variables which minimized the overall Wilks' lambda and had individual multiple F-statistics significant at p<.05 were entered in a stepwise fashion (Mardia, Kent, & Bibby, 1980), leaving a parsimonious selection of neurophysiological measures.

Results

The relative distributions of groups across sites did not differ (**Table S1**), and previous reports from our group from larger BSNIP samples demonstrate the lack of significant site or site-by-group effects on auditory ERPs (Ethridge et al., 2012; Hamm et al., 2012). Groups did not differ on number of useable trials for either paradigm or stimulus type and responded equally to targets during the oddball paradigm (**Table 1).** Spatial PCA reduced 64-sensor ERPs across 3 stimulus types to a total of 4 waveforms for each subject for comparisons: paired-stimuli (PS), oddball target component 1 (TGT1, equivalent to parietal P3b), oddball target component 2 (TGT2, equivalent to frontal P3a), and oddball standard (STD). Component weights (topographies) are available in **Figures S1-S3**. Time-bin clusters with significant overall group effects are depicted for each waveform are in figures 1-3. Simple effects from within these clusters are discussed below and means with standard deviations are provided in **Table 2**.

The PS waveforms for each group (**Figure 1a**) and the omnibus F-values compared to the permutated .05 probability threshold (**Figure 1b**) with significant time-bins shaded are displayed in **Figure 1**. Two time-bin clusters reached significance. The first was from 70-ms to 120-ms post S1 onset and included the N1, peaking at 95-ms ($F(3,171)=5.68$, $p<.001$). BDP and BDNP(-) groups did not differ but each had significantly lower amplitudes than H ($t(138)=4.08$, $p<.001$; $t(83)=2.69$, $p<.01$, respectively). BDNP(+) did not differ from H in the N1 time window. Family history of psychosis therefore appeared to moderate N1 amplitude reductions in BDNP.

The second significant time window lasted from 180-ms to 260-ms post S1 onset and included the P2, peaking at 225-ms ($F(3,171)=6.17$, $p<.001$). BDP and BDNP(+) groups did not differ but each had lower amplitudes than H ($t(138)=4.08$,$p<.001$; $t(88)=1.99$, $p<.05$, respectively). BDNP(-) had significantly stronger P2 responses than BDP ($t(83)=2.68$, $p<.01$). Importantly, BDNP(-) did not differ from H. Thus, a family history of psychosis also moderated the paired-stimuli P2 in BDNP, but in a manner opposite to N1; P2 reductions were associated with psychosis risk and not necessarily psychosis expression. This is consistent with a previous report showing that paired-stimuli P2 to S1 is equally reduced in psychotic individuals regardless of DSM diagnostic category (Hamm et al., 2012).

Figure 2 depicts the TGT1 waveforms for each group (**2a**) and associated omnibus F-values (**2b**). A single time-bin cluster lasting from 330-ms to 400-ms after target onset (P3b range) reached significance, peaking at 365-ms ($F(3,171)=5.00$, $p<.01$). BDP ($t(138)=3.25$, $p<.01$), and BDNP(+) ($t(88)=2.07$, $p<.05$), had significantly smaller amplitude responses than H. All between patient group comparisons, however, were non-significant, and all BD subgroup waveforms are highly similar in this time range. This pattern of effects indicates that the P3b is a non-specific marker of psychopathology and is not moderated by psychosis expression or risk.

The TGT2 waveforms and F-values are depicted as thinner lines in **Figures 2a and 2b**. Two significant time-bin clusters emerged in the omnibus test. The first included the N1 component and lasted from 60-ms to 110-ms post-target onset, peaking at 85-ms ($F(3,171)=6.85$, $p<.001$). Only the BD-P and BDNP patient groups had significantly smaller values than H: BDP ($t(138)=3.37$, $p<.001$, and $t(83)=3.85$, $p<.001$, respectively). Importantly, BDNP(+) had an N1 amplitude significantly larger than BDNP(-) ($t(33)=2.13$, $p<.05$). This family history moderation effect echoes the patterns seen in PS-N1. The other significant cluster included the P3a

component and lasted from 320-ms to 350-ms, peaking at 325-ms ($F(3,171)=3.57$, $p<.05$). BDP and BDNP(-) groups did not differ but each had smaller amplitudes than H ($t(138)=2.71$,$p<.01$; $t(83)=2.33$, $p<.05$, respectively). BDNP(+) did not differ from H in the P3a window for the TGT2 component. A family history of psychosis, therefore, also moderated the P3a in BDNP in a similar manner as it did the paired-stimuli N1 although the overall effect was smaller.

The STD waveforms are depicted in **Figure 3** for each group (**3a**) and the associated omnibus F-values (**3b**). Waveform divergences in three time-window clusters achieved between-groups significance. The first window included the N1 component and lasted from 60-ms to 110-ms post-standard onset, peaking at 85-ms ($F(3,171)=6.90$, $p<.001$). Like the PS-N1 and TGT2-N1, BDP and BDNP(-) groups did not differ but each had lower amplitudes than H ($t(138)=3.57$,$p<.001$; $t(83)=3.37$, $p<.001$, respectively). BDNP(+) did not differ from H in the N1 time window. The second window included the P2 component and lasted from 190-ms to 260-ms post-standard onset, peaking at 240-ms ($F(3,171)=4.68$, $p<.01$). Only BDP differed significantly from H with lower amplitude P2s ($t(138)=4.08$, $p<.001$); no other group comparisons reached significance. The third window was in the vicinity of the N2 component and lasted from 340-ms to 370-ms post-standard onset, peaking at 355-ms ($F(3,171)=4.07$, $p<.01$). BDP and BDNP(-) groups did not differ from each other, but BDP had significantly lower amplitude responses than H ($t(138)=2.52$, $p<.05$) and BDNP(+) ($t(88)=2.02$, $p<.05$). BDNP(+) did not differ from H in this time period.

Medication effects

As expected, BDP were taking significantly more antipsychotic medications than BDNP (particularly second generation antipsychotics [2nd APS]; **Table S2**). Status for all other medication classes did not differ between patient groups (see **Table S3** for more details). When

sample sizes permitted, t-tests were computed within patient groups and across all patients comparing subjects taking medication and those medication-free within a drug class (antipsychotics, lithium, anticonvulsants, antidepressants, sedatives) on each of the 8 effects of interest. In all cases effects were greater than p=.10 uncorrected except one; BDNP(+) subjects on anticonvulsant medication had lower P3a amplitudes (mean=-.02uV, stdev=2.30) than anticonvulsant-free BDNP(+) (2.87uV, 2.74). This effect ($t(18)=2.50$, $p=.020$) did not exist in any other patient group or in the sample as a whole, and did not survive alpha adjustment for multiple comparisons.

Clinical Scores

Young Mania and Montgomery-Asberg Depression Rating Scale scores were statistically equivalent across patient groups (**Table 1**), indicating equivalently moderate levels of affective symptomology. Global Assessment of Functioning scores (DSM-IV-TR Axis V) did not differ between patient groups. None of the 8 main ERP effects significantly correlated with any clinical score within or across patient groups.

Linear Discriminant Analysis

Discriminant analyses indicated that PS-N1, PS-P2, and TGT-N1 each added unique group discrimination variance, and adequately captured the group ERP differences covered by all variables. Results are displayed as bar graphs in **Figure 4**. The P2 was essentially the only effect out of the 8 total effects which included deviations from H for BDP and BDNP(+) but not BDNP(-), suggesting its potential utility in understanding psychosis liability. The overall group discrimination pattern for the PS-N1 and the oddball TGT-N1 were similar such that BDP and BDNP(-) were both significantly reduced compared with H, while BDNP(+) showed absent or largely attenuated, non-significant deviations from H. This implies that these N1 reductions,

though both moderated by familial psychosis history in BDNP patients and correlated at r=.49, each carry a degree of unique information across subjects within groups, perhaps related to differences in passive versus active listening contexts.

Discussion

This study investigated whether classically reported auditory neurophysiological biomarkers of psychotic disturbance (paired-stimuli and oddball ERPs) support a unitary representation of bipolar disorder based on psychosis status. The results indicate that auditory paired-stimuli and oddball ERPs do not clearly distinguish BD subgroups based on psychosis expression alone (Carroll et al., 2008; Fridberg et al., 2009). When family history of psychosis was considered, however, a pattern emerged that might partially account for inconsistencies and null findings in previous reports. The present results suggest novel interpretations for the pathophysiological meaning of auditory ERP deviations among psychiatric disturbances generally and bipolar disorder variations specifically.

The N1 to auditory stimulus onset was reduced in BDP, replicating previous reports (Ethridge et al., 2012; Hamm et al., 2012). Reduced N1 has been consistently reported in psychotic patients (for a review see 24). Some BDNP had N1 reductions at the same levels as BDP, but, importantly, BDNP at high-risk for developing psychosis (i.e. with close relatives experiencing psychosis) had normal N1s. This effect was present in both the paired-stimuli and oddball paradigms thus showing replication under three different stimulus-processing conditions in our samples. Studies of N1 amplitudes among relatives of psychosis patients have yielded conflicting results, which may be associated with variable frequencies of comorbid psychiatric conditions across relative samples (Turetsky et al., 2008). The present findings are consistent with this thesis, and may implicate alternative means for understanding BD's various etiological

substrates. For instance, genes controlling expression of GABA(A) signaling proteins, which influence a critical and ubiquitous receptor in cortical neuronal assemblies playing a role in synchronizing ensembles of pyramidal cells, show association with the N1 (Porjesz et al., 2002). Perhaps having intact basic auditory cortical circuitry strengthens the signal/noise ratio in a psychosis-prone bipolar patient's basic sensory processing system, protecting against inaccuracies in sensory registration contributing to hallucinatory phenomena. Recent clinical neuroscience work has promoted understanding resilience to major psychiatric disturbance (Frangou, 2011) and the genetics of individuals relieved from developing such neuropathologies despite being at high-risk thereof (Jonsson et al., 2012).

Both BDP and BDNP without a history of psychosis showed N1 reductions, perhaps indicating that N1 marks an indirect relationship to affective psychiatric disturbance while also being associated with psychotic auditory processing abnormalities. Alternatively, BDNP(+) might have hyperexcitable early auditory cortical responses relative to BDNP(-), perhaps indicating constitutional auditory sensory dysregulation in addition to downstream connectivity and/or signal processing deficits marked by reduced longer latency ERPs (e.g. P3b). While requiring additional work to understand its complete neuropathological significance, N1 auditory ERP have promise as specific targets for understanding bipolar disorder's variable clinical manifestations.

Like N1, the P2 in the paired-stimuli paradigm was reduced in BDP as previously reported (Hamm et al., 2012). Reductions in paired stimuli P2 in BDNP were also moderated by family psychosis history such that BDNP(+) showed equivalent P2 reductions to BDP, but BDNP(-) showed P2s at healthy levels (in contrast to the N1 effect pattern). Together with a previous study indicating that P2 has a general relationship to psychosis regardless of affective

psychopathology (patients with schizophrenia and BDP have equal P2 reductions; 25), this finding extends previous knowledge to indicate that heritable factors related not to psychosis expression but to general psychosis liability are captured by P2 amplitude deviations.

The N1 and P2 demonstrated a pattern of differential effects that have not been directly hypothesized by previous models of psychosis or affective neurophysiology. In addition to occurring later than N1, the P2 shows both superior temporal as well as associative cortical source generators (Godey, Schwartz, de Graaf, Chauvel, & Liégeois-Chauvel, 2001), indicating its association with more distributed cortical processing, temporal synchronization, and long range neural communication. An enhanced N1 in BDNP(+), therefore, may represent a functional compensation (not present in BDP) for an inherited cortical network disruption indexed by subsequent decreased signal propagation (reduced P2). While the P2 is commonly conceptualized with the N1 as part of an N1/P2 complex, P2 can vary independently of other auditory ERP components (Crowley & Colrain, 2004), e.g., showing attentional effects substantially different from the N1 (Näätänen, 1990). This differential relationship to attention could explain why group discriminations differed between passive (PS) and active (OB) listening paradigms for P2 but not for N1. These findings serve as viable clues in future work on the genetics of BD specifically and psychosis generally. For example, a set of genes may influence long range connectivity and synchronization (Linke et al., 2012), correlating with P2 and, theoretically, operating in ways related to, but indeterminate of, psychosis expression. Research on N1 as a resilience factor/marker and P2 as relating to psychosis liability should involve additional quantitative genetic and/or longitudinal approaches. The novelty of this pattern is at once interesting and indicative of the need for replication.

Importantly, a most widely studied ERP, the mesial parietal lobe centered P3b, showed no group specificity, being reduced and nearly equivalent in all BD groups. This finding converges with numerous previous reports of equivalent or similar reductions in P3b amplitudes across different psychotic and affective diagnostic categories (Blackwood et al., 2001; Ethridge et al., 2012), across different mood, medication, and psychosis states within BD (Fridberg et al., 2009), and within unaffected family members of BD (M-H Hall et al., 2009). Indeed, P3b abnormalities have been described for multiple behavioral deviations (Bruder, 1992; Johannesen, O'Donnell, Shekhar, McGrew, & Hetrick, 2012; Linden, 2005), indicating that this brain response may index generalized dysfunction.

The anteriorly-distributed P3a was reduced in BDP but additionally showed a relationship to family psychosis history status similar to the N1 (BDNP(+)>BDNP(-)). Previous reports have implicated the perhaps special importance of the P3a in BDP (Salisbury, Shenton, & McCarley, 1999), along with its closer relationship to variations in dopamine-related gene expression than the P3b (Marco-Pallarés et al., 2010). The P3a is believed to index an orienting responses to novel stimuli (Linden, 2005).A similar effect to N1 and P3a was also present for the later part of the N2 time range to standard stimuli in the oddball task. Responses to oddball standard stimuli in this time range are less commonly reported in the auditory ERP literature than N1 or P3. The N2 response, however, was reduced in both BDP and BDNP(-), but not BDNP(+), again signifying psychosis resilience among a subgroup of BD patients. This effect shared a similar topography and pattern of group discrimination with both N1 and P3a, but across all subjects (n=175) the STD-N2 correlated poorly with each N1 component (r=-.06, -.09, and -.03 for PS, TGT, and STD, respectively) but significantly with the P3a (r=.37). These effects indicate that the psychosis resilience marked by N1 may be separate from that marked by the P3a

and STD-N2 components, which may mark novelty-related and/or frontally distributed cognitive processing mediated by dopaminergic mechanisms (Linden, 2005; Marco-Pallarés et al., 2010).

Previous work has questioned whether familial (e.g. BDP or schizophrenia with first or second degree relatives with psychotic disorders) and sporadic (patients with no family history of psychosis) psychosis represent differentiable clinical or biological subgroups (Frommann et al., 2008; Malaspina et al., 1998; Roy & Crowe, 1994). The familial versus sporadic distinction may be related, but not equivalent, to the current analysis of psychosis risk versus expression in bipolar disorder. Our sample was not optimized to address the familial versus sporadic issue, but we specifically compared BD patients with familial (n=16) versus sporadic (n=51) psychosis (data were not certain for 3 BDP subjects). Only the paired stimuli N1 approached significance ($t(65)=1.76$, $p=.082$), with familial BDP having smaller N1s (mean=-0.33, stdev=1.11) than sporadic BDP (-0.94, 1.23). Interestingly, when compared with BDNP(+), BDP with familial psychosis had significantly smaller PS-N1s ($t(34)=2.73$, $p<.01$), further indicating a complex, perhaps additive or protective, relationship of N1 to psychosis expression and risk in BD.

The results of the current study mark a crucial step toward understanding how commonly described electrophysiological deviations relate to psychotic and affective psychopathology, and provide information on biomarkers that can be used to guide larger scale efforts to identify and interpret genetic underpinnings of psychiatric disturbance.

Disclosures

This work was supported by grants from the National Institutes of Health (R01s MH077945, MH077862, MH077851, MH078113, and MH085485). Authors JPH, LEE, JRS, GDP, CAT, GKT, and BAC do not have any commercial associations that might pose a conflict of interest in connection with this manuscript. Author JAS has served as a consultant for Takeda,

Inc., Pfizer, Inc., and Eli Lilly Pharmaceuticals and has received grant funding from Janssen, Inc. Author MSK has served as an Ad Hoc Consultant for PureTech Ventures, Eli Lilly Pharmaceuticals, Sunovion Pharmaceuticals Inc., Astellas Pharma US Inc., and Merck & Company, Inc. and has served on the advisory board for Intracellular Therapies Inc.

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	H (n=70)	**BDP** (n=70)	**BDNP(-)** (n=15)	**BDNP(+)** (n=20)	**Statistic**
%female	55.7%	55.7%	53.3%	55.0%	$X^2(2)$=0.032, p=0.998
Age (years)	38.4	38.2	41.9	36.7	F(3,171)=0.53, p=0.65
Paired Stimuli trials accepted	140 (SD=13.0)	141 (8.74)	143 (8.26)	142 (10.2)	F(3,171)=0.52, p=.669
Standard trials accepted	535 (45.4)	542 (45.3)	549 (24.5)	535 (44.5)	F(3,171)=0.64, p=.590
Target trials accepted	95.5 (7.05)	96.4 (5.64)	97.0 (4.02)	95.8 (6.44)	F(3,171)=0.38, p=.769
Percent targets detected	95.8 (SD=9.02)	93.3 (10.5)	88.7 (16.9)	91.2 (15.3)	F(3,150)=2.01,p=.114

SCALE	**BDP**	**BDNP (-)**	**BDNP (+)**	**Statistic**
GAF	60.6 (12.4,n=68)	63.6 13.6,n=14)	65.3 (10.0,n=20)	F(2,99)=1.31, p=.275
PANSS-Pos	12.2 (4.13,n=69)	-	-	-
PANSS-Neg	12.0 (3.66,n=69)	-	-	-
PANSS-Gen	28.1 (7.94,n=69)	-	-	-
MADRS	10.6 (9.29,n=67)	9.60(9.17,n=15)	8.00 (9.24,n=8)	F(2,87)=0.32, p=.725
YMS	5.57 (6.05,n=67)	4.87(5.30,n=15)	4.89 (9.58,n=9)	F(2,88)=0.11, p=.900

Table 2.1: Demographic and Clinical Statistics. H, healthy comparison subjects; BDP, bipolar disorder with psychosis; BDNP(-) bipolar disorder without psychosis without first-degree family history of psychosis; BDNP(+), bipolar disorder without psychosis with first-degree family history of psychosis; GAF, Global Assessment of Functioning; MADRS, Montgomery-Åsberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation; YMS, Young Mania Scale.

	H (n=70)	**BDP** (n=70)	**BDNP(-)** (n=15)	**BDNP(+)** (n=20)
PS-N1	-1.94 (1.36)	***-1.06 (1.18) ******	***-0.95 (0.88) *****	-1.60 (1.17)
PS-P2	2.10 (1.66)	***1.07 (1.28) ******	2.23 (2.05)	***1.25 (1.65)****
TGT1-P3b	3.60 (2.54)	***2.35 (1.97) *****	***2.46 (1.49)***	***2.34 (1.78)****
TGT2-N1	-2.15 (1.17)	***-1.46 (1.26) ******	***-0.92 (0.87) ******	-1.59 (0.97)
TGT2-P3a	1.69 (2.53)	***0.66 (1.88)*****	***0.02 (2.44)****	1.27 (2.81)
STD-N1	-1.67 (0.92)	***-1.10 (0.97) ******	***-0.82 (0.71) *****	-1.29 (0.88)
STD-P2	1.36 (0.96)	***0.75 (0.80)******	0.94 (1.02)	1.13 (1.20)
STD-N2	0.16 (0.78)	***-0.14 (0.63)****	*-0.25 (0.75)*	0.17 (0.58)

Table 2.2: Significant Main Effects. Two-tailed T-tests versus H significant at p<.001 indicated by ***, p<.01 indicated by **, and p<.05 indicated by *. H, healthy comparison subjects; BDP, bipolar disorder with psychosis; BDNP(-) bipolar disorder without psychosis without first-degree family history of psychosis; BDNP(+), bipolar disorder without psychosis with first-degree family history of psychosis; PS, paired-stimulus waveform; TGT1, target waveform 1 (parietally distributed); TGT2 target waveform 2 (frontally distributed); STD, standard waveform.

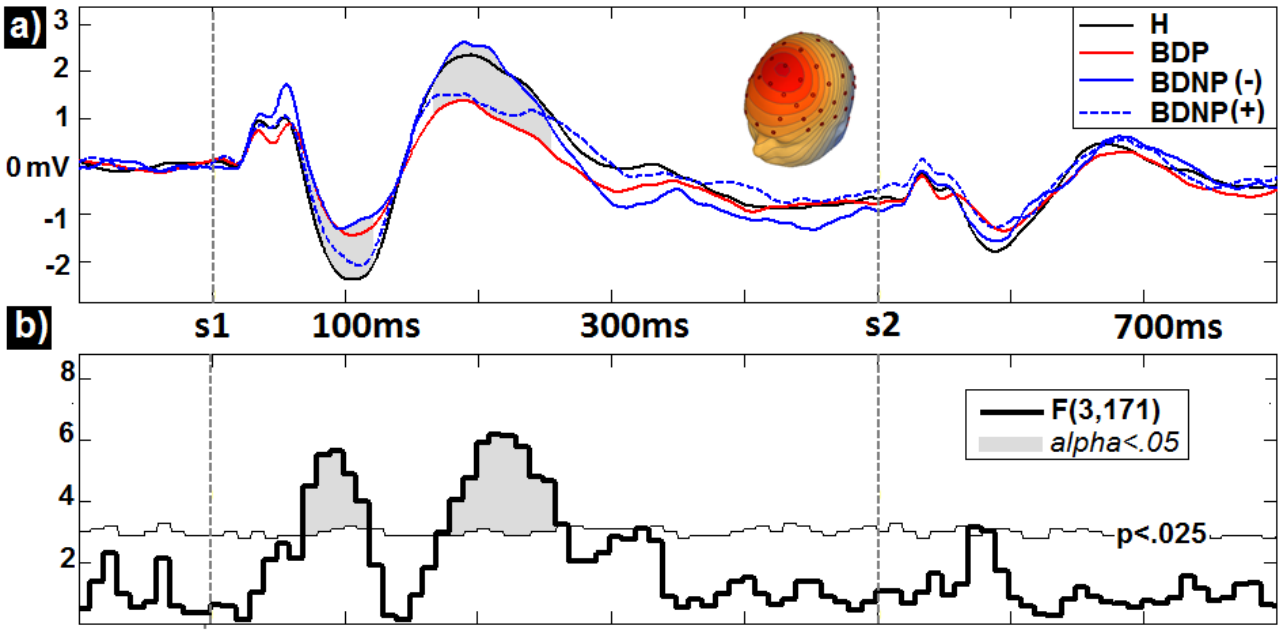

Figure 2.1: Paired Stimuli Waveforms. Group comparisons for PCA derived paired-stimuli ERP waveforms (a) averaged within group yield significant effects in the N1–S1 and P2–S1 ranges (shaded regions). F-values for these effects are also presented along with (b) a bootstrapped p<.025 probability line (thin horizontal line). Time regions reaching significance at FWalpha<.05 (three consecutive bins) are highlighted. H, healthy comparison subjects; BDP, bipolar disorder with psychosis; BDNP(-) bipolar disorder without psychosis without first-degree family history of psychosis; BDNP(+), bipolar disorder without psychosis with first-degree family history of psychosis.

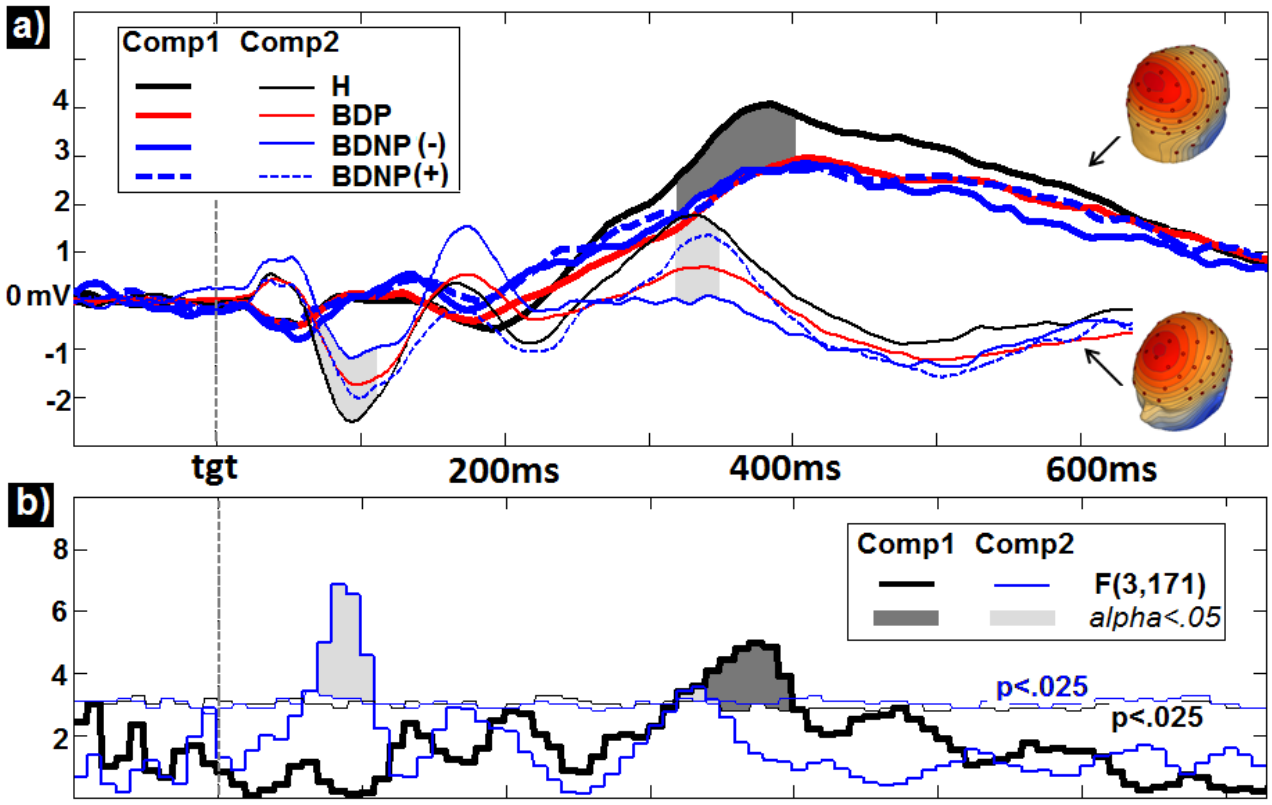

Figure 2.2: Oddball Target Waveforms. Group comparisons for PCA derived ERP waveforms to oddball target stimuli (a) averaged within group yield significant effects in the P3b range for component 1 (Pz maximum; dark shaded region) and in the N1 and P3a range for component 2 (FCz maximum; light shaded region). F-values for these effects are also presented along with (b) a bootstrapped p<.025 probability lines (thin horizontal lines). Time regions reaching significance at FWalpha<.05 (three consecutive bins) are highlighted. H, healthy comparison subjects; BDP, bipolar disorder with psychosis; BDNP(-) bipolar disorder without psychosis without first-degree family history of psychosis; BDNP(+), bipolar disorder without psychosis with first-degree family history of psychosis.

