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Abnormal Beta and Gamma Frequency Neural Oscillations Mediate Auditory Gating in Schizophrenia

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by

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Each person whose signature appears below certifies that this thesis in his/her opinion is adequate, in scope and quality, as a thesis for the degree Doctor of Philosophy.

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ABBREVIATIONS

CNS	Central Nervous System
EEG	Electroencephalography
P50	Positive Deflection Appearing Approximately 50ms
N100	Negative Deflection Appearing Approximately 100ms
N40	Negative Deflection Appearing Approximately 40ms
ERP	Event Related Potential
CZ	Central Channel
FCz	Frontal-Central Channel
ANOVA	Analysis of Variance
S1	Stimulus 1
S2	Stimulus 2
C	Conditioning Stimulus
T	Testing Stimulus
ISI	Interstimulus Interval
HC	Healthy Controls
SZ	Schizophrenia
S2/S1	Gating Ratio
S1-S2	Amplitude