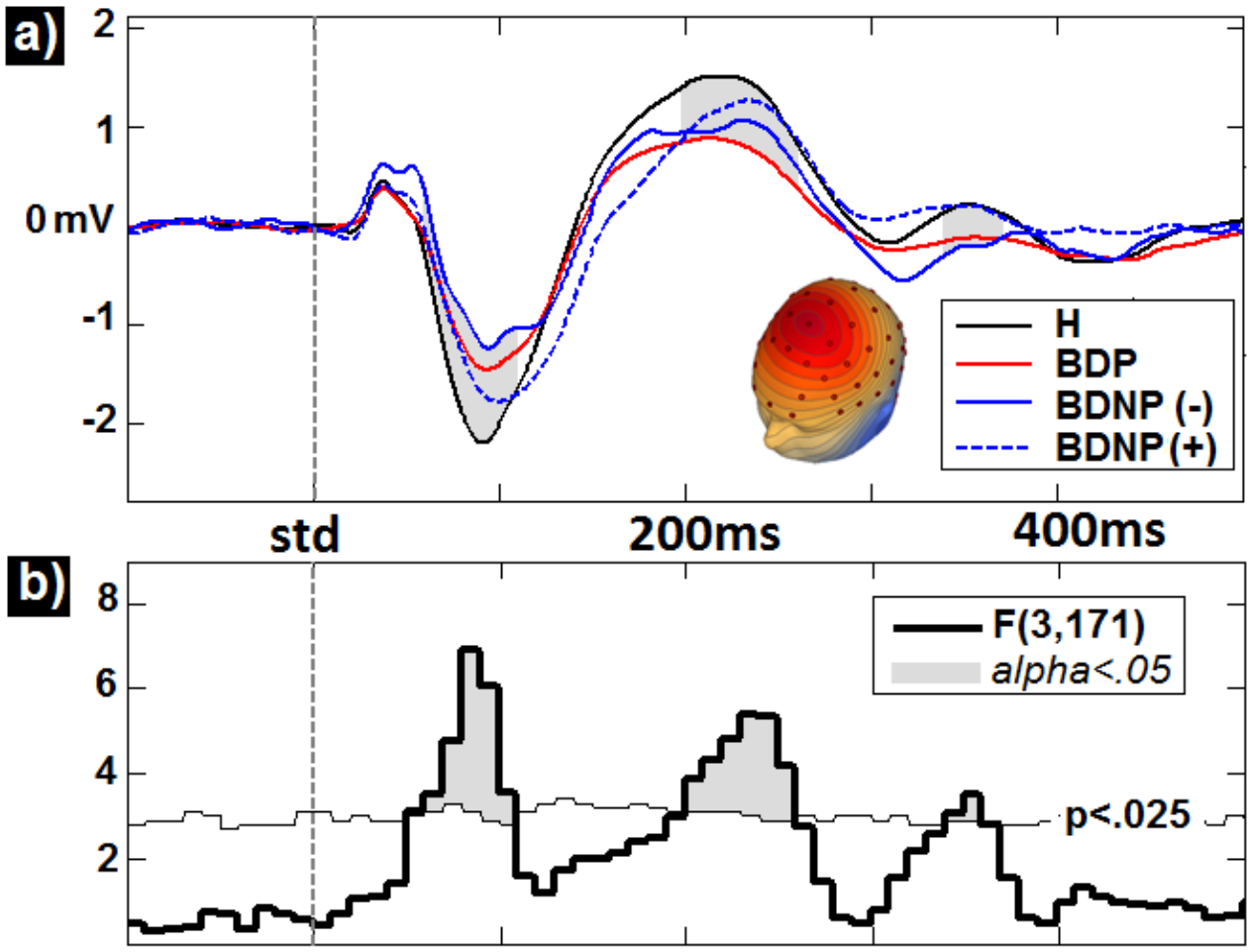

Figure 2.3: Oddball Standard Waveforms. Group comparisons for PCA derived ERP waveforms for oddball standard stimuli (a) averaged within group yield significant effects in the N1, P2, and late N2 time ranges (shaded regions). F-values for these effects are also presented along with (b) a bootstrapped p<.025 probability line (thin horizontal line). Time regions reaching significance at FWalpha<.05 are highlighted. H, healthy comparison subjects; BDP, bipolar disorder with psychosis; BDNP(-) bipolar disorder without psychosis without first-degree family history of psychosis; BDNP(+), bipolar disorder without psychosis with first-degree family history of psychosis.

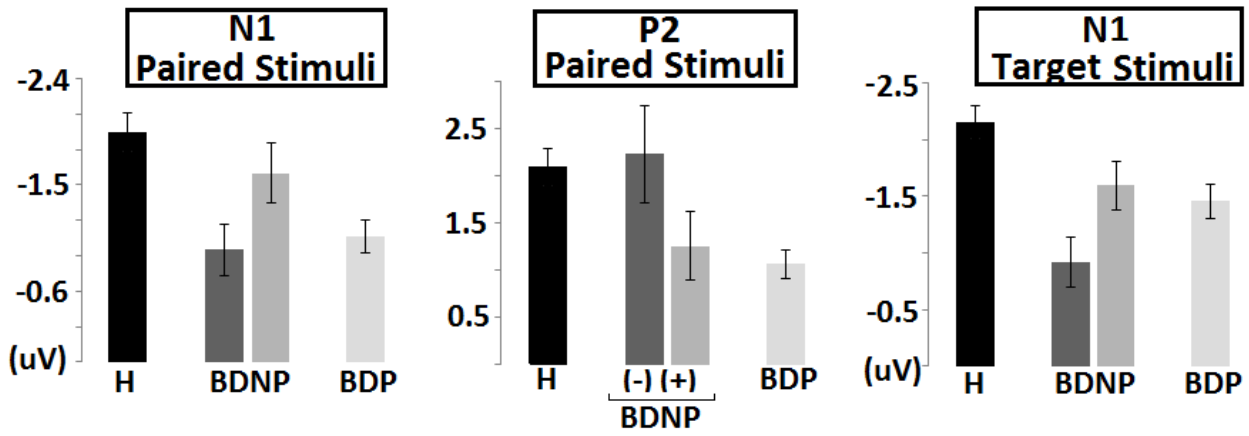

Figure 2.4: Unique Group Discriminators. Group averages and standard errors for three main group discriminators determined in the linear discriminant analysis: N1 to paired-stimuli S1, P2 to paired-stimuli S1, and N1 to oddball target stimuli. H, healthy comparison subjects; BDP, bipolar disorder with psychosis; BDNP(-) bipolar disorder without psychosis without first-degree family history of psychosis; BDNP(+), bipolar disorder without psychosis with first-degree family history of psychosis.

Number from each site					
	Healthy	**BDP**	**BDNP (-)**	**BDNP (+)**	**Statistic**
HU	13	9	2	0	$X^2(12)$=18.7, p=.100
UIC	19	16	3	8	F(3,171)=0.53, p=0.65
UM	9	24	6	3	F(3,171)=0.52, p=.669
UTSW	11	7	0	3	F(3,171)=0.64, p=.590
YU	18	14	4	5	F(3,171)=0.38, p=.769

Table 2.S1. Subjects by Site. HU, Harvard University; UIC, University of Illinois, Chicago; UM, University of Maryland; UTSW, University of Texas Southwestern; YU, Yale University/Institute of Living.

	Healthy	**BDP**	**BDNP (-)**	**BDNP (+)**	**Statistic**
n	70	70	15	20	-
1st Generation Antipsychotics	-	6	1	0	$X^2(2)$=184, $p=0.399$
2nd Generation Antipsychotics	-	45	4	4	**$X^2(2)$=16.2, p<.001**
Lithium	-	15	3	4	$X^2(2)$=0.028, p=0.986
Antidepressants	-	28	8	9	$X^2(2)$=0.943, p=0.624
Anticonvulsants	-	40	11	10	$X^2(2)$= 1.62, p=0.444

Table 2.S2: Medication Statistics.

Medication	**BDP**	**Avg Dose (mg)**	**BDNP (-)**	**Avg Dose (mg)**	**BDNP (+)**	**Avg Dose (mg)**
Antidepressants						
D.AMITRIPTYLINE	0		0		1	50.0
D.BUPROPION	8	250.0	2	200.0	3	317
D.BUSPIRONE	0		1	60.0	0	
D.CITALOPRAM	2	40.0	2	30.0	0	
D.CLOMIPRAMINE	2	50.0	0		0	
D.DESVENLAFAXINE	0		3	75	0	
D.ESCITALOPRAM	3	20.0	1	10.0	3	11.3
D.FLUOXETINE	3	43.3	1	40.0	0	
D.IMIPRAMINE	1	50	0		0	
D.MIRTAZAPINE	2	22.5	1	45.0	1	?
D.PAROXETINE	3	25	0		1	20
D.SERTRALINE	4	91.7	0		2	50.0
D.TRAZODONE	5	400.0	2	150.0	1	100.0
D.VENLAFAXINE	1	150.0	0		1	75.0
Subjects on at least 1 medication	**28**		**8**		**9**	
Anticholinergics						
D.BENZTROPINE	8	2.00	1	1.00	0	
Subjects on at least 1 medication	**8**		**1**		**0**	
Anticonvulsants/Mood Stabilizers						
D.CARBAMAZEPINE	1	400.0	2	1700.0	1	200
D.GABAPENTIN	4	1680	3	950.0	1	?
D.LAMOTRIGINE	18	217	4	483	5	250.0
D.LITHIUM	15	1080	3	1300.0	4	1030
D.OXCARBAZEPINE	4	900.00	1	600.0	0	
D.PREGABALIN	1	?	0		0	
D.TOPIRAMATE	3	300	0		0	

D.VALPROIC_ACID	17	1180	4	1000.0	4	875
D.ZOLPIDEM	4	10.0	0		0	
Subjects on at least 1 medication	**48**		**12**		**12**	
First Generation Antipsychotics						
D.FLUPHENAZINE	0		1	2.00	0	
D.HALOPERIDOL	6	10.3	0		0	
Subjects on at least 1 medication	**6**		**1**		**0**	
Second Generation Antipsychotics						
D.ARIPIPRAZOLE	12	16.9	1	30.0	1	4.00
D.CLOZAPINE	2	250	0		0	
D.OLANZAPINE	8	20.8	1	?	0	
D.PALIPERIDONE	1	?	0		0	
D.QUETIAPINE	17	368	2	175	3	333
D.RISPERIDONE	5	3.45	0		1	2.00
D.ZIPRASIDONE	4	93.3	1	40.0	0	
Subjects on at least 1 medication	**45**		**4**		**4**	
Sedatives						
D.ALPRAZOLAM	3	2.00	0		2	2.00
D.CHLORAZEPATE	1	?	0		0	
D.CLONAZEPAM	10	3.42	1	2.00	1	2.00
D.LORAZEPAM	4	1.00	1	1.00	0	
D.TEMAZEPAM	0		1	30.0	0	
Subjects on at least 1 medication	**17**		**3**		**3**	
Stimulants						
D.DEXTROAMPHETAMINE_AMPHETAMINE	3	22.5	0		1	40.0
D.METHYLPHENIDATE	2	20.0	0		0	
D.PEMOLINE	1	75.0	0		0	

Subjects on at least 1 medication	**6**		**0**		**1**	

Table 2.S3: Medication Information. Medication information for each patient group, with the total number of subjects taking at least one medication in each drug class.

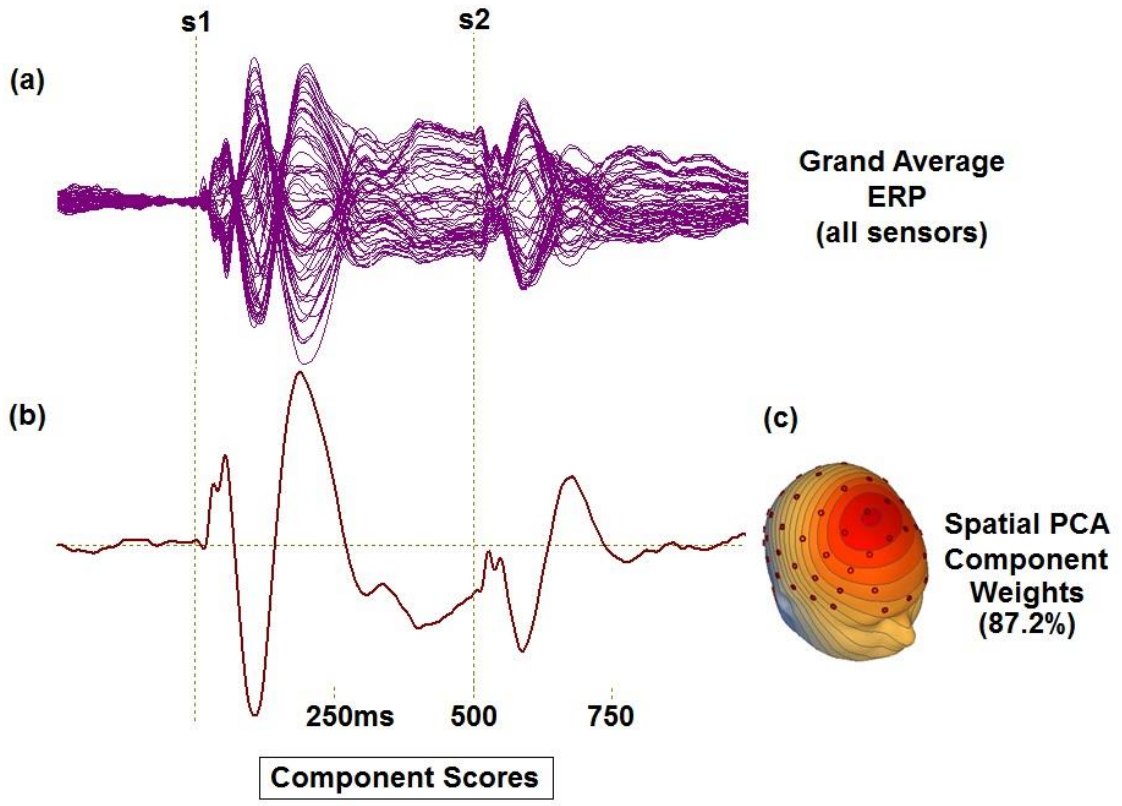

Figure 2.S1: PCA Paired-Stimuli. Spatial PCA completed on (a) grand averaged paired-stimulus ERP data (n = 175; displayed as a butterfly plot with each sensor represented as a line) yields a sole component with (b) component scores across time displayed as waveforms and (c) component weights (64) displayed as topographies (varying only in magnitude across the entire epoch). The proportion of ERP variance across accounted for by the component is displayed in parentheses.

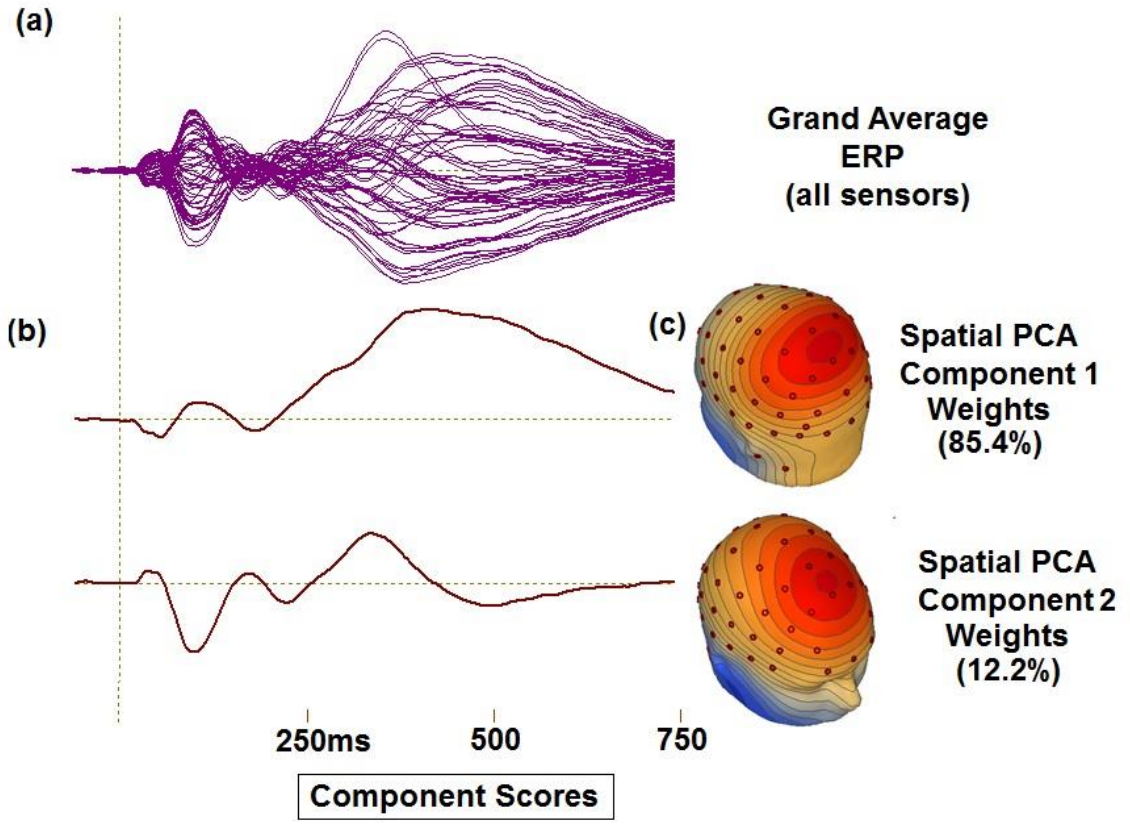

Figure 2.S2: PCA Oddball Target. Spatial PCA completed on (a) grand averaged oddball target ERP data (n = 175; displayed as a butterfly plot with each sensor represented as a line) yields two components with (b) component scores across time displayed as waveforms and (c) component weights (64) displayed as topographies (varying only in magnitude across the entire epoch). The proportion of ERP variance across accounted for by each component is displayed in parentheses.

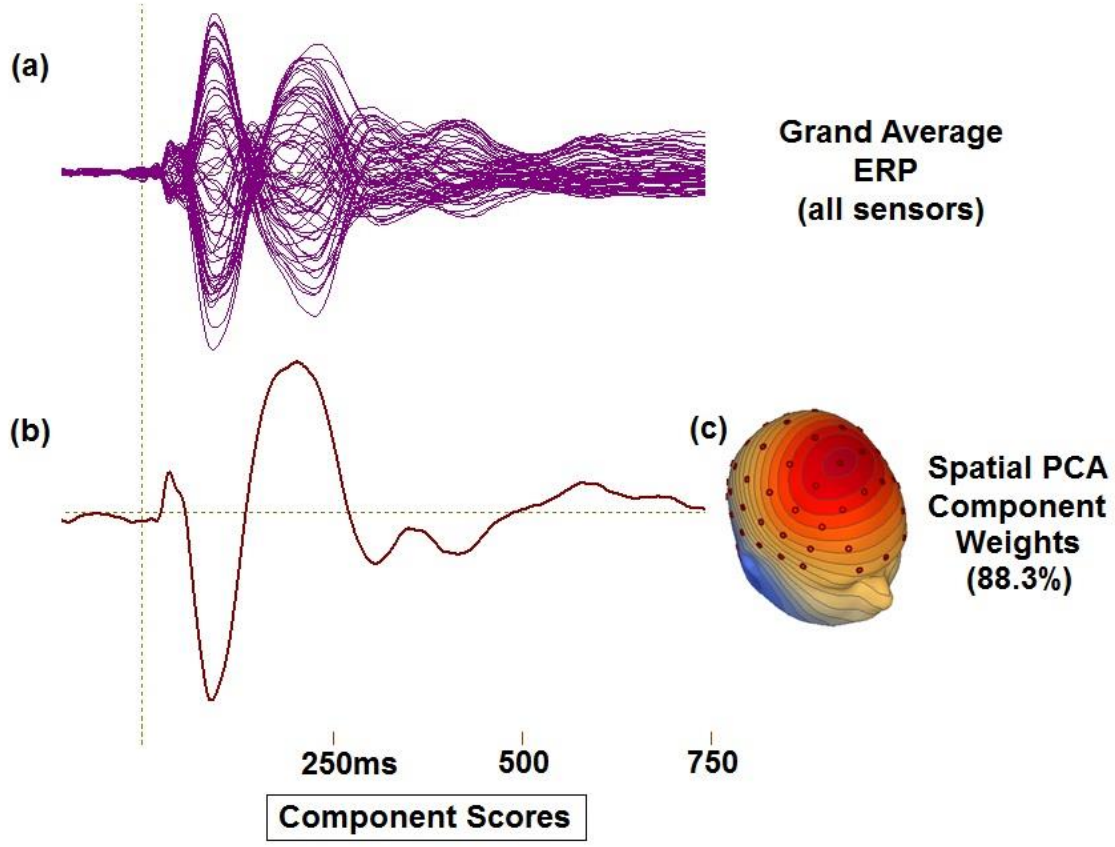

Figure 2.S3: PCA Oddball Standard. Spatial PCA completed on (a) grand averaged oddball standard ERP data (n = 175; displayed as a butterfly plot with each sensor represented as a line) yields a sole component with (b) component scores across time displayed as waveforms and (c) component weights (64) displayed as topographies (varying only in magnitude across the entire epoch). The proportion of ERP variance across accounted for by the component is displayed in parentheses.

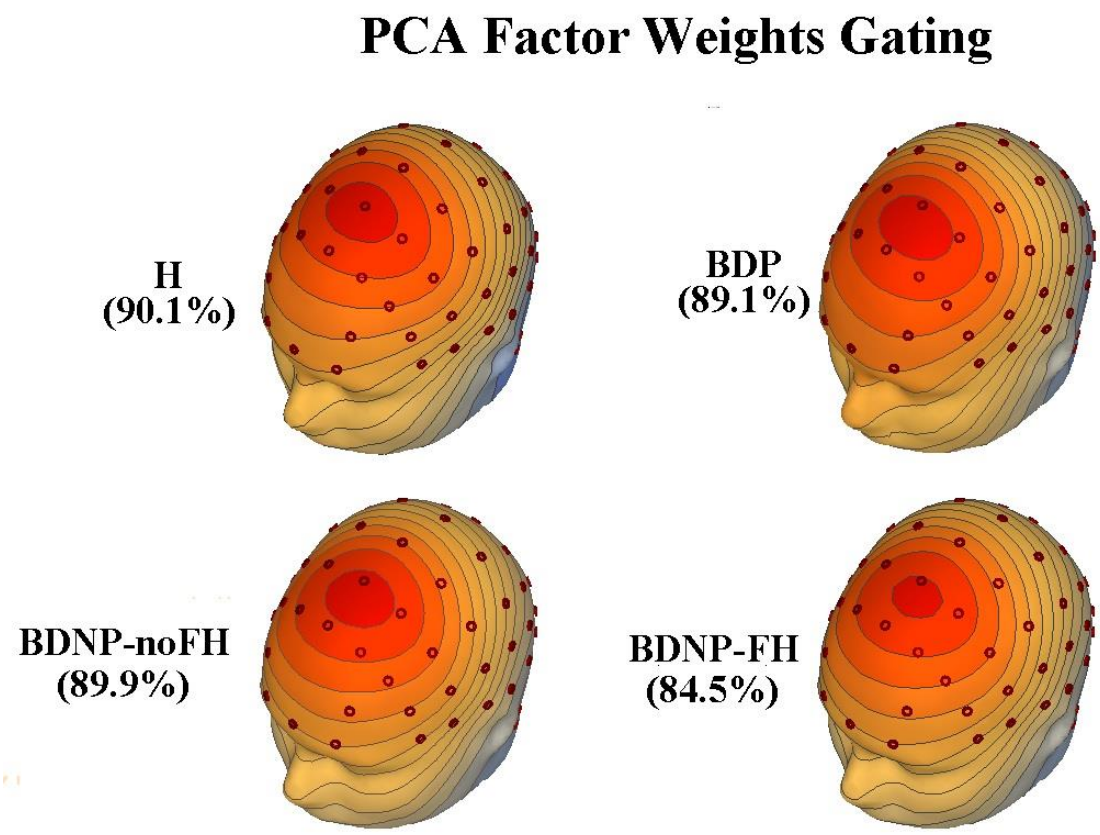

Figure 2.S4: Factor Weights Paired-stimuli. Factor weights (topographies) and percentage of total variance accounted for by the first factor (in parentheses) are displayed for each group's spatial PCA. Factor weights and variance percentages are nearly identical, all intercorrelating greater than r=.90 and correlating with the overall group result greater than r=.95, justifying a sample wide PCA.

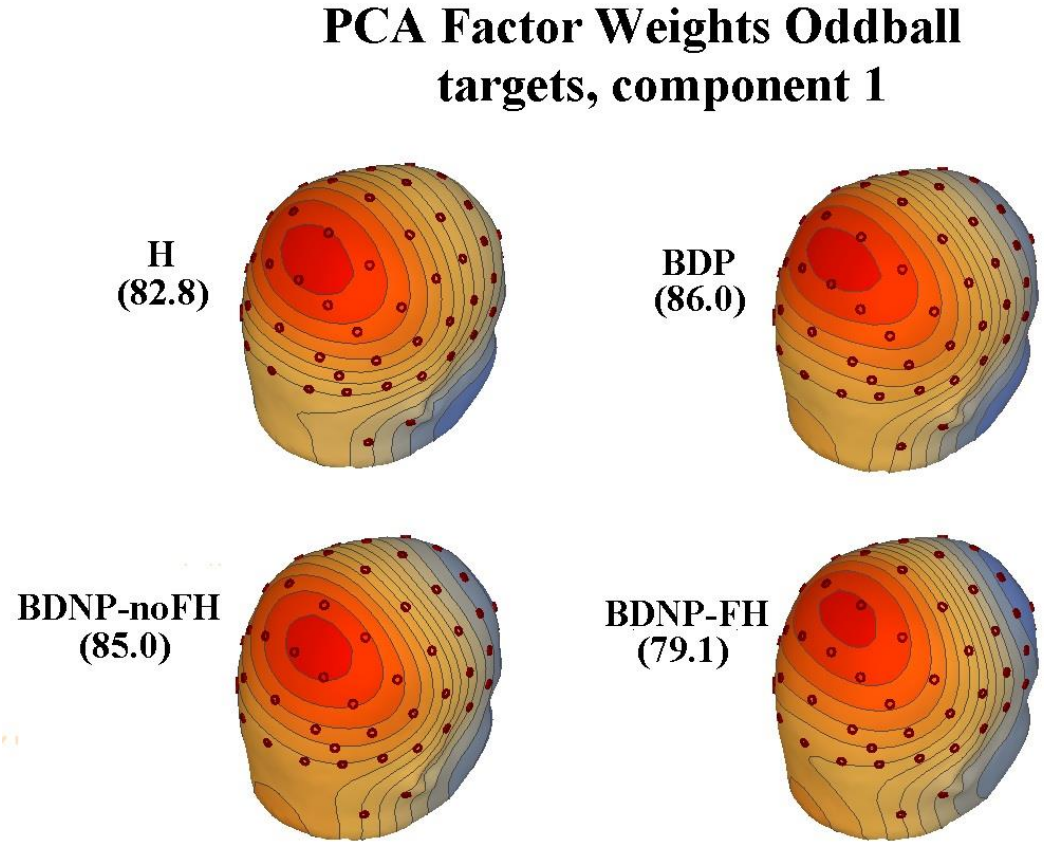

Figure 2.S5. Factor Weights Oddball Target-1: Factor weights (topographies) and percentage of total variance accounted for by the first factor (in parentheses) are displayed for each group's spatial PCA. Factor weights and variance percentages are nearly identical, all intercorrelating greater than r=.90 and correlating with the overall group result greater than r=.95, justifying a sample wide PCA.

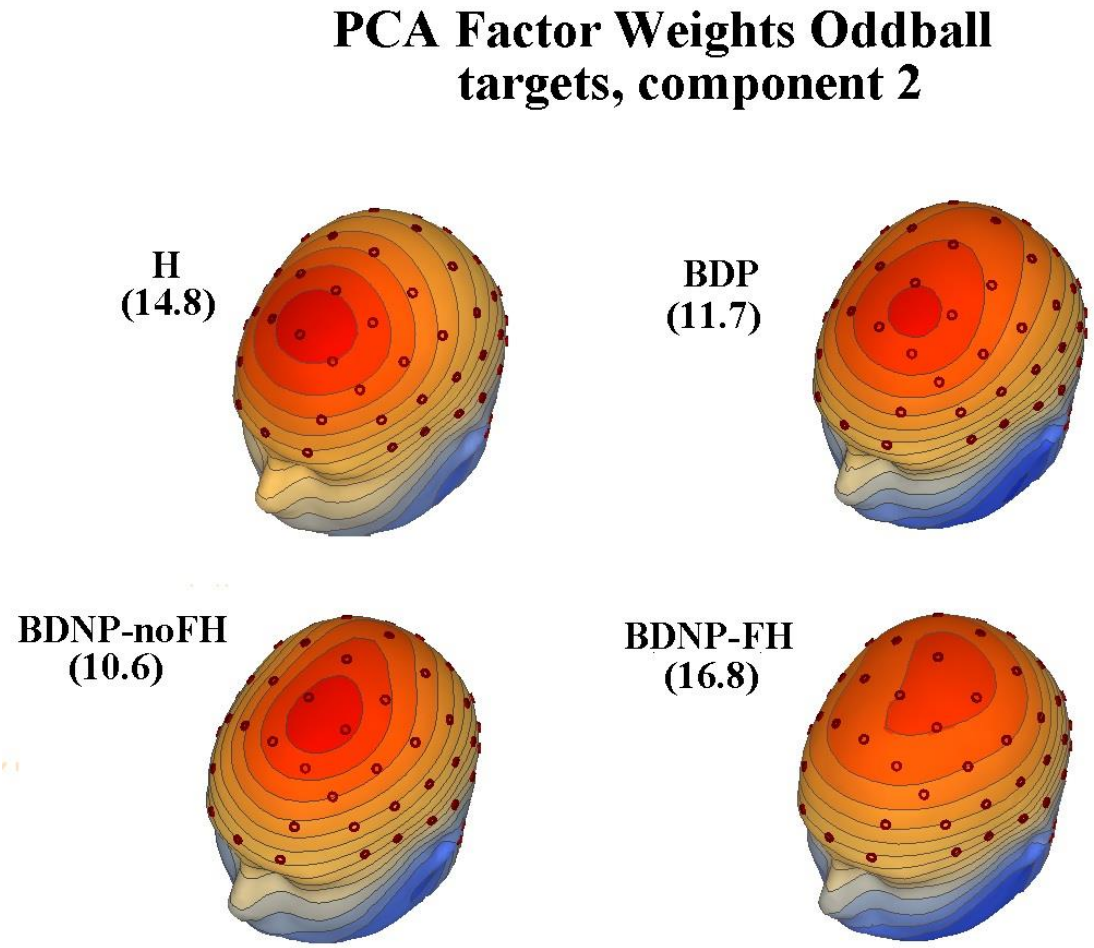

Figure 2.S6. Factor Weights Oddball Target-2: Factor weights (topographies) and percentage of total variance accounted for by the first factor (in parentheses) are displayed for each group's spatial PCA. Factor weights and variance percentages are nearly identical, all intercorrelating greater than r=.90 and correlating with the overall group result greater than r=.95, justifying a sample wide PCA.

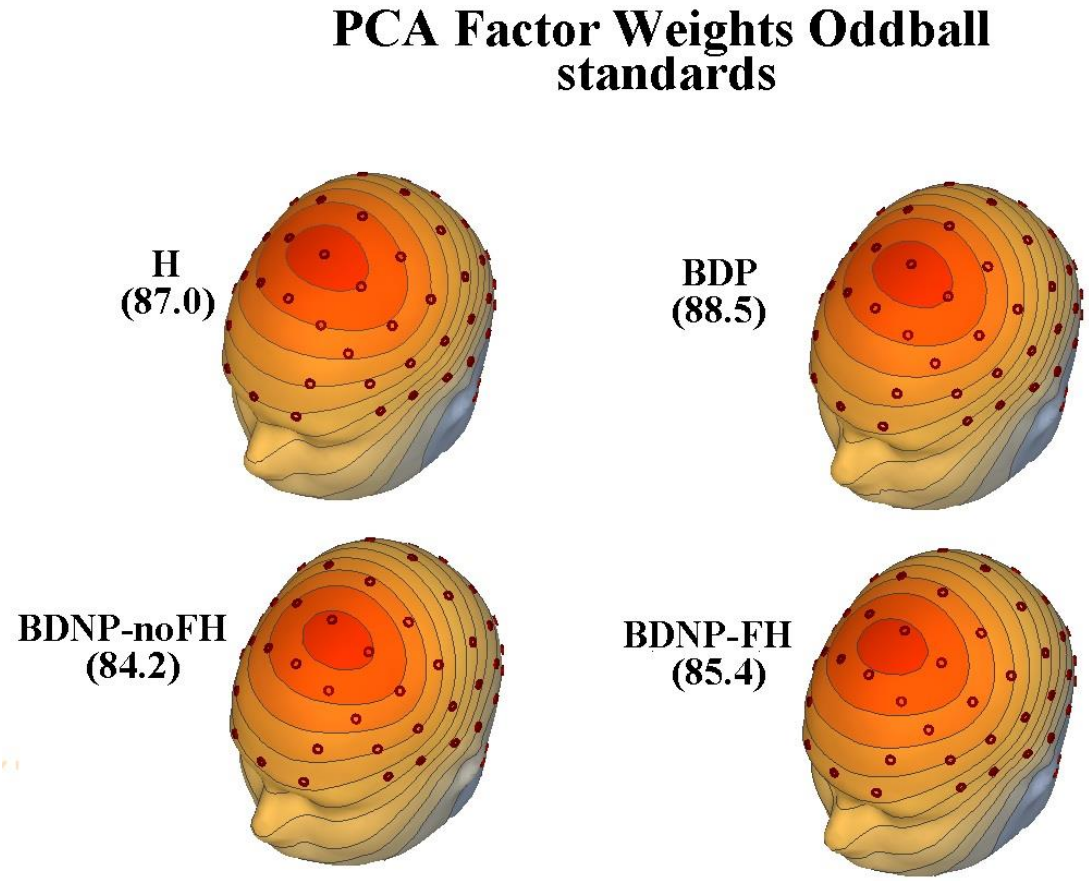

Figure 2.S7. Factor Weights Oddball Standard: Factor weights (topographies) and percentage of total variance accounted for by the first factor (in parentheses) are displayed for each group's spatial PCA. Factor weights and variance percentages are nearly identical, all intercorrelating greater than r=.90 and correlating with the overall group result greater than r=.95, justifying a sample wide PCA.

CHAPTER 3

DIAGNOSTIC SPECIFICITY AND FAMILIALITY OF EARLY VERSUS LATE EVOKED POTENTIALS TO AUDITORY PAIRED-STIMULI ACROSS THE SCHIZOPHRENIA-BIPOLAR PSYCHOSIS SPECTRUM[1]

[1]Hamm, J.P., Ethridge, L.E., Boutros, N.N., Keshavan, M.S., Sweeney, J.A., Pearlson, G.D., Tamminga, C.A., Clementz, B.A. 2013. Submitted to *Psychophysiology*, 10/18/13

Abstract

Disrupted sensory processing is a core feature of psychotic disorders. Auditory paired-stimuli (PS) evoke a complex neural response, but it is uncertain which aspects reflect shared and/or distinct liability for the most common severe psychoses, schizophrenia (SZ) and psychotic bipolar disorder (BDP). Evoked time-voltage/time-frequency domain responses quantified with EEG during a typical PS paradigm (S1-S2) were compared among proband groups (SZ [n=232], BDP [181]), their relatives (SZrel [259], BDPrel [220]) and healthy participants (H [228]). Early S1-evoked responses were reduced in SZ and BDP, while later/S2 abnormalities showed SZ/SZrel and BDP/BDPrel specificity. Relatives' effects were absent/small despite significant familiality of the entire auditorineural response. This pattern suggests general and divergent biological pathways associated with psychosis yet may reflect complications with conditioning solely on clinical phenomenology.

Introduction

The most recent version of the Diagnostic and Statistical Manual of Mental Disorders continues the Kraepelinian tradition (Kraepelin, 1919) by distinguishing bipolar I disorder with psychosis (BDP) and schizophrenia (SZ) as categorical diseases despite substantial BDP-SZ overlap and non-trivial within group heterogeneity on genetic disease risk (Craddock, O'Donovan, & Owen, 2009; Goes, Sanders, & Potash, 2008; Tamminga et al., 2013), clinical characteristics (Keshavan, Morris, et al., 2011; Tamminga et al., 2013), and biological profiles (Emsell & McDonald, 2009; Henry & Etain, 2010; Keshavan, Nasrallah, & Tandon, 2011; Nenadic, Gaser, & Sauer, 2012; Thaker, 2008). This distinction, therefore, may complicate understanding of etiology and disease processes underlying psychosis. Validation of empirically derived state-independent psychosis-related phenotypes may provide a valuable complimentary approach. Optimally, such phenotypic markers are heritable, index liability for illness, and are theoretically more proximal to gene transcription ("endophenotypes") (Gottesman & Shields, 1973) so provide a promising scaffold for unraveling the complex etiologies of psychosis pathology (Insel & Cuthbert, 2009). Given what is known about genetic risk for BDP and SZ (Smoller et al., 2013), one would expect to identify some measures that are unique to BDP, some unique to SZ, and some capturing shared BDP-SZ risk. The Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) (Tamminga et al., 2013) study, from which this project is derived, was specifically constructed to address these issues.

Disruptions in the neural substrates of basic auditory stimulus registration and expectation have been studied extensively in psychosis using auditory paired-stimuli (or P50 gating) paradigms (Light & Braff, 1999). In the simplest version of this paradigm, identical auditory "clicks" are presented in close succession (500 ms), with stimulus pairs separated by

long intervals (6–10 s). Evoked brain responses to the first (S1) and second (S2) stimuli are measured with electroencephalography (EEG), and larger differences between S1 and S2 responses have been reported for healthy subjects than those with SZ or BDP (Brockhaus-Dumke, Mueller, Faigle, & Klosterkoetter, 2008), caused by either larger ERPs to S2 (Sánchez-Morla et al., 2008) and/or an attenuated response to S1 (Clementz & Blumenfeld, 2001) among cases. Such abnormalities have been associated with low affinity nicotinic (Adler, Hoffer, Griffith, Waldo, & Freedman, 1992) and adrenergic receptor function (Adler et al., 1994), their underlying genetic promoters (Martin et al., 2007), yield possible links between the auditory paired-stimuli markers and biological mechanisms.

Traditionally, studies of auditory paired-stimuli processing in psychosis have focused on P50 and N100 peaks to S1 and S2 (positive/negative deflection at 50ms and 100ms, respectively) at a single vertex sensor (Cz). Wide variation in findings and effect sizes have been noted (Chang, Arfken, Sangal, & Boutros, 2011; de Wilde, Bour, Dingemans, Koelman, & Linszen, 2007), perhaps ultimately impeding the maturation of these biomarkers into clinically useful tools. Contemporary work has highlighted that neurophysiological understanding is augmented by broadening the spatial (scalp distribution) (Clementz & Blumenfeld, 2001) and temporal extent of data analyses (Clementz, Dzau, Blumenfeld, Matthews, & Kissler, 2003), and through inclusion of time-frequency domain information. For instance, Hamm et al (2012) identify in both BDP and SZ (i) reduced early auditory evoked responses 50-300ms after S1 in the context of (ii) augmented pre-stimulus gamma-band power, perhaps indicating a psychosis-related basic signal-to-noise ratio disruption in thalamo-cortical or sensory cortico-cortical circuits (Hamm, Ethridge, et al., 2012). In later time ranges, SZ were differentiated from BDP and healthy subjects by a shallower recovery function immediately prior to S2-onset and more positive-going

neural activations post-S2 (including the S2-P50), while BDP were unique in more excessive beta-band oscillatory power, perhaps indicating that more subtle deviations in cortical facilitation or sensorimotor excitability serve to differentiate these diagnoses.

Attempting to more fully capture the complexities of brain responses would be useful for sorting out specificity and overlap within clinical SZ and BDP diagnostic domains and may ultimately provide a powerful tool understanding the neurophysiological disease mechanisms associated with psychosis. If early and late auditory cortical response deviations yield biomarkers of psychopathological relevance, there should be evidence of familiality and similar subgroup separation among both proband groups and their family members. The current investigations specifically investigated these predictions using spatio-temporal and frequency domain analyses of auditory paired-stimuli data with large samples of SZ and SZrels, BDP and BDPrels, and healthy persons collected as a part of the B-SNIP project.

Methods

Subject recruitment, interviews, and EEG data recording were completed at B-SNIP consortium sites: Baltimore, Chicago, Dallas, Detroit/Boston, and Hartford (full details on recruitment and clinical and demographic characteristics are available in Tamminga et al, 2013). Clinically stable participants were recruited from the community, linked community facilities and programs, community advertisement, and local National Association on Mental Illness (NAMI) or NAMI-type groups. Medical history was acquired and participants were administered the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) diagnosis (patient or non-patient version as appropriate). Persons meeting a DSM-IV diagnosis of SZ or BDP were rated on the Positive and Negative Symptom (PANSS) (Lançon, Auquier, Nayt, & Reine, 2000), Young Mania Rating (YMRS) (Young, Biggs, Ziegler, &

Meyer, 1978), Montgomery-Asberg Depression Rating (MADRS) (Montgomery & Asberg, 1979), and Global Assessment of Functioning (GAF) scales by trained master's or doctoral-level nurses, psychologists, or psychiatrists. First-degree relatives of SZ (SZrel) or BDP (BDPrel) recruited for the study were additionally administered the Structured Interview for DSM-IV Personality Disorders (SIDP-IV) (Zanarini, Frankenburg, Sickel, & Yong, 1996) to evaluate psychosis spectrum personality traits/disorders. Exclusion criteria included serious medical, neuro-opthalmological, or neurological illness, mental retardation, head trauma with >30 min unconsciousness, current substance use ascertained by history and urine drug screens on the day of testing, abuse in the past 3 months, dependence within 6 months, or extensive history of drug dependence. Healthy persons (H) were absent lifetime psychotic disorder or a history of psychotic or bipolar disorders in their first degree relatives according to Family History Research Diagnostic Criteria (Andreasen, Endicott, Spitzer, & Winokur, 1977). This paper includes 1120 total subjects[a]. Age, sex, site distributions, and clinical scores are presented in Table 1. Among those with SZ, all but 40 were taking psychotropic medications. Among those with BDP, 24 were free of such medication. Detailed information regarding medication is presented in supplementary Table S1. The interested reader is referred to Tamminga et al (2013) for complete details on clinical procedures and information.

Stimuli

Recording conditions were equivalent and stimulus presentation and recording equipment identical across sites and intersite reliability maintained (Tamminga et al., 2013). A previous publication established absence of site effects (Hamm et al., 2012). While seated in a sound and electrically shielded booth (ambient sound=61-63 dB; luminance=0.11-0.12 foot-candles) subjects passively listened to 150 binaural broadband auditory click pairs (4ms duration at 75dB

[a] Data from 180 of the subjects (H and probands only) appeared in *Hamm et al (2012) Psychophysiology 49:522-30.*

sound pressure level; 500ms inter-click interval) occurring an average of every 9.5 sec (9-10 sec inter-pair interval) and delivered by two 8-ohm speakers located 50 cm in front of them. Participants who were smokers refrained from smoking 1 hour prior to testing.

Recording

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

Data 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). Data were converted to an average reference and digitally bandpass filtered from 0.5–55 Hz (zero phase filter; rolloff: 6 and 48 dB/octave, respectively). Blink and cardiac artifacts identified using Independent Components Analysis were removed (EEGLAB 9.0) (Delorme & Makeig, 2004). Data were segmented into epochs from 100ms before to 850ms after click-pair onset. The 100ms pre-S1 period served as baseline. Epochs containing activity greater than 75 μV were eliminated. Subjects with fewer than 60% of total trials accepted (<90 trials) were not included in further analyses (3 H, 3 SZ, 2 BDP, 4 SZrel, 5 BDPrel; final group numbers in Table 1). Total trials used did not significantly differ between groups (Table 1). Data from good trials were averaged across trial-types within a subject to create 64-sensor ERPs.

Spatiotemporal data reduction

In order to maximize use of available spatial, temporal, and oscillatory information in the evoked auditory response, a frequency-wise PCA of evoked power (Ivleva et al., 2013) was first conducted across all subjects to define frequency bands for analysis (see Supplemental Methods): i) LOW, 4-16Hz, ii) BETA, 17-33 Hz, and iii) GAMMA, 34-55Hz. Next a spatial PCA (Carroll et al., 2008; Dien, Khoe, & Mangun, 2007; Hamm, Ethridge, et al., 2012) was completed on the broadband grand averaged ERP waveforms (for traditional ERP analyses) and then once for each frequency band (see Supplemental Methods for details). Figure 1a-1d displays sPCA weights (topographies) for each waveform (ERP-voltage, LOW, BETA, and GAMMA). Weights were then multiplied by multisensor broadband ERP waveforms at each timepoint and summed across sensors, yielding a single "virtual sensor". An additional step for LOW, BETA, and GAMMA involved convolving the virtual sensor with modified-Morlet wavelets (4-55Hz, 4ms steps, 1 cycle at lowest to 8 cycles at highest) (Ethridge et al., 2012; Hamm, Dyckman, McDowell, & Clementz, 2012a; Hamm, Ethridge, et al., 2012) to derive oscillatory power waveforms for each frequency bin (Supplemental Methods). For BETA, 2 sPCA components were derived; weighted averages of the 2 power waveforms were summed to derive a single waveform for analysis. This resulted in 4 sets of component scores (Figure 1e-1h) that were analyzed instead of 64 separate sensors, efficiently summarizing the spatial distributions, minimizing the number of statistical comparisons necessary, and maximizing the signal/noise ratio of the ERP data (Carroll et al., 2008; Clementz & Blumenfeld, 2001; Ethridge et al., 2012; Hamm, Ethridge, et al., 2012).

Waveform Group Comparisons

As an initial step to determine time-voltage and time-frequency periods of psychopathological interest while considering possible age and gender effects between groups (Table 1), comparisons were completed as follows. First, healthy aging effects were modeled by regressing time-bin amplitudes on age for H. When beta coefficients for age effects were significant ($p<.05$), data for all subjects within the time-bin were adjusted by removing the predicted impact of age on waveform amplitude prior to group comparisons (Dukart, Schroeter, & Mueller, 2011). Healthy aging effects were equivalent between genders, generally small (all $r^2<.14$), and were scarcely significant except for P50 and early LOW amplitudes (<100ms) to S1/S2. Data from each of the 4 waveforms (ERP-voltage, LOW, BETA, GAMMA) were then grouped into 10ms bins and averaged within each bin across the entire epoch (95 separate bins per waveform). 3X2 ANOVAs (DX by GENDER) were calculated to determine H versus proband differences and group-by-gender interactions on waveform amplitudes. To account for significant effects due to a small number of large voltage values within a bin, non-parametric probability estimates were calculated via a bootstrap procedure. Monte-Carlo simulations determined that 2 adjacent time-bins significant at $p<.005$ or 3 at $p<.01$ was required to maintain family-wise alpha at $p<.01$ (see Supplemental Methods for details). Data from significant time-bin clusters were extracted for an analysis of independence and examination of H versus relative effects.

Variable reduction and relatives analysis

To efficiently summarize variables that uniquely discriminated proband and H (constituting unique candidate psychosis-related biomarkers), values from consecutive significant time-bins were averaged for each subject and submitted to linear discriminant

analysis with group as the dependent variable (H, SZ, BDP). Variables minimizing the overall Wilks' lambda with individual multiple F-statistics significant at $p<.01$ were entered in a stepwise fashion (Mardia, Kent, & Bibby, 1980), leaving a parsimonious selection of neurophysiological measures (Ethridge et al., 2012; Hamm, Ethridge, et al., 2012). Next, effect sizes comparing each proband and relative group to H were examined for each of the surviving variables. Glass's Δ, means, and standard deviations for all groups are reported in Table 2. Significance was assessed based on bootstrapped 95% confidence intervals. Initially, SZrel and BDPrel group statistics in Table 2 were computed including individuals with (i) history of any psychosis spectrum disorder (SZrels=31, BDPrels=18) and (ii) meeting all or all but one criterion for an Axis II Cluster A or B personality disorder (SZrel=52, BDPrel=36). Computed means, SDs, and effects sizes effects for relatives after excluding (i) and then (i + ii) are displayed in Supplemental Table S2.

Finally, to identify how EEG variables interrelate in their descriptions of group differences, multivariate functions were calculated with a canonical discriminate analysis (CDA). CDA is similar to PCA but uses pooled within-group covariance matrices and pits group means as variables and measurements as observations (Kshirsagar, 1972; Lawley, 1959). Thus, the n^{groups}-1 components (or functions) are extracted (in our case, 2) which are uncorrelated and maximize group differences. For each function, means and standard deviations were calculated and distributions were plotted for each group as a linear frequency plot (Figure 2).

Familiality Analyses

Because strong claims of traditional genetic heritability in the current sample are problematic given the absence of monozygotic twin pairs or second-degree relatives (Kendler & Neale, 2009), the more conservative term 'familiality' was chosen to refer to the degree to which

ERP measures are predicted by family membership. Familiality was assessed in proband-relative pedigrees via h^2_r estimates calculated using SOLAR [Sequential Oligogenic Linkage Analysis Routines (Almasy & Blangero, 1998)]. This approach is the same used to report "heritability" in previous reports with the same kind of family sample (Turetsky et al., 2008). Total phenotypic variance was partitioned into additive polygenic and random environmental components. We assessed effects of age and sex on each phenotype, and, when significant, adjusted for their effects in the familiality analyses. Statistical significance of h^2_r was determined by comparing the log likelihoods between the polygenic model and the sporadic model, where the h^2_r was constrained at zero (Hong et al., 2008) (blacked out h^2_r bins in Figure 1e-1h represent $p>.01$).

Results

Proband Effects

Average waveforms for all H, SZ, and BDP (Figure 1e-1h) along with relatives and plots of p-values for DX main effects (upper color-strip below waveforms in Figure 1e-1h) reveal several time-bins that significantly differentiated groups. Seven separate bin-clusters exceeded adjusted $p<.01$ for the ERP-voltage waveform:

1. S1_N100: 70 to 130ms after S1, peaking at 105ms, $F(2,627)=14.6$.
2. S1_P200: 200 to 260ms, peaking at 235ms, $F(2,627)=14.6$.
3. pre_S2: 420 to 510ms, peaking at 465ms, $F(2,627)=11.4$.
4. S2_P50: 530 to 600ms, peaking at 555ms, $F(2,627)=15.4$.
5. S2_N1/P200: 600 to 710ms, peaking at 685ms, $F(2,627)=9.00$.
6. S2_N200: 730 to 750ms, peaking at 735ms, $F(2,627)=6.28$.
7. S2_late: 770 to 850ms, peaking at 785ms, $F(2,627)=13.1$.

Four periods reached threshold for oscillatory power waveforms:

1. LOW_early: 40 to 160 ms after S1, peaking at 105ms, F(2,627)=14.4.
2. LOW_mid: 260 to 310ms, peaking at 275ms, F(2,627)=7.46.
3. BETA_early: 40 to 90ms, peaking at 55ms, F(2,627) =5.76.
4. preS1_GAMMA: -100 to -70ms, peaking at -85ms, F(2,627)=9.80.

No time-bins had significant DX by GENDER interactions. Adding a collection site factor revealed no group-BY-site interactions.

Discriminant Analysis

Linear discriminant analyses using the 11 variables with significant effects indicated that 5 of these variables explained unique group discrimination variance, thereby accounting for the between group variance explained by the 11 significant effects: preS1_GAMMA, N100_S1, LOW_early, P200_S1, and P50_S2. Group comparisons meeting significance level are bolded in Table 2.

Prior to S1, SZ and BDP had higher baseline GAMMA amplitude than H with similar effect sizes (Table 2). Amplitudes of N100_S1 and LOW_early were significantly reduced in both proband groups compared to H but with larger effect sizes in SZ than BDP (75%-115% larger). None of these measures showed significant reductions in relatives (all Glass's Δ<0.17/>-0.17).

Amplitudes of the S1_P200 were also reduced in both proband groups but showed the opposite pattern: BDP effect sizes were 75% larger than SZ. Relatives of BDP, but not of SZ, showed significant reductions of S1_P200. This effect was attenuated, but was still statistically significant, by exclusion of relatives with history of psychosis, dropping the effect size from -0.21 to -0.18.

SZ and BDP both deviated from H on S2_P50, but SZ had significantly more positive amplitudes than H in this time range while BDP were significantly more negative. Importantly, relatives of SZ also had more positive S2_P50 amplitudes than H (Δ=.21); this effect remained unchanged after the exclusion of subjects with psychosis and axis II personality disorder history (Δ=.22). BDPrel did not deviate from H in this time range.

Multivariate Canonical Analysis

The 5 variables surviving discriminant analysis were used to construct the 2 CDA functions, each of which significantly reduced Wilke's lambda estimates for overall variance ($p<.001$) (Lawley, 1959). Loadings (correlation) for the remaining variables describe the nature of the extracted functions (Table 3). The first function, called "Early ERP", was most heavily associated with activity before 300ms post-S1, including N100, lower frequency evoked amplitude (LOW_early/mid, BETA_early), and prestimulus GAMMA activity. For probands, this function showed a pattern of H>BDP>SZ, while relative groups were intermediate. The second function, called "Late ERP", was associated with ERP-voltage activity after 300ms post-S1, including the pre-S2 recovery (negativity) and the S2_P50. For probands and relatives, this function showed pattern of BDP(rel)<H<SZ(rel). Interestingly, the S1_P200, being intermediate in latency, loaded equally on both functions (Table 3).

Use of SKUMIX (Hamm, Dyckman, Ethridge, McDowell, & Clementz, 2010; Maclean, Morton, Elston, & Yee, 1976), which employs a maximum likelihood approach to test for significant skewness and multimodality, identified that both SZ and BDP distributions for the multivariate early ERP function were skewed ($\gamma^{SZ}=0.87$; $\gamma^{BDP}=0.56$), but not multimodal.

Familiality

Amplitudes of all waveforms displayed consistently significant h^2_r estimates throughout (lower color strip below waveforms in Figure 1e-1h). h^2_r in the current context indexes the proportion (bounded from 0.0-1.0) of phenotypic variance not due to age or gender that is attributable to factors shared with first degree relatives. For ERP-voltage waveforms, most time-points in the P50/N100/P200 complex to both S1 and S2 had significant h^2_r ranging from .2 to .5 and peaking in the early P200 range to S1 (h^2_r =.49) and again in the N100 range to S2 (h^2_r =.40).

LOW frequency waveforms showed significant h^2_rs across the entire epoch post-trial onset. The largest h^2_rs for this frequency band coincided with peak amplitude values to S1-onset (120-200ms) and reflected a substantial level of familiality (peak h^2_r=.59). BETA frequency waveforms showed significant h^2_rs for most post trial-onset timepoints. The largest h^2_rs for this frequency band coincided with (i) the S1-onset amplitude increase (-20-150ms) peaking at h^2_r=.59 at 140ms, and (ii) post-S2 amplitude peak (30-70ms) peaking at h^2_r=.66. Overall, LOW frequency amplitude peaks to S1 and BETA frequency amplitude peaks to both S1 and S2 showed the greatest familiality. GAMMA frequency waveforms showed h^2_rs that were more similar to ERP-voltage h^2_rs. Early timepoints post-S1 and S2 (in the vicinity of amplitude peaks) showed significant h^2_r in the low to moderate range (.2-.45).

Discussion

The current investigation comprehensively leveraged EEG information to detail abnormalities of basic auditory neural processing in large samples of SZ and BDP groups. The strongly familial ERP deviations neither perfectly separated psychotic subgroups nor conclusively united them, suggesting the same pattern of complex inheritance reported in recent large scale genetic studies (Owen, 2012; Smoller et al., 2013). Multivariate analyses indicated

that early peaks and low frequency oscillations constituted a broad, shared neuropathology between SZ and BDP, while late, slow developing neural activities showed both disease specificity as well as the strongest differentiation of relative subgroups.

Reduced N100 to S1 is one of the most replicated heritable biomarkers of psychosis (Rosburg, Boutros, & Ford, 2008; Turetsky et al., 2008) and indexes disruption of early sensory cortical feed-forward circuitry (Hamm, Gilmore, Picchetti, Sponheim, & Clementz, 2011; Sweet et al., 2007) that may underlie disordered perception (Heinks-Maldonado et al., 2007). The current results reiterated N100's psychosis pertinence and familiality, abnormality in BDP, and overlap and differentiation from low frequency evoked oscillations in the same time range. Although N100 and low frequency evoked oscillations to S1 did share similar group discriminations, the results of the linear discriminant analysis highlight that each captures some degree of unique pathology variance. Compared to the temporally and spatially more focal N100 indexing primary/secondary auditory cortical registration of a stimulus (Godey, Schwartz, de Graaf, Chauvel, & Liégeois-Chauvel, 2001; Yvert, Fischer, Bertrand, & Pernier, 2005) low frequency evoked oscillatory power may encompass the spread of information across a spatially more broad cortical network (Kopell, Ermentrout, Whittington, & Traub, 2000). Early S1 ERPs also showed SZ effects that were 75-115% larger than BDP, echoing previous findings (Hamm, Ethridge, et al., 2012; Ivleva et al., 2013), dimensional conceptualizations of psychosis (Ivleva et al., 2012), and supporting an additive inheritance model for early auditory psychosis biomarkers.

These N100 and low frequency effects were not present among relatives, departing from some (Hall, Taylor, Salisbury, & Levy, 2010; Hong et al., 2008; Turetsky et al., 2008) but not all, previous studies (Waldo, Adler, & Freedman, 1988; Winterer, Egan, Rädler, Coppola, & Weinberger, 2001). Both measures, along with similar BETA effects in the same time range,

however, did show substantial familiality, with evoked beta and LOW oscillations approaching h^2_r=.60. This discrepancy between familiarity and lack of statistical effects among relatives begs for clarification. One possibility is that early auditory processing phenotypes follow a relatively complex genetic inheritance, with some relatives at risk for, but not expressing, psychosis demonstrating enhanced auditory cortical circuitry as a protective factor (see, e.g., Hamm et al., 2013).

Prior to the onset of S1, both SZ and BDP displayed augmented gamma band power that covaried with diminished N100 and evoked low frequency oscillations. Increased intrinsic high frequency activity is a common finding in psychotic populations (Reinhart, Mathalon, Roach, & Ford, 2011; Rolls, Loh, Deco, & Winterer, 2008; Spencer, 2011), theorized to indicate reduced NMDA receptor modulation of inhibitory interneuron activity (Curley & Lewis, 2012; Hamm, Gilmore, & Clementz, 2012) and consequent disruption of signal to noise ratio (Rolls et al., 2008). Given that gamma was neither significantly augmented among relatives nor showed familiality, excessive gamma power may be related to disease expression and/or neural compensation in psychosis.

In contrast to intrinsic and basic auditory processing functions, later occurring evoked responses, which most likely index higher level cognitive and contextual processing, showed disease specificity in probands and relatives. First, the P200 peak to S1 was reduced in both SZ and BDP, but had a 75% larger effect size in BDP. P200 was also abnormal in BDPrel but not SZrel, and demonstrated significant familiality. While the precise relationship between auditory P200 and earlier ERPs is not well characterized, some evidence indicates independence of P200 and N100 sensitivity to arousal (Crowley & Colrain, 2004).

Second, the current results substantiate reduced pre-S2 negativity in SZ (Hamm, Ethridge, et al., 2012) but not BDP. While this effect has been uncommonly described in the paired-stimuli context, related impairments in top-down sensory cortical anticipation modulations, including impaired corollary discharge (Heinks-Maldonado et al., 2007), have been theorized to underlie sensory disruptions in SZ (Ford & Mathalon, 2012). Pre-S2 negativity, however, was not abnormal in SZrel and did it demonstrate substantial familiality, suggesting that it marks some aspect of SZ disease expression rather than risk. Finally, responses to S2 in the P50 time range were more positive in both SZ and SZrel than H, replicating numerous previous paired-stimuli reports of augmented S2 evoked responses in SZ (Chang et al., 2011). The current findings nonetheless add nuance when considered in context of the overall evoked response. BDP/BDPrel diverged significantly from SZ/SZrel in this time range but had more negative voltage throughout the post-S2 time period. In addition, when considered in the context of a higher pre-S2 baseline among SZ, it is uncertain whether the more positive voltage P50-range responses among SZ are best described as indexing poor stimulus filtering. In contrast to early ERPs, however, these later occurring deviations highlight SZ and BDP-specific alterations in cortical responses and may be indexing distinct inherited biomarkers for these psychoses (Gottesman & Gould, 2003).

Medication effects are a concern for any study comparing different diagnostic groups. These groups nonetheless showed more similarities than differences in medication treatment, a feature that likely reflects the similarities in psychosis manifestations. Most late ERP effects in the current study demonstrated both familiality and reductions in unmedicated, non-symptomatic relatives, undergirding the utility of these measures in future etiological studies and ruling out a pure medication-based explanation. Exclusion of psychosis history and axis II pathology mostly

did not significantly alter the early or late ERP means for SZrel or BDPrel, indicating that comorbid pathology does not likely account for the relatives effects. A remaining limitation of the current study is the age difference between relatives groups and H. Age effects were modeled in healthy subjects and applied, when statistically significant, to the entire sample to adjust for these discrepancies. Future efforts should be made to include more siblings and, further, to include unaffected monozygotic twins to directly assess heritability instead of simply familiality.

The current report examined complete time-voltage and time-frequency waveforms using information from the entire scalp in a parsimonious manner via spatial-PCA aided data reduction and tie binning. This empirically driven, comprehensive approach deviates from traditional auditory paired-stimuli studies of psychosis that have focused primarily on magnitudes and difference/ratio scores of P50 and N100 peaks, employing a series of data processing steps and filtering prior to peak measurements. In order to allow a more direct comparison of the current data set with previous reports, we scored P50 gating with the historical procedure (Olincy & Martin, 2005) and the less often studied N100 gating with the procedure employed by the Consortium on the Genetics of Schizophrenia (Turetsky et al., 2008) and others [(Rentzsch, Jockers-Scherübl, Boutros, & Gallinat, 2008); see Supplemental Methods]. A few outcomes of these analyses are worthy of note (see Supplemental Tables S3 and S4). The identification of a S1-N100 peak reduction in SZ and SZrel, along with significant familiality for this measure and a significant S1-S2 difference in probands but not relatives corroborates previous reports (Turetsky et al., 2008), and suggests, through an attenuation of effects in BDP/BDPrel, a specificity toward non-affective psychosis for these abnormalities (Hamm et al., 2012). S1-P50 peak reductions were present in SZ with small effect sizes (Δ=-.196) and were heritable as traditionally reported (Brenner et al., 2009; Chang et al., 2011; Clementz & Blumenfeld, 2001;

Thaker, 2008), yet proband and relatives effects with regard to S2-P50 amplitudes, S2/S1 ratio, and S1-S2 difference scores showed largely nonsignificant deviations from H. Psychosis P50 gating abnormalities have traditionally shown variability across reports and specific metrics, perhaps due to methodological variance (Chang et al., 2011; de Wilde et al., 2007).

The combination of early evoked response deviations shared between psychosis subgroups and later, slow, and S2 voltage deviations differentiating affective from non-affective psychoses provides clues towards the underlying neuropathology of SZ and BDP along with a more narrow, detailed set of targets for future genetic and epidemiological studies. Examinations of multivariate composite measures highlighted clear heterogeneity and overlap present both within and between these diagnostic categories (e.g. probands in Figure 2). This pattern of deviations together with the strong familiality of these measures at once suggest the utility of auditory neurophysiological phenotypes while highlighting the challenge significant biological heterogeneity poses to research in the context of the current diagnostic systems. Future studies that cut across multiple psychotic and non-psychotic diagnostic groups, and that seek to identify homogenous patient groups with respect to these familial auditory neurophysiological phenotypes, may be fruitful (Kapur, Phillips, & Insel, 2012; Keshavan, Clementz, Pearlson, Sweeney, & Tamminga, 2013).

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Author Notes

This work was supported by grants from the National institutes of Health (R01s MH077945, MH077862, MH077851, MH078113, and MH085485). Author JAS has served as a consultant for Takeda, Inc., Pfizer, Inc. Roche, and Eli Lilly Pharmaceuticals and has received grant funding from Janssen, Inc. Author GDP has served as an Ad Hoc Consultant for Bristol-Myers Squibb. Author CAT served on an advisory board for Intracellular Therapies (ITI, Inc) and as an Ad Hoc consultant for PureTech Ventures, Sunovion, Astellas, and Merck. Author MSK has received a grant from Sunovion. All other authors report no biomedical financial interests or potential conflicts of interest.

Table 3.1: Subject Demographic and Clinical Data. HU, Harvard University; UIC, University of Illinois, Chicago; YU, Yale University; UTS, University of Texas Southwestern; UM, University of Maryland; GAF, Global Assessment of Functioning; PANSS, Positive and Negative symptom; MADRS, Montgomery-Åsberg Depression Rating Scale ; APS, antipsychotic medication. Symptom scores are provided for probands and the subset of relatives of SZ and BD with a lifetime history of psychosis.

	H	**SZ**	**BDP**	**SZrel**	**BDPrel**
Subjects in analyses (# of females)	225 (131)	229 (78)	179 (109)	255 (171)	215 (139)
Age	37.40 (12.5)	35.11 (12.7)	36.13 (12.8)	43.52 (15.4)	40.40 (15.7)
HU (# of females)	53 (30)	39 (14)	23 (16)	39 (27)	17 (13)
UIC (# of females)	67 (37)	49 (19)	64 (44)	66 (47)	89 (57)
UM (# of females)	21 (16)	61 (19)	37 (20)	50 (21)	41 (30)
UTS (# of females)	38 (24)	26 (11)	19 (11)	29 (19)	22 (11)
YU (# of females)	46 (24)	54 (15)	36 (18)	71 (47)	46 (28)
Trials used	138.7 (12.4)	137.4 (14.2)	138.5 (12.0)	140.9 (10.9)	139.0 (13.3)
GAF	86.71 (6.61)	49.22 (12.2)	60.87 (12.5)	74.13 (14.1)	75.86 (13.5)
PANSS-positive	-	17.01 (5.49, n=220)	12.61 (4.29, n=176)	*16.07 (5.14, n=30)*	*13.80 (5.80, n=25)*
PANSS-negative	-	16.98 (5.72, n=220)	12.13 (3.78, n=176)	*13.67 (4.27, n=30)*	*12.76 (4.88, n=25)*
PANSS-general	-	32.90 (8.88, n=220)	28.48 (8.02, n=176)	*30.70 (8.04, n=30)*	*31.00 (7.34, n=25)*
MADRS	-	8.850 (7.81, n=207)	10.71 (9.32, n=168)	*6.529 (8.05, n=51)*	*7.333 (8.29, n=39)*
Young Mania Scale	-	5.636 (5.81, n=221)	5.102 (5.80, n=176)	*3.608 (4.47, n=51)*	*4.155 (6.29, n=38)*

Table 3.2: Primary Effects. Means, standard deviations (above), and effect sizes (below) for simple comparisons of variables uniquely discriminating proband groups. Effects with bootstrapped confidence intervals (2.5% and 97.5%) not including zero are indicate by bold type and *.

		Pre-S1 GAMMA	**S1 N100**	**LOW early**	**S1 P200**	**S2 P50**
MEAN (standard deviation)	H	12.76 (4.90)	-1.85 (1.33)	46.70 (4.58)	1.39 (1.50)	-0.58 (0.82)
	SZ	14.52 (4.80)	-1.11 (1.42)	43.87 (5.69)	0.98 (1.29)	-0.39 (0.80)
	BDP	14.04 (4.71)	-1.43 (1.40)	45.38 (4.91)	0.67 (1.38)	-0.74 (0.80)
	SZrel	13.22 (4.98)	-1.70 (1.55)	46.26 (5.54)	1.27 (1.52)	-0.41 (0.95)
	BDPrel	13.58 (4.61)	-1.74 (1.48)	46.07 (5.29)	1.07 (1.56)	-0.57 (0.87)
Glass's Δ (vs H)	SZ	***0.36****	***0.557****	***-0.618****	***-0.271****	***0.232****
	BDP	***0.261****	***0.320****	***-0.288****	***-0.475****	-0.19
	SZrel	0.095	0.113	-0.095	-0.08	**0.207***
	BDPrel	0.167	0.089	-0.137	***-0.214****	0.009

Table 3.3: Canonical Functions. Above: loadings (correlations) for each canonical function with each ERP variable. Below: Means and standard deviations for each group and function. Bottom: Familialities for each function.

	Canonical Functions	
	1. Early ERP: loadings	**2. Late ERP: loadings**
LOW_early	0.70	-0.31
S1_N100	-0.70	0.19
preS1_GAMMA	-0.50	0.03
LOW_mid[b]	*0.45*	*-0.12*
BETA_early[b]	*0.34*	*-0.13*
S2_P50	0.18	0.69
S1_P200	0.51	0.53
S2_P200[b]	*0.03*	*0.56*
S2_late[b]	*-0.06*	*0.52*
preS2[b]	*-0.24*	*0.49*
S2_N100[b]	*-0.03*	*0.47*
Group	**1. Early ERP: Means (stdev)**	**2. Late ERP: Means (stdev)**
H	0.42 (1.04)	0.07 (0.95)
SZ	-0.31 (1.03)	0.22 (0.99)
BDP	-0.14 (0.90)	-0.36 (1.07)
SZrel	0.27 (1.07)	0.18 (1.09)
BDPrel	0.17 (1.07)	-0.02 (1.05)
Familiality (h^2_r)	0.31, p<.001	0.17, p<.05

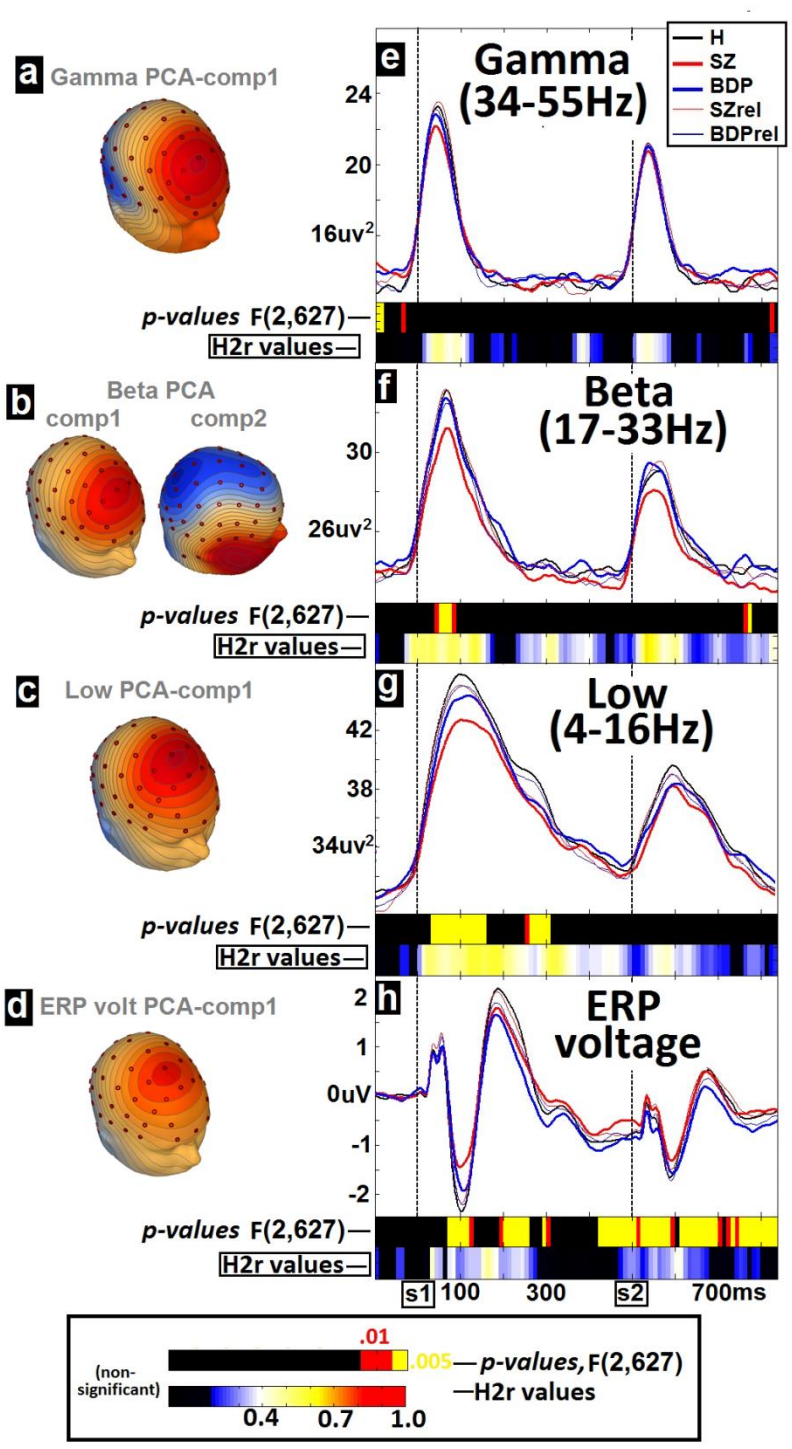

Figure 3.1: Waveform Comparisons. Left column (a-d): Spatial PCA component distributions for GAMMA, BETA, LOW, and ERP waveforms. Right column (e-f): Group average waveforms, SZ-BDP-H ANOVA p-values (above bar), and familiality values (h^2_r, below bar; e-f).

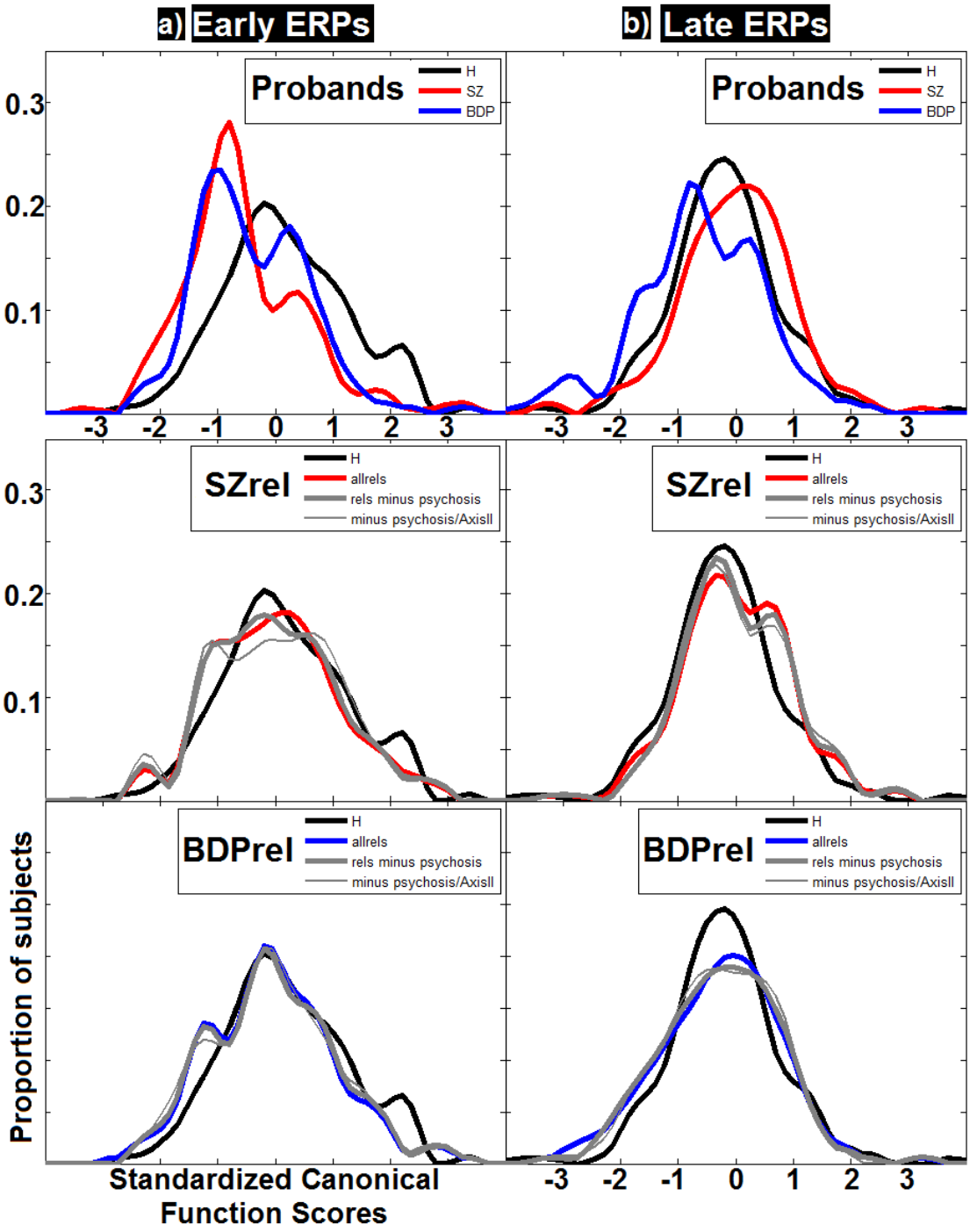

Figure 3.2: Frequency Plots of Canonical Functions. Proportion of the total group membership for probands (above) and each relative group (below; plotting also for exclusion of psychosis history and axis II pathology) for a) early and b) late ERP canonical functions.

Supplemental Methods

Frequency PCA

For each subject separately for each EEG channel, evoked oscillatory power for frequencies from 4 to 55 Hz was calculated in 1-Hz steps using a modified Morlet wavelet transformation every 4 ms (Ethridge et al., 2012; Hamm, Dyckman, McDowell, & Clementz, 2012; Hamm et al., 2012) on the grand averaged ERPs. The length of the wavelets increased linearly from 1 cycle at 4 Hz to 8 cycles at 55 Hz. In order to define frequency bins for analyses, power values for each subject and sensor were averaged across the entire epoch within each frequency (4-55Hz), yielding a matrix of 57 variables (frequencies) and nX64 observations (where *n* is the number of subjects). For each group, a PCA was carried out on the correlation matrix with promax (oblique) vector rotation and Kaiser normalization (Dien et al., 2007). Scree tests for each group identified three components accounting for greater than 90% of the variance across subjects and sensors. Resulting factor structures were essentially identical across all groups (see supplementary figure S1) so data from all subjects was included in a final PCA, identifying 3 components: i) LOW frequency band, 4-16Hz, ii) BETA frequency band, 17-33 Hz, and iii) GAMMA frequency band, 34-54Hz. This result altogether matches previously results from the current research group in the same paradigm with different subjects(Ivleva et al., 2013) and generally agreed upon cortically relevant frequency bands resolvable with EEG(Venables, Bernat, & Sponheim, 2009).

Spatial PCA

First, in addition to the broadband grand average "ERP voltage" waveform (64-channel ERPs averaged overall subjects), 3 separate grand average waveforms were created through the use of specifically tailored broadband filters (4^{th} order Butterworth type): LOW (median

frequency=10Hz, width 12Hz), BETA (mF=25 Hz, w=16Hz), and GAMMA (mF=44, w=20; see supplementary figure S1). For each waveform, a PCA with promax (oblique) vector rotation and Kaiser normalization (Dien et al., 2007) was calculated on the 64X64 sensor covariance matrix (time-points as observations). Scree tests were used in each case to determine the optimal number of components (Cattell, 1966). All sPCAs were completed first for each analysis group (H, SZ, BDP, SZrel, BDPrel). In all cases, the extracted number of components was identical, and intergroup correlations for sPCA weights were all above r=.95. This replicates a previous analysis done by the current group but with an age/gender/collection-site matched sample (Hamm, Ethridge, et al., 2012), suggesting that this sPCA method is robust at capturing basic aspects of the auditory neurophysiological response which are not affected by psychopathology.

For the grand sample ERP voltage sPCA a sole component with a frontal-central maximum (FCz) that accounted for 87.0% of the variance in waveforms across sensors (supplementary figure S1a). For the LOW frequency sPCA, a sole component with a frontal-central maximum (FCz) that accounted for 94.0% of the variance in waveforms across sensors (supplementary figure S1c). For the BETA frequency sPCA, two components were extracted. The first had a frontal maximum (Fz) that accounted for 72.9% of the variance in waveforms across sensors; the second had a parietal maximum (Pz) that accounted for 18.2% of the variance in waveforms across sensors (supplementary figure S1d). For the GAMMA sPCA a sole component with a frontal maximum (Fz) that accounted for 91.3% of the variance in waveforms across sensors (supplementary figure S1e). No additional components in any sPCA accounted for more than 10% of the total spatial variance across the waveforms.

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, reducing

waveforms from one for each sensor to one waveform per component for each subject for ERPs, LOW, BETA1, BETA2, and GAMMA (5 total). For LOW, BETA1, BETA2and GAMMA, time-frequency decomposition was reapplied to the virtual sensor waveforms, resulting in power waveforms (averaged within groups in figure 1a-d). Notably, for BETA band, 2 sPCA components were derived; therefore, a weighted average of the power values of the 2 components was computed within a subject to derive the "virtual sensor".

Bootstrapped parametric p-values for waveform comparisons

To control for aberrant significant effects due to a small number of large voltage values within a bin, F value distributions were created using a bootstrap procedure. For each condition and effect, the same one-way ANOVAs were run 5000 times with group membership randomly shuffled at each step (sampling with replacement). Non-parametric probability estimates (p) of observed F values were then calculated as the proportion of randomly generated F values greater than the actual estimate (Figure1e-h). To control for family-wise error due to multiple comparisons, a clustering method was implemented using Monte Carlo simulations calculated across time-bins using AlphaSim (Forman et al., 1995; Hamm et al., 2012); this procedure identified a criterion of two sequential time-bins significant at $p<.005$ or 3 at $p<.01$ was required in order to maintain a family-wise alpha of .01.

Traditional p50 and n100 gating analyses

To enable a more direct comparison of the current effects with the majority of past reports of p50 and n100 gating in psychotic patient groups, we conducted analyses using traditionally described methods. For analyses of the p50, methods mirrored that of Olincy et al (2005) and many others. Each subject's evoked potential waveform from the vertex sensor (Cz) was bandpass filtered from 10 to 55 Hz. A 7-point moving average was applied twice to smooth

the waveforms. The maximum value between 35ms and 75ms after the onset of each stimulus was marked as the peak, and amplitude was calculated relative to the preceding trough. For analyses of the n100, methods mirrored that of Turetsky et al (2008) and Rentschz et al (2007). Each subject's evoked potential waveform from the vertex sensor (Cz) was bandpass filtered from 0.5 to 55Hz and was baseline corrected relative to the 50 ms interval preceding each click. N100 amplitude was measured as the minimum trough occurring 75ms–135ms after each stimulus. Dependent measures for P50 and for N100 were amplitudes to S1 and S2, a ratio measure (1-(S2/S1)), and a difference measure (S1-S2). Subjects without a clear peak to S1, or with values exceeding +/- 5 standard deviations (a conservative threshold) were excluded from the analysis. When p50 and n100 peaks were absent to S2, a 0.0 uV was assigned (Rentzsch et al., 2008; Turetsky et al., 2008).

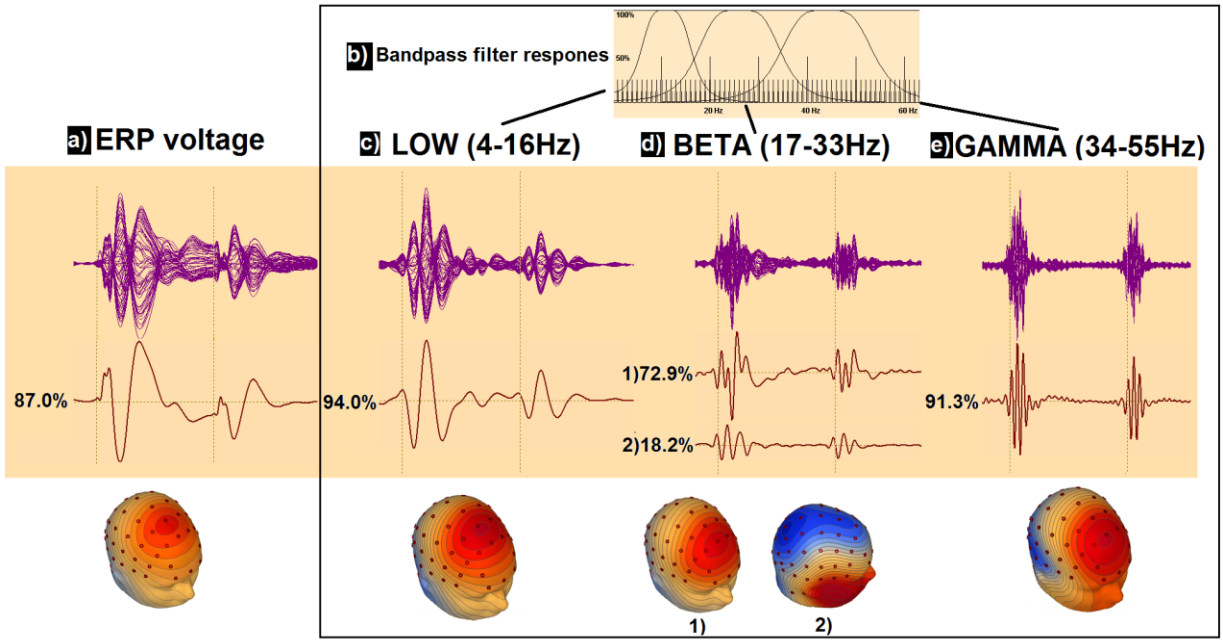

Figure 3.S1: Spatial PCA Results. PCA on grand averaged ERPs (a-top) reveal 1 component (a-bottom) accounting for 87.0% of the spatial variance of the ERP voltage waveforms across sensors. Bandpass filters (b) fit to grand averaged ERP in (a) reveal distinct waveforms for each frequency band (c-d, top). Spatial PCA results, virtual sensors, and percentage of spatial variance accounted for are displayed (c-d, bottom).

	SZ	BDP	SZ-rel	BDP-rel
Total (n)	229	179	255	215
Unknown Medication History	3	2	2	2
No Medication taken	6	6	71	61
Not on Psychotropic Medications	12	11	174	145
On more than one Psychotropic Medications	172	132	36	28
Anticholinergic/Antiparkinsonian	36	16	3	2
Antidepressant (Any)	93	76	47	38
A. Tricyclic	5	4	2	1
B. MAO Inhibitors	0	0	0	0
C. SSRIs/SNRIs	51	43	35	29
D. Miscellaneous	37	29	11	7
Antipsychotic (Any)	192	143	23	15
A. First Generation	45	15	2	1
B. Second Generation	170	127	21	14
Anxiolytic/Sedatives/Hypnotic	61	49	22	20
Mood Stabilizer (Any)	98	83	18	14
A. Lithium	10	49	3	3
B. Anticonvulsants	36	16	15	11
Miscellaneous, Psychotropic/Centrally Active	5	5	1	0
Stimulants	17	16	7	5

Table 3.S1: Medication Information. Number of subjects in each proband (SZ, schizophrenia; BDP, bipolar I disorder with psychosis) and relative group taking each medication type at the time of testing.

		Pre-S1 GAMMA	S1 N100	LOW early	S1 P200	S2 P50
MEAN (standard deviation)	H	12.76 (4.90	-1.85 (1.33)	46.70 (4.58)	1.39 (1.50)	-0.58 (0.82)
	SZrel	13.22 (4.98)	-1.70 (1.55)	46.26 (5.54)	1.27 (1.52)	-0.41 (0.95)
	SZrel[i]	*13.30 (4.94)*	*-1.73 (1.56)*	*46.33 (5.55)*	*1.27 (1.54)*	*-0.40 (0.96)*
	SZrel[ii]	*13.47 (4.74)*	*-1.79 (1.59)*	*46.52 (5.61)*	*1.22 (1.56)*	*-0.40 (1.03)*
	BDPrel	13.58 (4.61)	-1.74 (1.48)	46.07 (5.29)	1.07 (1.56)	-0.57 (0.87)
	BDPrel[i]	*13.60 (4.50)*	*-1.78 (1.50)*	*46.22 (5.31)*	*1.11 (1.58)*	*-0.59 (0.83)*
	BDPrel[ii]	*13.54 (4.38)*	*-1.76 (1.46)*	*46.03 (5.24)*	*1.11 (1.56)*	*-0.61 (0.82)*
Cohen's D (vs H)	SZrel	0.095	0.113	-0.095	-0.08	**0.207***
	SZrel[i]	*0.111*	*0.092*	*-0.081*	*-0.079*	***0.218****
	SZrel[ii]	*0.146*	*0.049*	*-0.038*	*-0.111*	***0.218****
	BDPrel	0.167	0.089	-0.137	**-0.214***	0.009
	BDPrel[i]	***0.173****	*0.054*	*-0.105*	***-0.183****	*-0.012*
	BDPrel[ii]	*0.161*	*0.069*	*-0.147*	***-0.183****	*-0.038*

Table 3.S2: Primary Effects in Relatives by Comorbidity Status. Means, standard deviations (above), and effect sizes (below) for simple comparisons of key variables of interest determine by linear discriminant analysis between healthy comparisons (H) and all relatives (SZrel, BDPrel), as well as subsets of relatives who were **(i)** free of lifetime history of psychosis and those who were **(ii)** free of both lifetime history of psychosis and current meeting of all or all-but-one criterion of an axis II personality disorder (cluster a or b). Effects with bootstrapped confidence intervals (2.5% and 97.5%) not including zero are indicate by bold type and *.

		S1	S2	Ratio Score	Difference Score
MEAN (standard deviation)	H (n=217)	1.033 (0.729)	0.593 (0.421)	0.128 (1.037)	0.440 (0.619)
	SZ (n=216)	0.890 (0.726)	0.506 (0.346)	0.100 (1.085)	0.384 (0.650)
	BDP (n=176)	0.932 (0.685)	0.616 (0.486)	0.133 (0.810)	0.316 (0.590)
	SZREL (n=245)	1.023 (0.734)	0.565 (0.382)	0.181 (0.995)	0.457 (0.663)
	BDPREL (n=207)	0.983 (0.773)	0.535 (0.366)	0.023 (1.309)	0.448 (0.670)
Glass's Delta	**SZ**	**-0.196***	**-0.205***	-0.027	-0.091
	BDP	-0.138	0.056	0.005	**-0.200***
	SZREL	-0.014	-0.065	0.052	0.028
	BDPREL	-0.068	-0.138	-0.101	0.014
Familiality h^2r		**.430***	**.234***	.123	**.330***

Table 3.S3: Traditional P50 Analysis. Means, standard deviations (above), and effect sizes (below) for simple comparisons of traditional P50 measures (S1 amplitude, S2 amplitude, 1-[S2p50/S1p50], and S1p50-S2p50). Effects with bootstrapped confidence intervals (2.5% and 97.5%) not including zero are indicate by bold type and *.

		S1	S2	Ratio Score	Difference Score
MEAN (standard deviation)	H (n=214)	-2.433 (1.625)	-1.205 (1.221)	0.483 (0.497)	-1.229 (1.444)
	SZ (n=202)	-1.726 (1.467)	-0.873 (1.026)	0.340 (0.945)	-0.854 (1.260)
	BDP (n=170)	-2.011 (1.460)	-1.102 (1.200)	0.391 (0.719)	-0.909 (1.369)
	SZREL (n=233)	-2.026 (1.522)	-1.005 (1.150)	0.407 (0.874)	-1.022 (1.354)
	BDPREL (n=206)	-2.167 (1.638)	-1.196 (1.142)	0.230 (1.045)	-0.972 (1.473)
Glass's Delta	**SZ**	**0.435***	**0.272***	-0.289	**0.260***
	BDP	**0.260***	0.084	-0.185	**0.221***
	SZREL	**0.250***	0.164	-0.154	0.143
	BDPREL	0.164	0.007	**-0.510***	0.178
Familiality h^2r		**0.330***	**0.211***	0.050	**0.203***

Table 3.S4: Traditional N100 Analysis. Means, standard deviations (above), and effect sizes (below) for simple comparisons of traditional N100 measures (S1 amplitude, S2 amplitude, 1-[S2p50/S1p50], and S1p50-S2p50). Effects with bootstrapped confidence intervals (2.5% and 97.5%) not including zero are indicate by bold type and *.

CHAPTER 4

STIMULUS TRAIN DURATION BUT NOT ATTENTION MODERATES GAMMA-BAND ENTRAINMENT ABNORMALITIES IN SCHIZOPHRENIA[1]

[1]Hamm, J.P., Bobilev, A.E., Hayrynen, L.K., Hudgens-Haney, M.E., Oliver, W.T., Parker, D.A., McDowell, J.E., Buckley, P.A., Clementz, B.A. 2013. Submitted to *Biological Psychiatry,* 11/10/2013

Abstract

Background: Studies of auditory steady-state responses (aSSRs) probing neural entrainment in the low gamma range (40Hz) consistently report deficient responses in people with schizophrenia (SZ), but these studies have mostly employed short duration (500ms) stimulus trains in a passive listening paradigm. A few investigations with longer trains or an ongoing attentional task report absent or even opposite SZ aSSR effects, challenging simplistic interpretations of previous findings. The current study systematically varied stimulus duration and attentional contexts to detail the nature of SZ gamma-band entrainment deviations.

Methods: Eighteen SZ and 18 healthy comparison subjects (H) were presented binaural pure-tones with or without sinusoidal amplitude modulation at 40-Hz. Stimulus duration (500-ms or 1500-ms) and attention (via a button press task) were varied across 4 separate blocks. Evoked potentials recorded with dense-array electroencephalograms were analyzed in the time-frequency domain.

Results: SZ showed reduced 40Hz aSSRs over all conditions. H significantly reduced 40Hz entrainment in long duration contexts, while SZ failed to modulate, even showing a slight increase. Interestingly, aSSRs predicted task auditory discrimination performance in the short, but not long, stimulus duration context. In contrast, low frequency evoked responses were reduced in SZ, yet these effects interacted with attentional context instead of stimulus duration.

Conclusions: Gamma-band aSSRs are dynamically modulated by both attentional and stimulus duration contexts, but only the later modulation is abnormal in SZ, suggesting that pre-attentive sensory circuit dysfunction is a primary deficit in SZ. Furthermore, aSSRs and low-frequency evoked responses display divergent properties and may represent physiologically distinct indicators of psychotic disturbance.

Introduction

Auditory stimuli presented at a constant and rapid rate elicit steady-state responses (aSSRs), or sustained auditory neural entrainment in the listener. Human aSSRs, measured at the scalp with electro/magnetoencephalography (E/MEG), show a particular resonance in mid gamma-band frequencies (30-50Hz, i.e. a stimulus every 20-33ms) compared to other frequency bands (Galambos, Makeig, & Talmachoff, 1981; Terence W Picton, John, Dimitrijevic, & Purcell, 2003). In theory, this resonance arises from an interaction between driving thalamo-cortical glutamatergic stimulation and the propensity of local cortical networks to oscillate in this frequency range due to the specific timing properties of GABA-a receptor mediated inhibitory currents (C. a Brenner et al., 2009; Gonzalez-Burgos & Lewis, 2008; Traub, Bibbig, LeBeau, Buhl, & Whittington, 2004). Given that aSSRs in the gamma-band (particularly 40Hz) are frequently shown to be reduced in persons with schizophrenia (SZ) and given that aSSRs at frequency bands below gamma (e.g. 20Hz) are relatively spared in SZ (C. a Brenner et al., 2009), abnormalities involving local GABA-ergic interneuronal circuits (Vierling-Claassen, Siekmeier, Stufflebeam, & Kopell, 2008), and in particular, the interaction of thalamocortical drive on local cortical circuits via the NMDA glutamate receptor (Hamm, Gilmore, & Clementz, 2012), have been specifically hypothesized to be the neurophysiological deficit underlying aSSR abnormalities (Shin, O'Donnell, Youn, & Kwon, 2011; Uhlhaas & Singer, 2010) as well as other perceptual (Curley & Lewis, 2012) and cognitive deviations (Uhlhaas, Pipa, Neuenschwander, Wibral, & Singer, 2011) in SZ.

The abundance of studies finding SZ 40Hz aSSR reductions compared to healthy persons (H) have i) recorded aSSRs while subjects were passively listening to or attending away from aSSR stimuli and ii) used mostly short duration stimuli (500-1000ms). Altogether, this

consistency is at once promising and unsatisfying, especially in the context of two recent studies. First, while other MEG studies of 40Hz aSSRs in SZ have indicated left hemisphere reductions to be robust (Teale et al., 2008; Tsuchimoto et al., 2011a; Vierling-Claassen et al., 2008), Hamm et al (2011) demonstrated sufficient SZ entrainment at 40Hz in left hemisphere, notably employing stimulus trains of 1500ms while participants made auditory discriminations of amplitude modulated (aSSR stimuli) versus unmodulated noise burst stimuli (Hamm, Gilmore, Picchetti, Sponheim, & Clementz, 2011). Second, using similar stimulation parameters but with EEG and without an attentional component, Hamm et al (2012) showed an augmentation in SZ relative to healthy subjects in 40Hz aSSRs (Hamm, Gilmore, et al., 2012). In H, allocation of attention to stimulus trains via a behavioral task has been demonstrated to enhance gamma-band aSSR (B Ross, Picton, Herdman, & Pantev, 2004; Saupe, Widmann, Bendixen, Müller, & Schröger, 2009), although insufficient task difficulty leads to subthreshold significance of this enhancement (Griskova-Bulanova, Ruksenas, Dapsys, Maciulis, & Arnfred, 2011). The influence of attention on aSSR amplitude is unknown in SZ. The specific impact of stimulus train duration on aSSRs is far less frequently studied. Alpha-band visual steady-state entrainment abnormalities in SZ are known to differ as a function of train duration (Brett A Clementz, Keil, & Kissler, 2004). Treatment with NMDA-receptor antagonists [a well-established animal model of psychosis which elicits psychosis-like symptomology in humans; (Javitt, Zukin, Heresco-Levy, & Umbricht, 2012)] appears to enhance 40Hz aSSRs in humans and rats when long duration trains are employed (Plourde, Baribeau, & Bonhomme, 1997; Vohs, Chambers, O'Donnell, Krishnan, & Morzorati, 2012) while reducing 40Hz aSSRs when more traditional 500ms trains are used (Sivarao et al., 2013).

A systematic comparison between H and SZ groups of the within subject influences of contextual properties, both with regard to stimulus duration and attention, is therefore necessary for making progress toward understanding the neurophysiological underpinnings of and effectively refining this promising marker of psychotic pathology. If SZ reductions in aSSR power are indeed dependent on contextual variables, or are abnormally modulated by behaviorally relevant or sensory conditions, such a finding would have important implications for how aSSR studies in SZ are interpreted and for how the gamma-band aSSR is utilized as a biomarker in future etiological and pharmacological research.

In contrast to aSSRs, auditory event-related potentials including the N100 and P200 are large, transient cortical events elicited by a change in auditory stimulus energy (e.g. onset or offset of aSSR stimuli). The N100/P200 complex is among the most investigated electrophysiological biomarkers in the psychosis literature, showing consistent, robust reductions in SZ in most contexts (Ethridge et al., 2012; Hamm, Ethridge, et al., 2012; Rosburg, Boutros, & Ford, 2008). The complexity of this SZ biomarker can be efficiently and reliably summarized in the evoked time-frequency domain focusing on low-frequency (2-14Hz) responses (LFRs) in 75ms-300ms post-auditory events (Hamm, Ethridge, et al., 2012; Ivleva et al., 2013). While the gamma-band aSSR is understood to mostly reflect entrainment in early, primary auditory circuits overlapping with mid-latency potentials [≈50ms post-stimulus (Franowicz & Barth, 1995; Gutschalk et al., 1999; Bernhard Ross, Picton, & Pantev, 2002)], LFRs reflect dispersed auditory cortical synchronized events across secondary and associative cortices (Godey, Schwartz, de Graaf, Chauvel, & Liégeois-Chauvel, 2001; Yvert, Fischer, Bertrand, & Pernier, 2005). A principal components analysis (PCA) of SZ auditory abnormalities effectively separated LFRs from gamma-band aSSRs, showing differential relationships to psychosis symptomology (Hamm

et al., 2011). Additionally, even in contexts where SZ show augmented aSSRs, LFRs to the onset of stimuli are reduced (Hamm, Gilmore, et al., 2012), indicating that evoked low-frequency aberrations carry their own etiological significance separate from the gamma-band (Moran & Hong, 2011). The current study further examined this differentiation by analyzing LFRs and aSSRs with respect to attentional and stimulus duration parameters.

Aside from the fact that hallucinations specifically in the auditory domain are a characteristic feature of SZ (Goodwin, Alderson, & Rosenthal, 1971) and other psychoses (Baethge et al., 2005), SZ also typically display deficiencies in basic auditory processing and feature discrimination which are independent of higher-level cognitive dysfunction (Rabinowicz, Silipo, Goldman, & Javitt, 2000) and may reflect core pathology (Javitt, 2009). Because auditory processing is by nature a temporally precise modality and more sensitive to time perception abnormalities in SZ than e.g. vision (C. A. Carroll, Boggs, O'Donnell, Shekhar, & Hetrick, 2008), it follows that abnormalities in rapidly elicited neuronal activities, such as the aSSR, could theoretically relate to auditory perceptual difficulties. An understanding of the relationship between aSSR and auditory processing, however, has not been established in SZ.

The current study specifically addressed whether the stimulus duration (500ms versus 1500ms) and attentional context (inclusion of an auditory discrimination task) of the recording block influenced SZ gamma-band auditory neural entrainment. The answer will help clarify whether SZ aSSR reductions are due to general abnormalities of gamma range neural oscillators (deficient GABAergic coordination of pyramidal cells) or additionally relate to more dynamic thalmo-cortical or cortico-cortical modulation of sensory processing. Additionally, aSSR measurements were i) couched in the context of more established low-frequency transient evoked responses to the onset and offset of the steady-state stimuli and ii) regressed on auditory

discrimination performance to establish for the first time whether SZ aSSR abnormalities relate to auditory perceptual dysfunction.

Methods

2.1 Subjects

Eighteen persons with DSM-IV SZ (Mean +/-SD: 45.6 +/-8.3 years, 9 females) and 18 healthy persons (40.8 +/-9.9 years, 7 females) participated. SZ were recruited through community advertisements and through outpatient services of the Medical College of Georgia (Georgia Regents University, Augusta, GA); healthy subjects were recruited from the community. SZ were diagnosed using the Structured Clinical Interview for DSM-IV (First & Gibbon, 1997). At testing time, 7 SZ were taking first-generation antipsychotics (Haloperidol), 9 were taking second-generation antipsychotics (5 Quetiapine, 2 Risperidone, 1 Ziprasidone, 1 Lurasidone), and 2 were not taking antipsychotics. Chloropromazine dosage equivalents are presented in Table 1. Additionally, 9 SZ were taking antidepressants (8 selective serotonin reuptake inhibitors, 1 tricyclic), 3 were taking anticholinergics (Benzotropine), 2 were taking anticonvulsants (Valproate and Oxcarbazepine), and one was taking Lithium. The Positive and Negative Syndrome Scale (PANSS) quantified severity and extent of symptomatology(Kay, Fiszbein, & Opler, 1987) which is presented in Table 1. All subjects were free of substance use disorders in the 6 months prior to testing. SZ were chronic patients with typical age of illness onsets. All participants provided informed consent and were paid for their time. This study was approved by the Institutional Review Boards at University of Georgia and Georgia Regents University.

2.2 Stimuli

Four blocks of 130-165 tones (carrier pitches 500, 1000, or 2000-Hz; randomly ordered) were presented binaurally through Etymotic insert earphones (Etymotic Research, Elk Grove Village, IL) at 76 dB SPL with an average 3 s ISI (range 2.7–3.3 s) while participants sat in a dark room with eyes open and fixated on a small cross presented on a computer monitor. Tones were either sinusoidally amplitude modulated (Krishnan et al., 2009) at 40Hz (90%; "standards") or unmodulated pure-tones (10%; "targets"). To the listener, "standards" resembled, for example, a phone ringing, while "targets" sounded like a smooth dial-tone. In 2 of the blocks, tones had a 500ms duration (Kwon et al., 1999), while in the other 2 blocks each tone lasted 1500ms (Hamm, Gilmore, et al., 2012). Further, in 2 of the blocks, participants were instructed to make a button press to "target" tones ("task" condition), while in the other 2 blocks participants were instructed to simply listen to the tones while fixating ("no-task" condition). Thus the 4 conditions were short-duration task, short-duration no-task, long-duration task, and long-duration no-task. Order of conditions was counter-balanced across subjects. Subjects' comprehension and ability to perform the task was confirmed prior to data collection.

2.3 EEG recording

EEG data were recorded vertex-referenced using a 256 sensor Geodesic Sensor Net and NetAmps 200 amplifiers (Electrical Geodesics Inc.; EGI, Eugene, OR). Sensor impedances were kept below 50 kO, as is standard when using high input impedance amplifiers. Data were sampled at 500 Hz with an analog filter bandpass of 0.1–200 Hz.

2.4 Data screening

Sensors from the neck/face were excluded leaving 211 sensors for analysis. Raw data were inspected offline for bad sensors, which were interpolated (<5% for any participant) using a

spherical spline interpolation method (BESA 5.0; MEGIS Software, Grafelfing, Germany). Data were then converted to an average reference montage and digitally bandpass filtered from 0.5–100 Hz (zero phase filter; rolloff: 6 and 48 dB/octave, respectively). A notch filter was applied at 60 Hz (2Hz width) to eliminate line noise. Blink and cardiac artifacts were identified using Independent Components Analysis and removed (EEGLAB; 40). Because the aSSR was the primary measure of interest and because of the low signal-to-noise ratio for target evoked responses (~13 trials per condition), only EEG data from standard trials were analysed (Hamm et al., 2011). Data were segmented into single trial epochs beginning 750ms before and ending 2250ms after stimulus onset, and voltage values averaged from -100 to 0ms were defined as the baseline and were subtracted from all timepoints on individual trials. Trials with activity >120 mV at any sensor were eliminated. One SZ subject and one H subject were dropped from the study due to excessive artifact, yielding 18 SZ and 18 H. The number of remaining standard trials did not differ between groups for any carrier frequency for any condition (all p>.09; **Table 1**).

2.5 Data Analysis

Data from remaining standard trials (i.e. 40Hz steady-state stimuli) were averaged for each subject within each condition and carrier pitch, yielding ERPs with 211 channels and 1500 timepoints. Because carrier pitch (500, 1000, 2000Hz) did not systematically interact with aSSR topographies or SZ versus H differences for any condition (see **Supplementary Methods and Figure S1**), average ERPs were recalculated across all standard trials within a condition regardless of carrier pitch, resulting in 4 separate 211x1500 point ERPs per subject and enhancing the overall signal to noise ratio and, thus, the stability all evoked measurements (T W

Picton et al., 2000). Again, the number of trials included in combined ERPs did not differ between groups for any condition after this combination (all p>.09; **Table 1**).

Next, in order 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 PCA was completed on 211-channel grand average waveforms concatenated across all 4 conditions (C. a Carroll et al., 2008; Hamm, Gilmore, et al., 2012; Hamm et al., 2013) using Matlab (The Mathworks, Matick, MA). A PCA with promax (oblique) vector rotation and Kaiser normalization was calculated on the 211X211 sensor covariance matrix (Dien, Khoe, & Mangun, 2007). A scree test (Cattell, 1966) determined that the optimal number of components was 2, with the first component accounting for 79% of the variance in waveforms across sensors and being maximal at frontal-central electrodes [FCz; typical of aSSR and LFR responses, (Hamm, Gilmore, et al., 2012; Hamm, Ethridge, et al., 2012)]. The second component accounted for 14% of the total variance, had a more posterior topography with a central-parietal maximum (CPz), and was counter-phased to component 1 [typical of LFR responses (Hamm, Ethridge, et al., 2012); **Supplementary Figure S2**]. When these steps were completed separately for H and SZ groups, the scree test again indicated 2 components that were virtually identical to each other and to the grand average PCA result (all r's >.90; see **Supplementary Methods and Figure S3**). Therefore, the weights from the PCA on the ERPs across all subjects were used for all further analyses (Ethridge et al., 2012; Hamm, Ethridge, et al., 2012).

Each set of component weights was then multiplied by each subject's grand average data, summed across sensors, and divided by the plus sum of the component weights, reducing the ERPs to one waveform per component for each subject for each condition. This resulted in component scores that were analyzed instead of single sensors (i.e. as 1-2 "virtual sensors"),

minimizing the number of comparisons and maximizing the signal/noise ratio of the ERP data. From 500ms pre- to 2000ms post-stimulus onset (allowing 250 ms padding at the beginning and end of epochs), 500ms windows centered on each sample of ERP for each virtual sensor were multiplied by a 250-sample Hanning window (500ms). The window was shifted in one-sample (2ms) steps and the squared absolute value of the Fast Fourier Transform (FFT; 2-Hz resolution) was calculated at each step (C. a Brenner et al., 2009) yielding a time-frequency power plot ranging from -500 to 2000ms and 0 to 55Hz for each subject, component, and condition (**Figure 1 and S4**). Power values were log transformed to ensure normality (C. a Brenner et al., 2009; Delorme & Makeig, 2004).

For statistical analysis of aSSRs, a mixed model ANOVA with DIAGNOSIS (H, SZ) as a between subjects factor and ATTENTION (no-task, task) and DURATION (500ms, 1500ms) as a within subject factors was carried out for 40Hz power averaged within the first 500ms after stimulus onset. Evoked power in theta-band (2-6Hz) and alpha-band (8-14Hz) was analysed with the same model but for 0 to 300ms after stimulus onset (determined based on the shape of the evoked power waveform**, Figure 1**). Theta and alpha-band responses were also present to the offset of steady-state stimuli and were similarly analysed. A preliminary set of ANOVAs established that no differences existed in the pre-stimulus period (-500ms to -250ms to avoid overlap with post-stimulus-onset timepoints) for any frequency band, so pre-stimulus power was subtracted from post-stimulus-onset power for all analyses. Follow-up comparisons on interaction effects were carried out using paired-samples t-tests (two-tailed). Condition specific effect sizes between H and SZ were also calculated when interactions were present (Glass's Δ) and statistical significance was determined by bootstrapping 95% confidence intervals, recalculating 10000 times after shuffling group membership (sampling with replacement).

For analyses of behavior (in the task conditions only), button presses happening between 100ms after stimulus onset and 250ms before the subsequent stimulus onset counted as responses. The difference between the z-transformations of the hit rate and the false alarm rate (*d'* or sensitivity index) and the average correct response latencies (RTs) were calculated (Macmillan & Creelman, 2005). A mixed model ANOVA with DIAGNOSIS (H, SZ) as a between subjects factor and DURATION (500ms, 1500ms) as a within subject factor was carried out for differences on *d'* and RTs for each stimulus duration condition. Correlations were calculated between each of these measures and aSSR, theta, and alpha-band responses which demonstrated DIAGNOSIS or ATTENTION related effects. The stability of r values was assessed by bootstrapping 95% confidence intervals by recalculating r values 10000 times after resampling with replacement.

Results

While several main effects and interactions were present in PCA component 1, PCA component 2 did not yield significance main effects or interactions involving DIAGNOSIS. Thus results are only reported for PCA component 1 (**Figures 1-4**). Group mean time-frequency spectra for PCA component 2 are available in **Supplemental Figure S4**.

3.1 40Hz Auditory Steady-State Response

A DIAGNOSIS main effect ($F(1,34)=9.24$, $p<.01$) and a DIAGNOSIS by DURATION interaction ($F(1,34)=8.13$, $p<.01$) were present for aSSRs. While H showed a significant decrease of 40Hz power for long compared to short duration stimulus trains ($t^{paired}(17)=3.05$, $p<.01$; short mean=3.44 [std=1.1], long=2.93 [1.3]; **Figure 2**), SZ did not show a similar effect ($t^{paired}(17)=-1.72$, $p=.21$; short=1.81 [1.2], long=2.07 [1.1]). H versus SZ effect sizes for the short-duration

conditions (Glass's Δ=1.47, CI=[0.79,2.13]) and the long-duration conditions (Δ=0.65, [0.05,1.23]) were both significantly different from each other and zero.

Consistent with the ambiguity of previous reports, the main effect of ATTENTION on aSSRs only approached significance (F(1,34)=3.35, p=.07), hinting at a slight increase in entrainment power during the task (2.75 [1.6]) compared to the no-task condition (2.38 [1.1]). This effect was, however, equivalent between SZ and H as the ATTENTION by DIAGNOSIS interaction was not present (F(1,34)=0.94, p=.34).

Overall, H, but not SZ, reduced gamma-band neural entrainment when long duration stimulus trains were presented. This resulted in larger H-SZ effect sizes for traditionally used 500ms stimulus trains as compared to 1500ms. Attentional context, or requiring a behavioral response to aSSR stimuli, does not impact SZ aSSR reductions.

3.2 Low Frequency Response

A DIAGNOSIS main effect was present for theta-band LFRs (2-6Hz) to the onset of stimulus trains (F(1,34)=6.49, p<.05) showed driven by H having larger magnitude responses across all conditions (3.78,[1.0]) than SZ (2.91,[1.0]; **Figure 3a**). Theta-band LFRs to the offset of stimulus trains also showed only a DIAGNOSIS main effect (F(1,34)=4.80, p<.05) driven by H having larger magnitude responses across all conditions (1.94,[1.0]) than SZ (1.27,[0.8]; **Figure 3a**).

An ATTENTION main effect (F(1,34)=8.20, p<.01) as well as an ATTENTION by DIAGNOSIS interaction (F(1,34)=4.62, p<.05) was present for alpha-band LFRs (8-14Hz) to the onset of stimulus trains . The interaction effect was driven by a significant increase in alpha LFRs in the task condition for SZ (t^{paired}(17)=2.89, p<.01; task=1.69 [1.11], no-task=0.98 [0.9]; **Figure 3b**) but not for H (t^{paired}(17)=0.71, p=.49; task=1.80 [0.9], no-task=1.70 [0.9]).

Additionally, DIAGNOSIS effect sizes reached significance for the no-task (Δ=0.79, [0.14,1.44]) but not for the task (Δ=0.12, [-0.60,0.85]) condition.

No other main effects or interactions were present for the onset or offset of theta-band or alpha-band LFRs. In sum, while theta-band LFRs showed context invariant reductions in SZ, LFR reductions in SZ in the alpha-band were only present in the passive listening context.

3.3 Behavior

There was a significant effect of DIAGNOSIS on d-prime scores ($F(1,34)=11.2$, $p<.01$), driven by SZ having significantly worse discrimination performance overall (mean=4.56, [stdev=2.57]) than H (6.82, [1.28]; $t(34)=3.34$, $p<.01$). No main effects or interactions involving duration were present.

With regard to response latency, a significant effect of DIAGNOSIS ($F(1,34)=9.76$, $p<.01$) was driven by SZ showing slower responses overall (1210ms[561]) than H (849ms[415]; $t(34)=3.12$, $p<.01$). Subjects also displayed slower responses when provided with longer stimuli (925ms[338] versus 1130ms[492]; $t(17)=4.18$, $p<.01$). No DIAGNOSIS by duration interaction was present.

Across all subjects, short duration aSSR power significantly correlated with both task performance (d-prime; r=.47 [.20, .74]; p<.01) and response latency (r=-.41, [-.66, -.12]; p<.05; **Figure 4**). When these analyses were limited to SZ or H groups, short aSSR correlations with d-prime retained the same direction and stability (r^{H}=.18 [.08, .83]; r^{SZ}=.37 [.08, .83]). Correlations of short aSSRs with response latency were relatively unstable when calculated within groups (r^{H}=-.12 [-.76, .02]; r^{SZ}=-.31 [-.75, .02]). Long duration aSSRs did not correlate with d-prime or latency in either group.

Discussion

Gamma-band aSSR abnormalities in schizophrenia are moderated by the duration of the stimulus train, being less dramatic in contexts where short (500ms) compared to long (1500ms) trains are employed. In contrast, the presence of an ongoing auditory discrimination task, compared to passive listening, did not significantly affect SZ aSSR abnormalities, but ameliorated SZ's reduced transient alpha-band LFR to stimuli onset. Transient theta-band LFR reductions in SZ to the onset and offset of auditory stimuli display no such modulation, showing a general contextual invariance. This pattern of findings provides key implications for i) the further refinement and understanding of gamma-band aSSRs as a biomarker for SZ and ii) the interrelationship of this robust neural deviation and a more traditional, equally as robust, transient LFR auditory biomarker.

The current results replicate the substantial SZ reductions in 40Hz entrainment reported in 9 of 11 previous studies which used 500ms stimulus trains (Gilmore, Ca, & Buckley, 2004; Hong et al., 2004; Kirihara, Rissling, Swerdlow, Braff, & Light, 2012; Kwon et al., 1999; Light et al., 2006; Rass et al., 2012; Spencer, Salisbury, Shenton, & McCarley, 2008; Teale et al., 2008; Teale, Carlson, Rojas, & Reite, 2003; Tsuchimoto et al., 2011b; Vierling-Claassen et al., 2008). In blocks when longer (1500ms) stimulus trains were presented in the current study, H reduced 40Hz entrainment power relative to 500ms blocks, but SZ did not. One possible explanation of this pattern of results involves GABA-ergic neurotransmission, which may be selectively impaired in SZ given previously established anatomical alterations in (Gonzalez-Burgos & Lewis, 2012) and reduced excitatory drive on inhibitory cortical interneurons (Carlén et al., 2012). The generation of coherent gamma-band oscillations is dependent on GABAa receptor-mediated inhibition (Gonzalez-Burgos & Lewis, 2008; Sohal, Zhang, Yizhar, &

Deisseroth, 2009). In the current study, the aggregate of multiple long duration stimulus trains (i.e. blocks of 1500ms stimuli) might have attenuated steady-state gamma-band entrainment in healthy auditory neural ensembles relative to more brief gamma stimulation contexts by generating enough post-synaptic GABA release to activate extrasynaptic GABAb receptors (Kohl & Paulsen, 2010), which suppress gamma-oscillations (Brown, Davies, & Randall, 2007). Altogether, impaired GABA neurotransmission in SZ therefore could have attenuated gamma-entrainment in sparse stimulation contexts (500ms, GABAa) and *failed to* attenuate gamma-entrainment in dense stimulation contexts (1500ms, GABAa and GABAb).

Alternatively, dysfunction of the alpha-7 subunit of the nicotinic acetelycholinergic (ACh) receptor has long been associated with both SZ and hippocampal mediated auditory cortical suppression of redundant stimulation (63). Muscarinic ACh receptors (M1), which influence sensory cortical plasticity (Shideler & Yan, 2010) and neural response gain (Rodriguez, Kallenbach, Singer, & Munk, 2004), directly modulate gamma-generating cortical assemblies (Bartos, Vida, & Jonas, 2007). M1 expression is reduced by up to 75% in SZ (Scarr & Dean, 2008) and may therefore also play a key role in the duration dependent aSSR modulation. Still, the allocation of attention to aSSR stimuli elicited an increase in gamma-band entrainment in both H and SZ at comparable levels. Because arousal related enhancements in sensory cortical gamma are controlled by ACh signaling (Rodriguez et al., 2004), this finding diminishes some enthusiasm for a purely ACh based theory of aSSR reductions in SZ.

While the results of the current study advance the notion that stimulus train duration affects SZ aSSR entrainment abnormalities, they also indicate that duration, along with attentional context, cannot fully explain the SZ gamma-band augmentations shown in Hamm et al (2012). Hamm et al (2012) also employed 1500ms aSSR stimulus trains, but utilized more

aurally dense broadband noise carriers (500-4000Hz) instead of pure-tones. If bandwidth and/or temporal density (instantaneous clicks versus amplitude modulation) moderate SZ aSSR abnormalities, this finding might point at fundamental deviations in lateral inhibition mechanisms in cortical and/or subcortical auditory pathways. Above all, the number of molecular pathways and circuit functions which influence the generation of gamma-band oscillations is almost as large as the number of candidate mechanisms of SZ etiology. Consideration of nuanced context specific alterations like the effects presented herein and in future studies will be needed to mature the 40Hz aSSR into a truly valuable disease biomarker and/or endophenotype.

Both H and SZ subjects who generated substantive 40Hz auditory cortical entrainment to aSSR stimuli also differentiated such stimuli from unmodulated tones more quickly and more accurately in a perceptual task. This study may therefore be the first to report that reduced 40Hz aSSRs in SZ relates to fine temporal auditory perceptual dysfunction (Javitt, 2009) and thus carries functional disease relevance. Curiously, this association of entrainment power to behavior was only present for short stimulus contexts, suggesting that divergent and/or more downstream perceptual strategies are employed in both groups when longer, more information-abundant trains are available. Electrophysiological correlates of these strategies were not available in the evoked responses in this study, but this long-short distinction further echoes the idea that aSSR stimuli of different durations probe somewhat distinct neurophysiological processes involved in gamma oscillations.

Evoked theta-band responses were reduced in SZ to both the onset and offset of aSSR stimuli, regardless of stimulus train duration or attentional context. That theta-band oscillations are reduced to a variety of auditory stimuli in SZ is one of the most consistent findings in the SZ

literature (Başar & Güntekin, 2008; Başar-Eroglu, Başar, Demiralp, & Schürmann, 1992; Brockhaus-Dumke, Mueller, Faigle, & Klosterkoetter, 2008; B A Clementz & Blumenfeld, 2001; Ethridge et al., 2012; Hamm et al., 2011; Hong et al., 2008). This consistency contrasts the relative inconsistency of evoked gamma and beta-band alterations seen in a variety of electrophysiological studies of SZ, wherein augmentations, reductions, and null findings are frequently reported (Moran & Hong, 2011). The evoked low frequency response is both spatially and temporally broad, likely reflecting synchronization and registration of an event across a dispersed cortical network (Buzsaki, 2009). The consistency of evoked theta-band reductions seen in this study could therefore mark deficient gross network synchronization in SZ common to all auditory processing, perhaps relating to frontal and temporal lobe white matter degradation (Whitford et al., 2007).

In contrast to the theta-band, alpha-band evoked responses were present only in the no-task condition. While this differentiation is not commonly reported, an EEG study of a large age/gender matched sample illustrates that in passive listening settings (auditory paired-stimulus), psychosis-related evoked oscillatory reductions extend above 10Hz (Hamm, Ethridge, et al., 2012). In an active listening setting (auditory oddball) in the same sample, evoked response reductions were limited to 5Hz and below (Ethridge et al., 2012; Hamm, Ethridge, et al., 2012). The fact that evoked alpha-band responses are reactive to attentional modulation is not particularly surprising given the extensive literature on the subject (Klimesch, Sauseng, & Hanslmayr, 2007), yet curiously, SZ, but not H, appear to employ this alpha-specific modulation. Perhaps enhancement of certain cortical circuit activities comprises a compensatory mechanism to partially make up for impaired local (gamma) or long range (theta) neurotransmission, but the fact that alpha-band evoked responses did not correlate with behavior performance in the current

study does not directly support this assertion. Importantly, the results of this study demonstrate that low frequency evoked responses and entrained gamma-band abnormalities in SZ vary differentially across listening contexts. Disrupted theta, alpha, and entrained gamma auditory neural activities could ultimately comprise unique biomarkers of distinct or divergent etiological pathways in major psychotic pathology (Keshavan, Clementz, Pearlson, Sweeney, & Tamminga, 2013; Thaker, 2008).

Acknowledgements:

The authors are grateful to Assaf Hod, Abby Weinberger, and Sophie Arkin for their assistance with data collection and management, as well as the support of the Franklin Foundation Neuroimaging Training Program. This work was supported by NIH grant MH094172.

Financial Disclosure:

Mr. Hamm, Ms, Bobilev, Ms Hayrynen, Mr. Hudgens-Haney, Mr. Oliver, Mr. Parker, Dr. McDowell, Dr. Buckley, and Dr. Clementz report no financial interests or potential conflicts of interest.

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	H	SZ	statistic	p-value
% female subjects	**39**	**50**	$\chi 2[1] = 0.45$	.502
Age (in years)	**41** (25-54)	**46** (25-55)	t(34)=1.56	.126
Medication dosage (CPZ equivalents in mg)	-	**207** (20-533)	-	-
PANSS positive	-	**13.7** (8-27)	-	-
PANSS negative	-	**14.8** (8-28)	-	-
PANSS general	-	**33.9**(17-64)	-	-
Trials short no-task	**117** (97-138)	**111** (72-139)	t(34)=1.49	.145
Trials short task	**120** (97-139)	**111** (74-149)	t(34)=1.77	.090
Trials long no-task	**94** (75-114)	**87** (69-111)	t(34)=1.54	.131
Trials long task	**94** (75-113)	**94** (76-110)	t(34)=-0.16	.878

Table 4.1: Subject Demographic and Clinical Data. Means presented with ranges. Trials indices display number of useable trials for each condition. H, healthy control subjects; SZ, schizophrenia subjects; CPZ, chloropromazine; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms.

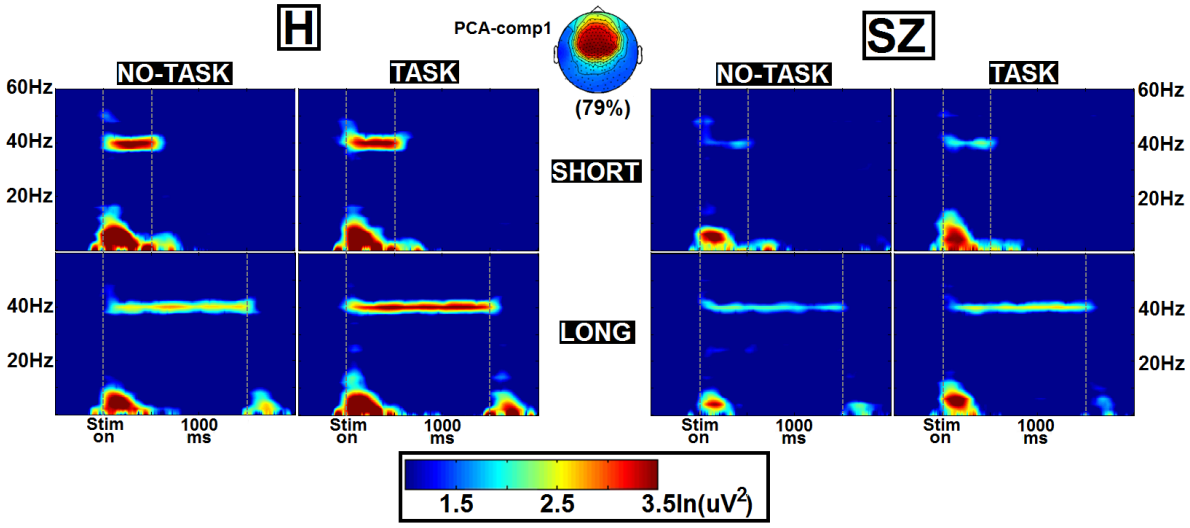

Figure 4.1: Time-frequency Spectra. Evoked power is plotted in heat maps as a function of time (x-axis) and frequency (y-axis) for each group and condition for spatial PCA component 1. Displayed in top-center as a topography are the component weights of PCA component 1, which accounted for 79% of the total spatial variance of the grand-average evoked potentials across all conditions.

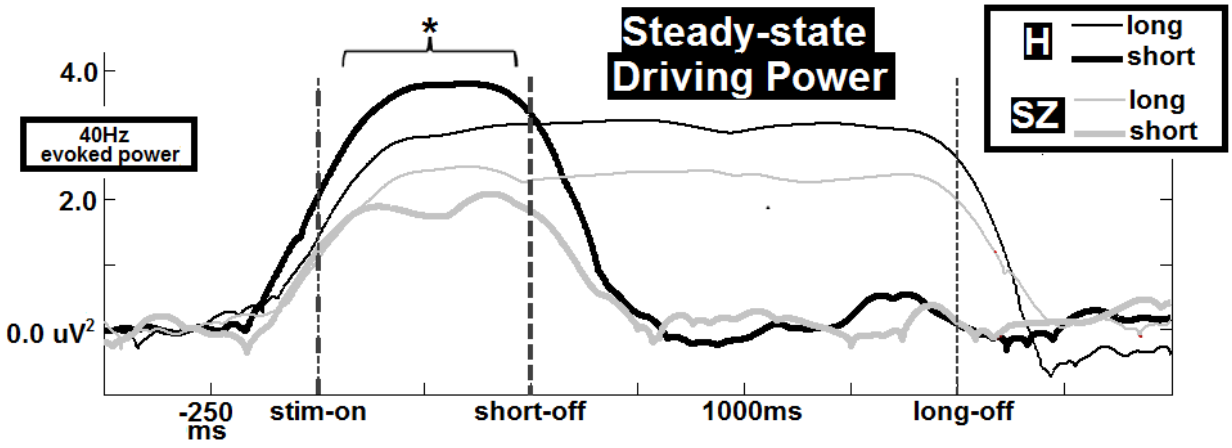

Figure 4.2: Steady-state Driving Power. 40Hz power (aSSR, PCA-comp1) is displayed for each group and duration condition. An asterisk (*) denotes a significant DX by DURATION interaction effect for power in the first 500ms after stimulus onset.

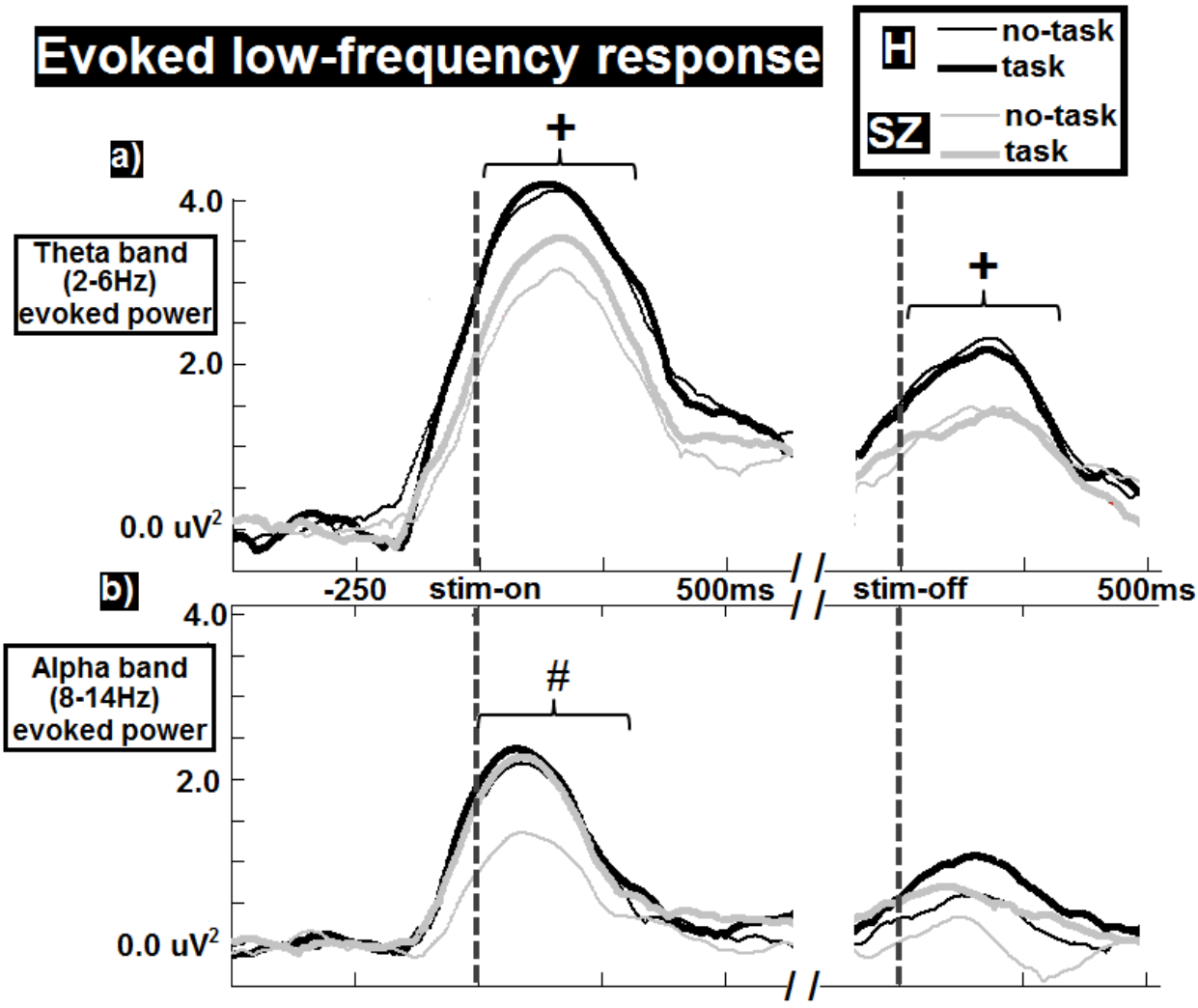

Figure 4.3: Evoked Low-frequency Response. Low frequency response power (LFR, PCA-comp1) are displayed for each group and duration condition. Line plots of theta-band power (a) demonstrate a significant group main effect (denoted by a plus sign (+)) at both the onset and offset of aSSR stimuli. Line plots of alpha-band power (b) demonstrate a significant DX by ATTENTION interaction effect (denoted by a pound sign (#)) at the onset of aSSR stimuli.

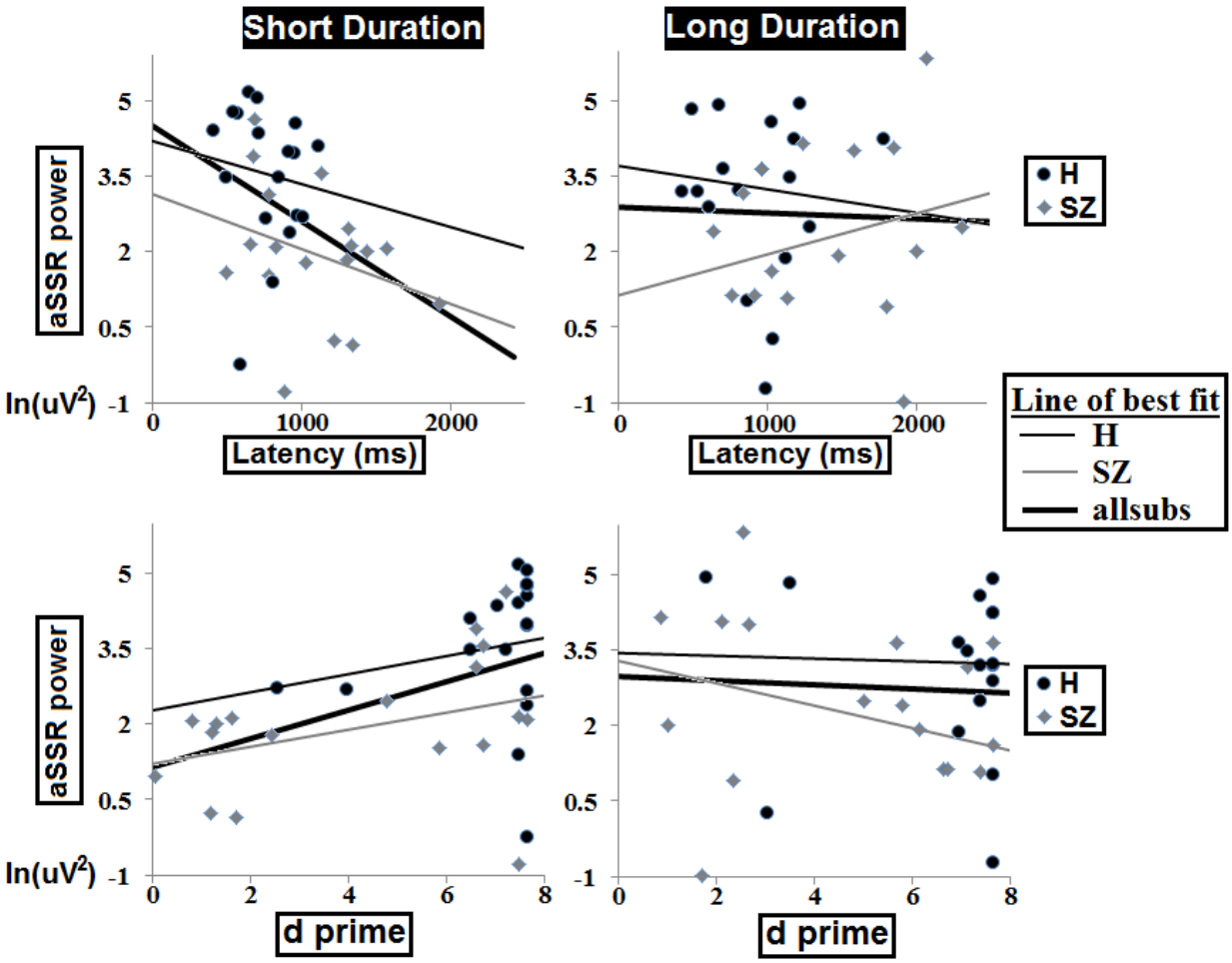

Figure 4.4: Behavior Scatterplots. Scatterplots of 40Hz aSSR power (task condition only) plotted against response latency (above) and d-prime scores (below) reveal significant correlations for short duration (left) but not long duration contexts (right). Lines of best fit based only H, only SZ, and entire sample are overlaid for each plot.

Supplemental Methods

Analysis of Carrier Frequency

In order to establish whether H and SZ group differences in aSSR magnitudes and topographies essentially differed as a function carrier frequency (500Hz, 1000Hz, 2000Hz), we initially transformed each subject's 211 by 1250 point ERPs for each condition (short no-task; short task; long no-task; long task) and carrier frequency to time-frequency space as follows. From 500ms pre- to 2000ms post-stimulus onset (allowing 250 ms padding at the beginning and end of epochs), 500ms windows centered on each sample of ERP for each "virtual sensor" were multiplied by a 250-sample Hanning window (500ms). The window was shifted in one-sample (2ms) steps and the squared absolute value of the Fast Fourier Transform (FFT; 2-Hz resolution) was calculated at each step (C. a Brenner et al., 2009) yielding a time-frequency power plot ranging from -500 to 2000ms and 0 to 55Hz for each subject, channel, carrier frequency, and condition (Figure 1 and S4). Power values were log transformed to ensure normality and baseline (-500 to -250ms) corrected via subtraction (Delorme & Makeig, 2004; Hamm, Gilmore, et al., 2012).

We then compared aSSRs (40Hz power, 0 to 500ms post-stimulus onset) via a mixed model ANOVA with DX (H, SZ) as a between subjects factor and CARRIER FREQUENCY (500Hz, 1000Hz, 2000Hz) as a within subject factor. This was carried out for each condition separately, and then after averaging over all conditions (**Figure S1**). Overall, the 10 peak aSSR sensors remained unchanged across all carrier frequencies, groups, and conditions and consisted of midline locations CZ, FCZ, and FZ and 7 others flanking on the left and right. DX effects were consistent across conditions and carrier frequencies in frontal and central electrode locations (H>SZ). Lower frequencies showed statistically greater magnitude aSSRs at central

locations (consistent with past research; see Pichton et al, 2003 for a review), yet no DX by CARRIER FREQUENCY effects were present for any condition.

While four previous SZ aSSR studies used amplitude modulated pure-tone carriers of 1000Hz pitch (C. A. Brenner, Sporns, Lysaker, & O'Donnell, 2003; Gilmore et al., 2004; Krishnan et al., 2009; Teale et al., 2008), the current study additionally utilized 500 and 2000 Hz carriers. The results presented here indicate no significant modulation of SZ aSSR abnormalities as a function of carrier pitch. Hamm et al (2012) found augmentations in the SZ 40Hz aSSR (surprisingly opposite of 9 of 10 previous EEG reports), yet deviated from previous EEG investigations of aSSRs in SZ in not only the duration of the stimulus trains but also in the auditory bandwidth of the carrier stimuli. Hamm et al (2012) used sinusoidally amplitude modulated broadband noise carriers (500-4000Hz) known to generate robust aSSRs in humans (John, Lins, Boucher, & Picton, 1998). The current findings establish that basic abnormalities at particular pitches could not underlie the deviations in SZ aSSR effects seen by broadband noise generated aSSRs and, likewise, encourage the direct comparison of pure-tone and broad-band aSSR carriers in future SZ investigations.

Group wise Spatial PCA

Spatial PCA was initially completed on grand average ERPs separately for H and SZ groups using Matlab (The Mathworks, Matick, MA). 211-channel grand average waveforms concatenated across all 4 conditions, and a PCA with promax (oblique) vector rotation and Kaiser normalization was calculated on the 211X211 sensor covariance matrix (Dien et al., 2007). Results for each group, and the entire sample, are summarized in Figure S2. For the H group, a scree test determined that the optimal number of components was 2, with the first component accounting for 76% of the variance in waveforms across sensors and being maximal

at frontal-central electrodes [FCz; typical of aSSR and LFR responses, (7; 24)]. The second component accounted for 18% of the total variance, had a more posterior topography with a central-parietal maximum (CPz). For the SZ group, a scree test determined again that the optimal number of components was 2, with the first component accounting for 71% of the variance in waveforms across sensors and being maximal at frontal-central electrodes [FCz; typical of aSSR and LFR responses, (7; 24)]. The second component accounted for 14% of the total variance, had a more posterior topography with a slightly left of central-parietal maximum (CP1-3).

Completing spatial PCAs on grand average auditory ERPs generally provides a robust solution which does not differ substantively between H and psychiatric groups, but maximally uses available spatiotemporal information while minimizing the influence of intersubject variability in ERP topography as well as extraneous EEG noise (C. a Carroll et al., 2008; Ethridge et al., 2012; Hamm, Gilmore, et al., 2012; Hamm et al., 2013; Hamm, Ethridge, et al., 2012; Ivleva et al., 2013). The results of the current investigation do not deviate from this norm.

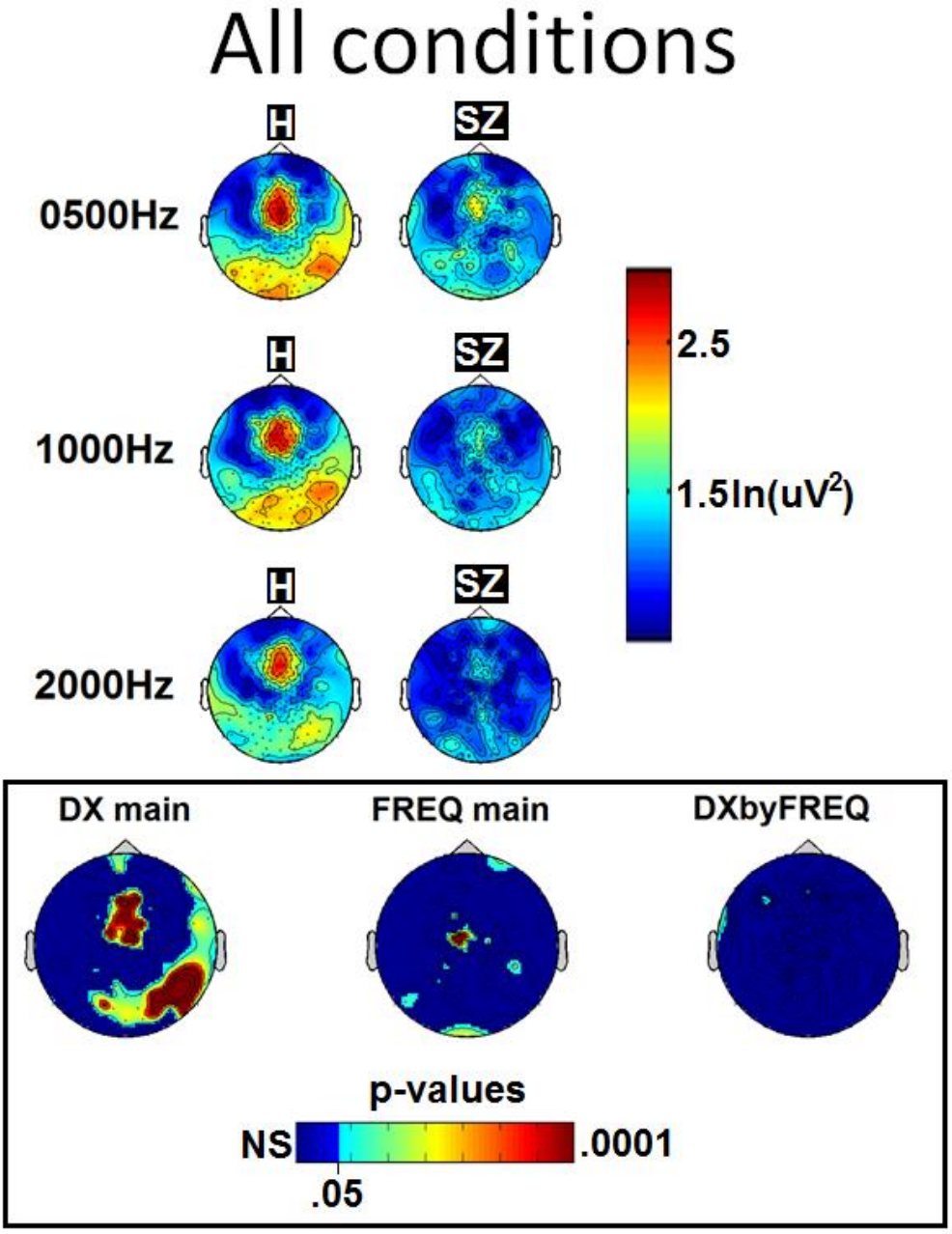

Figure 4.S1: Carrier Frequency Analysis. Group averages for baseline-corrected aSSR power (40Hz) for each carrier frequency, averaged over all conditions (above), reveal similar topographies for each group and carrier. Significance plots (below) confirm this similarity while highlighting a difference in magnitude between groups and between carrier frequencies.

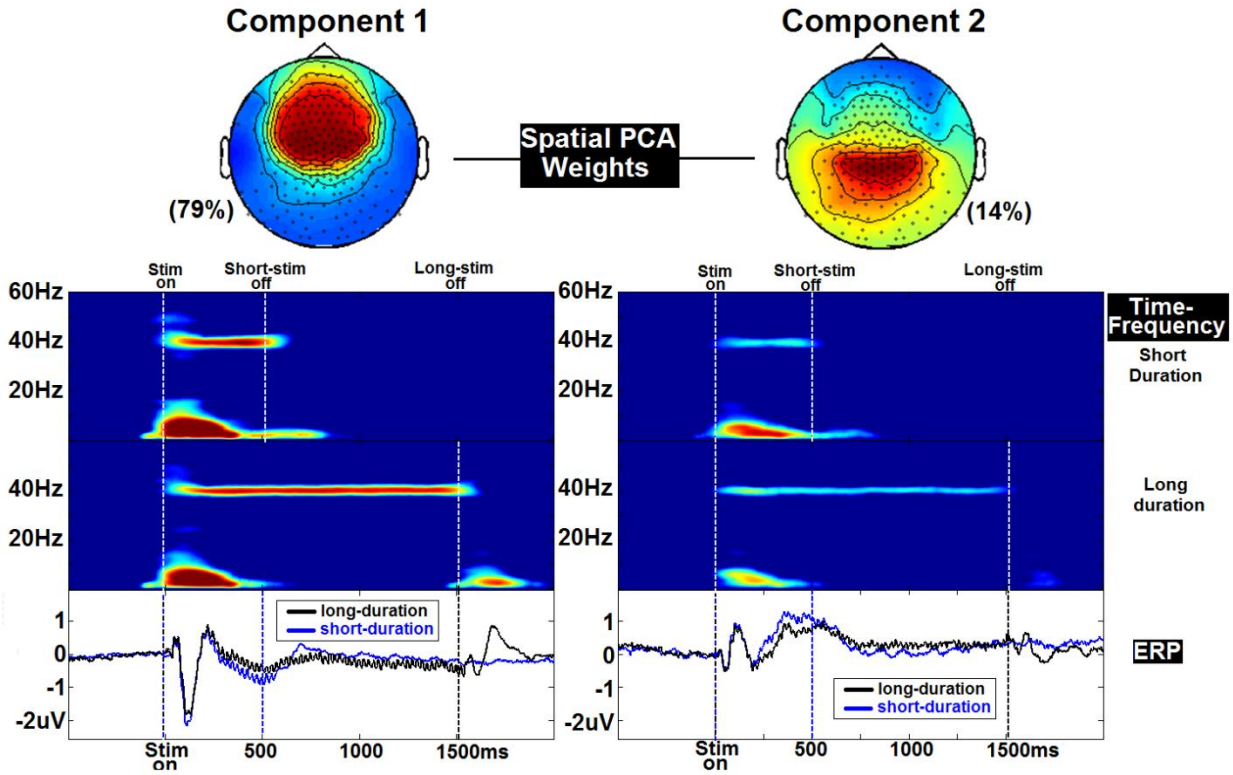

Figure 4.S2: Spatial PCA Weights. Spatial PCA weights (above; flanked with the amount of total variance explained in parentheses) and scores (averaged over all subjects) displayed as time-frequency plots (middle), and time-voltage (below) are presented for each principal component.

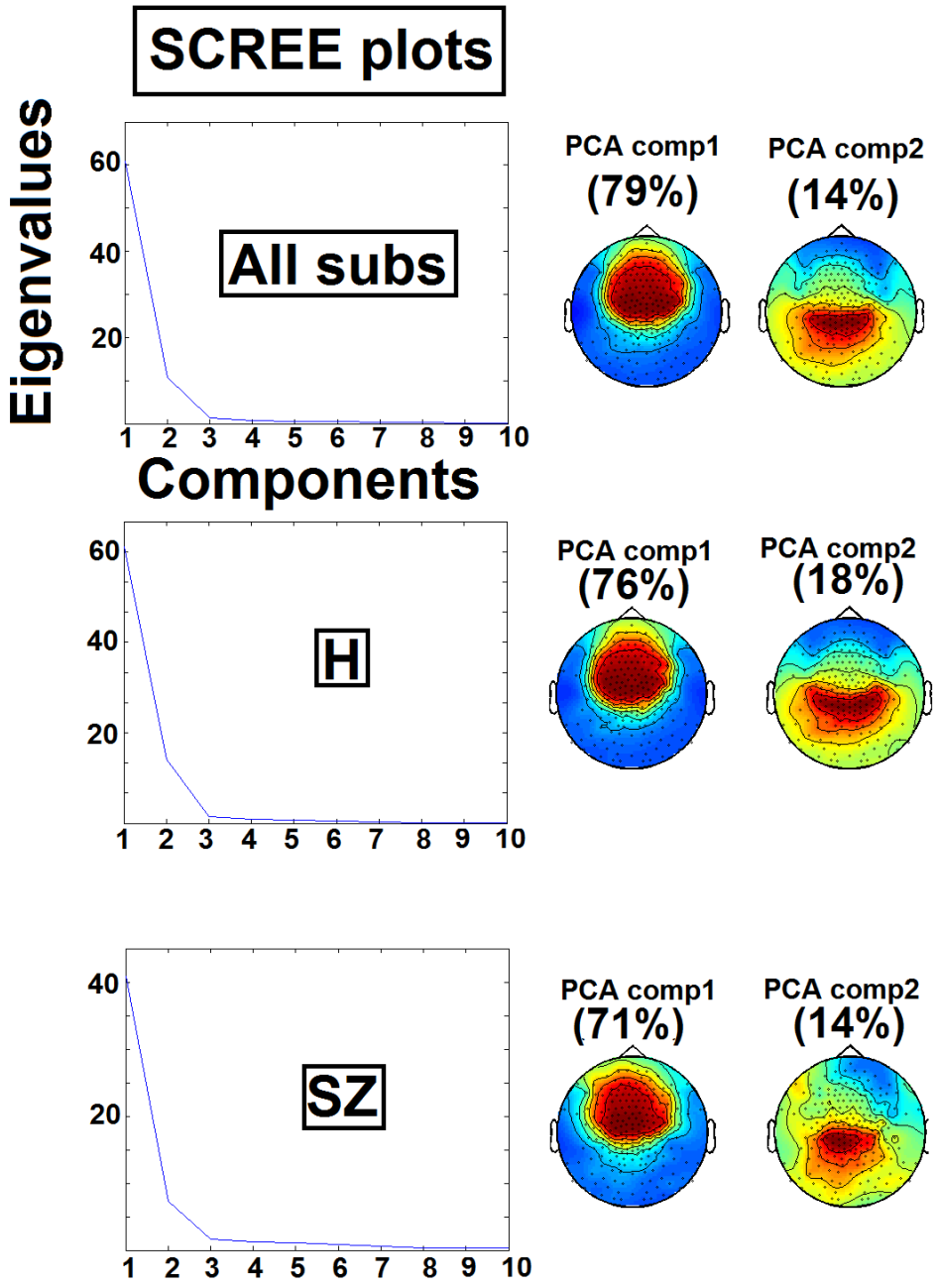

Figure 4.S3: **Scree Plots.** Scree plots (left) indicate for both groups and for the overall sample that extraction of 2 components is warranted. Component weights (right) for each of these components are highly similar for all three iterations of the PCA, with each set correlating across iterations at r>.90.

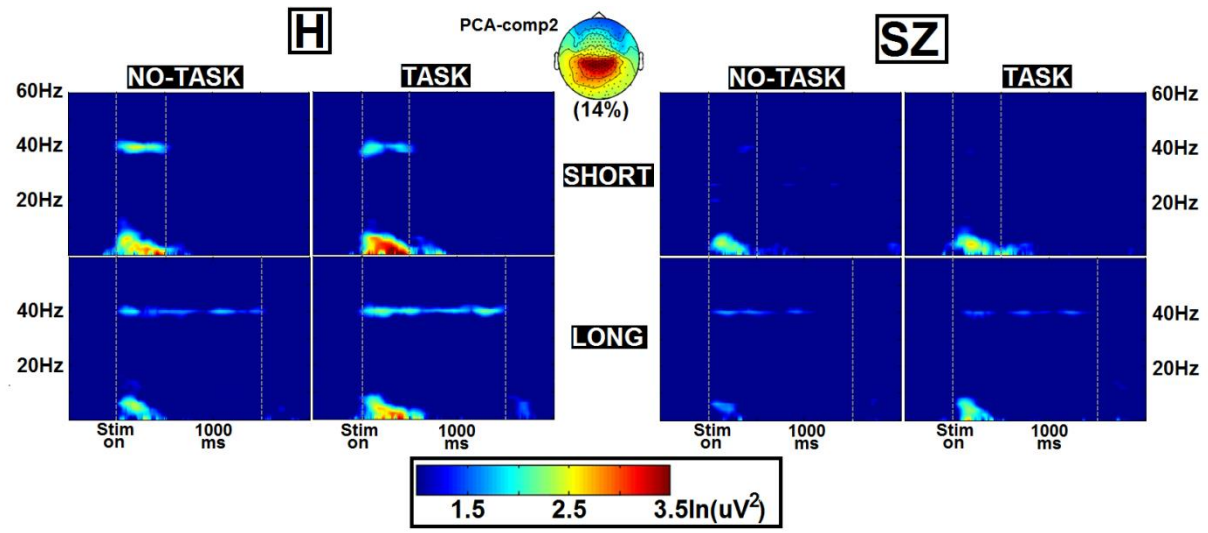

Figure 4.S4: **Component 2 Time-frequency Spectra.** Evoked power in time-frequency domain for PCA-component 2 displayed for H (left) and SZ (right). Group differences did not reach significance for baseline power for aSSRs, theta, or alpha, nor did they reach significance for aSSRs or for onset or offset responses for theta or alpha.

CHAPTER 5

DISCUSSION AND CONCLUSIONS

Symptomology (American Psychiatric Association, 2000), familial risk (Potash, 2006), and putative genetic pathways (Craddock, O'Donovan, & Owen, 2009; Smoller et al., 2013) demonstrate both distinctive and overlapping elements in schizophrenia (SZ) and bipolar disorder with psychosis (BDP) diagnostic groups. The sum of results from **chapters 2-4** indicate that, through a careful consideration of the complexity of the auditory cortical response manifold across a variety of listening contexts, abnormalities in auditory neuropathology among persons with these disorders follow this same pattern of partial overlap. Taken together, the findings presented in the preceding text might provide fruitful leads toward the biological mechanisms of psychosis along with potent leads for future genetic studies utilizing intermediate phenotypes (Gottesman & Gould, 2003). **Chapter 2** compared auditory event related potentials (ERPs) between psychotic and non-psychotic persons with bipolar disorder in both passive (paired-stimulus) and active (oddball) listening settings to detail, in combination with previous reports (Ethridge et al., 2012; Hamm, Ethridge, et al., 2012), the specificity of auditory neural abnormalities to affective and/or psychotic pathological domains. Importantly, the psychotic family history appeared to modulate neural responses in a manner which suggested protective properties of intact early auditory circuits. **Chapter 3** focused on establishing effect sizes and familiality estimates of the complex constellation of abnormalities seen previously in passive paired-stimulus listening settings (Hamm, Ethridge, et al., 2012) using a large sample of SZ and BDP probands and unaffected first-degree relatives. A dichotomy of shared versus disorder-

specific auditory neural deviations emerged for early/low-frequency versus late/sustained potentials, respectively. A more general picture of ubiquitous familiality indicted that the entire auditory neural response, early and late, contains utility for investigating disease related genetic risk. **Chapter 4** systematically examined basic gamma-band entrainment capabilities along with low (theta and alpha) frequency transient response abnormalities across different stimulus duration and attentional contexts. This report established that theta frequency auditory neural oscillation abnormalities are context invariant, while higher frequency oscillatory abnormalities are dependent on the physical properties of the stimulus (duration; gamma) or whether attention is to be paid to the stimuli (alpha). A series of patterns pervade these three reports with regard to oscillatory frequency and specific spatiotemporal nodes in the auditory cortical circuit.

Low vs. High Frequency Oscillations in Psychosis

Reduced low frequency evoked oscillatory responses (lfERs; 1 – 7Hz; delta/theta band) to the onset of auditory stimuli in persons with SZ or BD may represent an elemental deficit in major psychiatric disorders given their i) invariance across numerous attentional and stimulus-parameter contexts and ii) commonality to both affective and psychotic domains of psychopathology. Previous reports from the current research group (Ethridge et al., 2012; Hamm, Ethridge, et al., 2012) along with the large sample demonstration in **chapter 3** indicate that lfERs to the onset of auditory stimuli in this low band are present regardless of DSM diagnostic group membership (i.e. BDP or SZ). **Chapter 2** also demonstrates that lfER reductions in general may index both affective and psychosis domain abnormalities within BDP. P3b components in oddball settings are mostly driven by low frequency oscillations in the delta range (Başar-Eroglu, Başar, Demiralp, & Schürmann, 1992) and, likewise, showed no-specificity with regard to affective or psychosis risk or expression in the results of **chapter 2.** This result agrees with

previous reports concerning the p3b (Ford, Mathalon, Kalba, Marsh, & Pfefferbaum, 2001; Linden, 2005).

While the exact neurophysiological processes or mechanisms indexed by lfERs are unknown, a relationship has been posited (Buzsaki, 2009) between the wavelength of a scalp EEG signal and the size of the network indexed thereby. Lower frequency oscillations index synchronization across broader cortical/subcortical nodes, while higher frequency oscillations index local synchronizations on the scale of interlaminar communication within a column or a few neighboring cortical columns (Uhlhaas, Pipa, Neuenschwander, Wibral, & Singer, 2011). This relationship likely reflects the physiological limits of neural signal transduction including axonal and synaptic conduction delays (Kopell, Ermentrout, Whittington, & Traub, 2000), but may also highlight the electrophysiological properties of thalamic reticular cells responsible for establishing distal cortical synchronization (Hughes & Crunelli, 2005). In this light, it is perhaps unsurprising that lfER disruptions would show non-specificity with regard to cognitive and clinical phenomenon since this index would likely be sensitive to the most distributed set of network nodes and, thus, insensitive to any one particular cortical auditory subcircuit carrying a disease specific process. Indeed, the time-window which must be used to estimate lfER magnitudes is wider than other frequency bands when using wavelet-based approaches (Roach & Mathalon, 2008), extending approximately 300ms and including P50, N1, p2, and n2 peaks in its calculation. It is still encouraging, however, that despite this temporal overlap, results in **chapter 3** indicate N1's, P2's, and lfER's all carry specific group discriminatory power. That is, as abnormalities, they vary somewhat independently across patients and healthy comparisons subjects.

In the past, the current research group (Clementz & Blumenfeld, 2001) and others (Hong, Summerfelt, Mitchell, O'Donnell, & Thaker, 2012) have grouped alpha-band evoked responses (abERs; 8-14Hz) together with lower frequency bands in lfERs as their amplitudes to vary together (Ivleva et al., 2013). Most of these reports, including the PCA-based analysis establishing their equivalence in **Chapter 3** and in Ivelva et al (2013), measured lfERs to brief "clicks" in a passive listening context (e.g. paired-stimuli). **Chapter 4**, to the contrary, demonstrates that auditory abERs are normal in SZ when stimuli are attended, contrasting the invariant lfER reductions. Time-frequency F-plots in Hamm et al (2012) and Ethridge et al (2012), taken together, further echo this attentional invariance of lfER but not abER reductions in psychosis. Hamm et al (2012), using a paired-stimulus paradigm which requires no active task, demonstrated that significant lfER reductions to the first auditory "click" extending above 10Hz, yet Ethridge et al (2012) identified lfER reductions during an oddball paradigm requiring attentive listening (a button press to 'targets'; see **chapter 2**) that were limited to approximately 7Hz and below.

The fact that SZ have more severe lfER reductions than BDP in **chapter 3** (defined as 3 to 17Hz) could indeed reflect this delta/theta versus alpha differentiation and emphasize the relative importance of evoked alpha-band, or faster latency auditory cortical responses, in understanding the interacting pathophysiology of affective and psychotic domains of psychiatry (see also the N1 effects in **chapter 2**). Interestingly, variants in genes directly controlling function of the GABA-b receptor, a slow acting extra-synaptic, normally inhibitory chloride ion channel (Kohl & Paulsen, 2010), have been associated with lower resting (or passive) alpha band power (Winterer et al., 2003). Other oscillatory abnormalities in SZ (Hamm, Gilmore, & Clementz, 2012) have been theorized to relate to this receptor in direct contrast to BD (Farzan et

al., 2010). The lack of both passive and active listening contexts in the **chapter 3** dataset prevented the direct disentanglement of this specific abER versus lfER effect. Future studies should focus on testing for a differentiation between SZ and BDP in lfERs (perhaps with a paradigm similar to **chapter 4**), along with potential ties to the previously under-investigated GABA-b association with non-affective psychotic pathology.

Abnormalities in the gamma range (30-55Hz), like lfERs, did not specifically differentiate SZ and BDP and, in contrast to lfERs, showed a highly variable presentation across contexts and samples. Baseline gamma-band oscillatory power was augmented in persons with psychosis in **chapter 3**, confirming some (Hamm, Ethridge, et al., 2012) but not all previous reports (Hamm, Gilmore, et al., 2012). Curiously, baseline gamma was normal in psychosis in the report in **chapter 4** and the dataset in **chapter 2**, which notably utilized identical parameters to **chapter 3** (gamma-band results reported in Hamm et al 2012 poster at *Biological Psychiatry* conference). This variability across samples could indicate the possibility that SZ and BDP, while classic phenomenologically defined diagnostic classes in psychiatry, actually contain a number of biologically heterogeneous categories (Keshavan, Clementz, Pearlson, Sweeney, & Tamminga, 2013). In fact, this possibility is more generally supported an appreciable degree of heterogeneity and overlap in SZ and BDP samples with regard to the evoked auditory cortical response manifold (demonstrated by the multivariate distributions displayed in **chapter 3;** figure 3.2). Thus the separate samples presented in different chapters and studies might inadvertently capture more neurophysiologically homogenous subgroups with regard to baseline gamma-band oscillatory activity, which could be augmented in only some persons with SZ and BDP.

Studies using an auditory steady-state paradigm invoking gamma-band entrainment in auditory cortices (or aSSRs; see **chapter 1**) might be better suited to test basic gamma-band

oscillatory capabilities (Brenner et al., 2009). While prestimulus gamma-band augmentations do not display heritability (**chapter 3**), aSSR abnormalities are, indeed, present in unaffected first degree relatives (Rass et al., 2012), suggesting their relationship to underlying disease processes. Still, contradictory results of reductions (Kwon et al., 1999), null effects (Hong et al., 2004), and augmentations (Hamm, Gilmore, et al., 2012) in 40Hz entrainment in SZ probands have been reported. **Chapter 4** added important information to this pattern of seeming inconsistency in the aSSR literature. While 40Hz entrainment in psychiatrically healthy individuals was enhanced when stimulus trains were expected to be short, 40Hz entrainment in persons with SZ remained at similar levels regardless of expected duration. This pattern of results explains the relatively consistent presence of 40Hz aSSR reductions when 500ms duration trains were used (Brenner et al., 2009) compared to diminished or opposite effect sizes when 1000 or 1500ms duration trains were used in the literature (Hamm, Gilmore, et al., 2012; Hamm, Gilmore, Picchetti, Sponheim, & Clementz, 2011; Krishnan et al., 2009).

Given the purported local versus global relationship between high and low frequency oscillatory brain processes, gamma-band measures could reflect focal cortical processes under diminished cognitive or higher-order control in psychosis. Lower-frequencies responses could reflect the interlobular/interhemispheric manifestations of cross-cortical synchrony constituting the basis of that control. Thus the disintegration of this low-frequency indexed synchrony could be the elemental deficit of major psychotic disorders, while the variable presentation of gamma-band deviations is a downstream consequence of this disrupted synchrony. Moran and Hong (2012) suggested that studies investigating phase-amplitude locking between low and gamma-band oscillations (amplitude of gamma modulated by phase of delta/theta/alpha oscillations) might resolve the variable gamma-band abnormality findings. Compared to point amplitude

measurements of oscillations, calculations of phase-amplitude locking might more closely resemble essential neural code (Buzsaki, 2009). None of the paradigms used in the current set of reports provided an optimal set of parameters for such an investigation since stimulus durations were relatively brief compared to the duration of a complete delta cycle (300-1000ms and longer), and stimuli were not held in working memory, a cognitive task known to invoke substantive phase-amplitude locking (Axmacher et al., 2010). Interestingly, working memory impairment has been theorized to comprise a core cognitive deficit in psychotic disorders (Glahn et al., 2003, 2007). Future studies should use long duration aSSRs with working memory components to test these important possibilities.

Matching a neurotransmitter system or circuit to a single EEG frequency band is a tempting enterprise given the notion that oscillations are highly controlled by regulatory genes directly influencing the disease-relevant neurochemical processes of the brain (Begleiter & Porjesz, 2006). This endeavor is nonetheless complicated both by a lack of understanding of the relationship of EEG oscillatory indices to elemental brain processes and by a general absence of spatial compartmentalization of major transmitter systems and biological pathways across cortical nodes. Indeed, animal and human pharmacological and genetic studies have provided evidence for a variety of putative systems driving variance in spontaneous and evoked oscillations.

Low frequency oscillations at rest are augmented in both SZ and BD psychotic groups (Clementz, Sponheim, Iacono, & Beiser, 1994), and this increase shares genetic variance with decreased to lfERs in psychosis (Hong et al., 2012). Importantly, variations in dopamine metabolism in the prefrontal cortex due to a val-158-met polymorphism have been shown to underlie low frequency abnormalities in psychosis (Venables, Bernat, & Sponheim, 2009). The

classic dopamine theory of psychosis pathophysiology posits reduced dopaminergic transmission in the prefrontal cortex and augmented dopaminergic transmission in the associative striatum (Laruelle, 2013). The fact that administration of dopamine agonists leads to greater than normal gamma-band aSSRs even at short durations (Albrecht, Price, Lee, Iyyalol, & Martin-Iverson, 2013) and has little effect on lfERs (Başar & Güntekin, 2008) presents problematic evidence against the dopamine theory when one considers the pattern of neural oscillatory abnormalities seen in **chapters 2-4**. Due to compensatory mechanisms in neural circuits, studies employing long-term administrations of DA antagonists might more accurately model the psychotic state and could, theoretically, give rise to i) the more nuanced state of hypo/hyperdopaminergia seen in psychosis and ii) the complex pattern of oscillatory abnormalities seen in the aforementioned reports.

Still, psychosis models and etiological theories based around disruptions in glutamatergic neurotransmission at the N-Methyl-D-aspartic acid (NMDA) receptor, the activation of which invokes a sustained post-synaptic excitation and plays a critical upstream role in synaptic plasticity, have gained attention in recent years. NMDA based models of psychosis can parsimoniously account for the cognitive and sensory abnormalities, as well as negative symptomology, seen in psychotic disorders (Javitt, 2009). Such frameworks assert that brain-region-specific dopamine dysregulation seen in psychosis is a downstream effect of a more primary NMDA dysfunction given the interaction of these two systems (Javitt, 2010). Additionally, pharmacological disruption of the NMDA-receptor site (with MK-801 or ketamine) not only recreates with appreciable fidelity the cognitive and perceptual distortions in psychosis (Javitt, Zukin, Heresco-Levy, & Umbricht, 2012), but also can manifest in a pattern of oscillatory abnormalities that mirror the above described effects. For instance, application of

NMDA antagonists, but not dopamine agonists, leads to both an decrease in lfERs and a dysregulation of gamma-oscillations in mice (Ehrlichman et al., 2009). This pattern is also seen in humans given NDMA antagonists as well (Hong et al., 2010). Chronic application of NMDA antagonists leads initially to a decrease of lfERs, followed later by gamma-band baseline and evoked power abnormalities in mice (Featherstone, Nagy, Hahn, & Siegel, 2013), suggesting a similar temporal priority of low to high frequency abnormalities seen in the current reports.

Glutamate and Gamma-Aminobutyric acid (GABA) neurotransmission are physiologically linked and comprise the vast majority of excitatory and inhibitory signaling in cortical neural circuits, respectively. Glutamic acid decarboxylase 67, or GAD67, is an enzyme which converts glutamate to GABA. GAD67 is selectively down regulated in neurons known to control gamma oscillations (Sohal, Zhang, Yizhar, & Deisseroth, 2009), i.e. basket cells containing parvalbumin, in the cerebral cortex of persons with schizophrenia and psychotic bipolar disorder (Veldic et al., 2007). GABAergic basket cells controlling theta-band oscillations (cholecystokinin cells) additionally show functional down regulation as well in psychosis (Curley & Lewis, 2012). Together with a down regulation of GAT1 transporters (which remove GABA from the extracellular space) and an up regulation of GABAa receptors in excitatory chandelier cells (Lewis, 2011), GAD67 alterations could ultimately reflect downstream effects due to deficits in glutamate neurotransmission (Behrens et al., 2007). While some previous theories have suggested that NMDA-hypofunction on basket cells could underlie both decreases (Rotaru, Lewis, & Gonzalez-Burgos, 2012) and increases (Hamm, Gilmore, et al., 2012) in gamma-band oscillations, recent work has challenged this idea given the subcellular distribution and temporal kinetics of NMDA receptors (Rotaru et al., 2012). Thus the link between NMDA

hypofunction, GABA-ergic alterations, and neural oscillatory abnormalities in psychosis remains unclear.

To further complicate the picture, acetylcholinergic (ACh) signaling has a modulatory effect on GABA-ergic control of gamma oscillations (Gonzalez-Burgos & Lewis, 2008) and enhances lfERs (Jones et al., 2006). ACh innervation of the cerebral cortex is widespread and generally serves to support arousal based enhancements in neural functioning (Hsieh, Cruikshank, & Metherate, 2000; Witte, Davidson, & Marrocco, 1997). Because attention driven gamma-band synchronization (Rodriguez, Kallenbach, Singer, & Munk, 2004) appeared to be intact in psychosis in **chapter 4**, the current data do not directly support an ACh based model of psychosis per se. Still, dysfunction of the alpha7 subtype of nicotinic ACh receptor has been linked to auditory cortical response modulation (Adler et al., 1998) and to genetic risk for schizophrenia (Martin et al., 2007). The CHRM2 gene, which directly controls muscarinic ACh receptor expression in the cerebral cortex, was associated with lfER magnitude and, in particular, the p3a potential in humans (Jones et al., 2006). The magnitude of the p3a was not only reduced in persons with psychosis but also appeared to comprise protective factor against developing psychosis in individuals at risk in **chapter 2,** suggesting an important role for CHRM2 in psychosis relevant biological pathways.

While the set of reports in **chapters 2-4** cannot completely sort out the neurochemical mechanisms of psychotic and affective pathology, they still provide new starting points for future pharmacological, optogenetic, or genetic-knockout animal studies to begin to narrow down or elaborate on these diverse mechanisms potentially underlying low and high frequency abnormalities in psychosis. That is, any animal model of psychosis should produce a reduction in lfERs across a variety of attentional and stimulus property contexts. Further, investigators should

measure baseline gamma-band magnitudes and should take into account physical stimulus properties (stimulus train duration and density) when utilizing the potent aSSR index.

Early, Transient vs. Late, Sustained Cortical Events

The question of whether to conceptualize a physical phenomenon as a wave or a particle has comprised a classic dialogue in modern science. When Hans Berger first described human EEG (Berger, 1929), he noted a clear wave-like rhythmicity in the scalp potentials at approximately 10Hz which came to be known as the alpha rhythm. Although advancements in computation eventually led cognitive and clinical EEG researches to focus on event related potentials (ERPs) and peak measurements thereof (a particle like conceptualization), consideration of oscillatory indices, especially as stimulus evoked events, have come to the forefront of EEG research in recent decades (Moran & Hong, 2011; Roach & Mathalon, 2008; Uhlhaas, 2011). This return to EEG oscillations is perhaps in part due to the observation that distinct cortical neural ensembles synchronize and perform key computations via population oscillations (Fries, Roelfsema, Engel, König, & Singer, 1997). The results in **chapter 3** and in Hamm et al (2012) highlight the advantage of examining both ERP time-voltage and time-frequency indices. That is, while oscillations may show close correspondence to neurochemical and genetic functions (Başar & Güntekin, 2008; Begleiter & Porjesz, 2006), time-voltage ERPs can add information about particular nodes in the auditory neural circuit and information regarding cortical sensory recovery functions indicated by baseline offsets and slow potentials. In addition to this improvement in theoretical explanatory power, the amount of group discrimination variance is demonstrably maximized through such a comprehensive approach (table 3.1).

The N1 ERP occurring approximately 100ms after stimulus onset is known to index the neural registration of an auditory event as it propagates to secondary auditory cortex (Rosburg, Boutros, & Ford, 2008; Yvert, Fischer, Bertrand, & Pernier, 2005). The N1 therefore represents a relatively early stage in auditory processing. Indeed, it is modulated by both physical properties of the stimulus (Verkindt, Bertrand, Perrin, Echallier, & Pernier, 1995) and cognitive context (Hillyard, Hink, Schwent, & Picton, 1973). **Chapters 2-4** demonstrate that the N1 ERP i) shows a complex relationship to psychotic and affective domains of psychopathology that appears in passive and active listening settings and ii) marks pathology independent of later ERPs (P2) and concomitant lfERs (**chapter 3**).

In both **chapters 2 and 3**, and also in demographic matched subsets of the same dataset (Ethridge et al., 2012; Hamm, Ethridge, et al., 2012), the N1 peak was unequivocally reduced in persons with psychosis. Hypofunctioning early auditory neural circuitry in psychosis has been theoretically linked to impaired GABA/NMDA mediated summation processes in feed-forward primary auditory cortical circuits (Hamm et al., 2011; Sweet et al., 2004). Such early impairments could contribute to a reduced signal to noise ratio in downstream auditory processing, resulting ultimately in perceptual disturbances and impaired differentiation of internally versus externally generated activation (Javitt, 2009; Perez et al., 2012). Indeed, reduced N1 amplitudes covary with auditory hallucinations in persons with psychosis (Hubl, Koenig, Strik, Garcia, & Dierks, 2007). Still, **chapter 2** demonstrates that N1 reductions are also present in non-psychotic BD (BDNP), suggesting that they additionally track with affective domains of psychopathological disturbance. N1s are not reduced in all BDNP. Persons with BDNP despite a family history of (and, theoretically, a risk for) psychosis have normal N1s to stimuli, and this effect is present in both active and passive listening contexts. Perhaps N1's

relationship to the biological processes underlying the affective psychopathological domain is not directly or indirectly causal, yet an intact N1 may serve to protect against the development of psychosis, suggesting a mechanistic role of early auditory circuitry in the expression of psychotic domains of psychopathology.

Interestingly, N1 amplitude in SZ was more severely reduced than in BDP (Glass's delta = .56 in SZ, .32 in BDP; also see supplemental table 3.3) replicating a previous report (Hamm, Ethridge, et al., 2012). Unlike the psychosis risk versus expression differentiation between BDNP and BDP, this differentiation was dependent on contexts, being absent when stimuli are actively attended (Ethridge et al., 2012). Because both abERs and lfERs could contribute to N1 amplitude, and because SZ abER reductions are limited to passive listening contexts, SZ could display disorder-specific abnormalities that are unique to passive-brain states. Complicating this interpretation is the fact that longer ISIs have been shown to elicit greater SZ N1 reductions than short ISIs (Rosburg et al., 2008). Oddball paradigms used in Ethridge et al (2012) used 1100ms ISI, while the paired stimulus paradigm employed in **chapter 3** had inter-pair intervals of 9000ms. Regardless of the causal mechanism, the BDP/SZ differentiation in this respect, nonetheless, suggests that separable auditory cortical processes involved in N1 generations are differentially related to affective and non-affective psychoses. In sum, the reports in **chapters 2-3** demonstrate that N1 reductions might actually reflect an number of overlapping disrupted auditory cortical processes both related directly and indirectly to affective, psychotic, and cognitive pathological processes.

The auditory P2 component occurs later than the N1 (approx. 180 to 250ms post stimulus onset), yet it demonstrates an equal (or even greater) signal-to-noise ratio and reliability to earlier auditory components (Rentzsch, Jockers-Scherübl, Boutros, & Gallinat, 2008). Further, the P2 is

reduced in psychosis at effect sizes clearly comparable to the N1 (**chapter 3**). It is therefore curious why the P2 is much less often studied in psychiatry, especially given the promise that it might carry additional pathophysiological variance than earlier components (**chapter 3**, discriminant analysis) and ultimately reflect unique cortical processes (Crowley & Colrain, 2004). EEG and MEG studies employing source analyses have concluded that the p2 might be generated by similar auditory cortical regions as the N1, but also including downstream, more tertiary auditory and associative cortices (Godey, Schwartz, de Graaf, Chauvel, & Liégeois-Chauvel, 2001). The P2 is more neuroplastic than the N1 as it is enhanced by auditory discrimination practice (Trainor, Shahin, & Roberts, 2003). Psychotic patients are particularly deficient in auditory discrimination tasks (Rabinowicz, Silipo, Goldman, & Javitt, 2000). Thus the P2 may represent the recruitment of associative and higher-order cortices which reinforce and/or formally process the auditory signal propagated from earlier nodes in the circuit. This interpretation is consistent with the fact that the P2, unlike earlier auditory components, is actually enhanced with age (Picton, Stuss, Champagne, & Nelson, 1984). Reduced P2 amplitude specific to persons experiencing (**chapter 3**) or at risk for (**chapter 2**) psychosis may therefore reflect an inability to properly amplify environmental auditory stimuli. Given that early auditory processing of the same stimuli may vary stochastically due to fluctuation in sensory cortices (Mathewson et al., 2011), an impaired ability to recover or amplify low fidelity signals might be reflected in both auditory perceptual disruption and P2 reduction.

The P2 was slightly more reduced in BDP compared to SZ, and it also showed reductions in BDP-rel but not SZ-rel. Given the differential relationship of the P2 to arousal compared to earlier auditory components (Crowley & Colrain, 2004), the results in **chapter 3** are consistent

with the increased autonomic arousal seen in BD (Levy, 2013). The fact that only passive listening was involved in **chapter 3** precluded a direct test of this hypothesis.

Two later components in the paired-stimulus paradigm more completely differentiated SZ from BDP/BDNP: a pre-stimulus positivity reflecting an earlier return to baseline for SZ than BDP or H, and an increased positivity in post-S2 potentials seemingly related to previous p50-suppression deficits in SZ (Chang, Arfken, Sangal, & Boutros, 2011). These effects were both significantly familial and differentiated non-psychotic first-degree relatives of SZ from relatives of BDP (**chapter 3**), suggesting their relationship to genetically relevant disease processes. Examining the waveforms in figure 3.1, it becomes apparent that these later ERP components might actually reflect an overall reduction in a slow going cortical negativity specific to SZ in this paradigm, showing similarities to the stimulus preceding negativity (SPN) previously demonstrated to be both reduced in psychosis (Wynn, Horan, Kring, Simons, & Green, 2010). The SPN reduction in SZ could be related to impaired cognitive processes such as executive function (Foster et al., 2013) and/or abnormal sensory expectation processes theoretically related to hallucinatory phenomena in SZ (Heinks-Maldonado et al., 2007). Perhaps this very association of psychosis to sensory and cognitive related deviations, rather than mania, fundamentally differentiates SZ from BDP.

ACh neurotransmission occurs broadly across the entire cerebral cortex playing a modulatory role in basic glutamatergic/GABAergic circuits (Gonzalez-Burgos & Lewis, 2008). ACh signaling also has a temporally sustained enhancing effect on neurotransmission (Hsieh et al., 2000). Disrupted ACh neurotransmission plays a pivotal role in Alzheimer's related psychosis (Marcello, Epis, Saraceno, & Di Luca, 2012), which, like schizophrenia, is preceded first by general cognitive decline (Addington & Barbato, 2012). Thus abnormalities specific to

pre-S2 sustained drift could theoretically stem from non-affective-psychosis-specific abnormalities in the ACh receptor, including the alpha-7 nicotinic site previously linked to SZ disruptions in sensory processing of multiple stimuli (Martin et al., 2007) and critically important in hippocampal circuits (Luntz-Leybman, Bickford, & Freedman, 1992). Paired-click studies, though they have traditionally focused on p50 peak measurements, should quantify the pre-S2 recovery function and binned post-S2 negativity in a search for mechanisms or genetic underpinnings of non-affective psychosis in particular.

Conclusion

The reports presented in **chapters 2-3** provide steps toward i) fine tuning our definitions of auditory cortical response markers for future, mechanism based research (e.g. considering stimulus duration in 40Hz aSSR studies) and ii) matching neurophysiological abnormalities with emerging genetic vulnerability markers. For instance, Smoller et al (2012) carried out a large scale, genome-wide association study seeking to identify genetic risk loci for both SZ and BD, along with 3 other major neuropsychiatric disorders. Notably, the CACNA1C and CACNB2 genes showed linkage specific to SZ, BD, and other major mood pathology. These genetic loci code for subcomponents of voltage sensitive calcium channels ubiquitously critical for action potential initiated neural signaling in the brain. Given the high degree of familiality of lfERs in comparison to other measures (**chapter 3**), their theoretical relationship to globally present neural processes, and their relative invariance across psychiatric disorder states (**chapters 2-4**), future research might benefit by using lfER's as an intermediate phenotype used to elucidate details of the pathologically relevant biological pathway from CACNA1C and CACNB2 genes to the psychotic/affective syndromes.

Above all, auditory cortical processing of even apparently simple stimuli is exceedingly complex, involving a number of transient events and sustained processes with different spatial and temporal-oscillatory scales. These neural components are additionally sensitive to both behaviorally relevant and seemingly quotidian variations in context alike. Alterations in this sensitivity might lie at the heart of the neuro-pathophysiology of psychotic disorders. If psychiatry is to progress towards a neurobiologically defined taxonomy, it is imperative that its search for biomarkers and electrophysiological starting points appreciate this complexity, which likely exceeds the complexity of even the human kidney (Meehl, 1989).

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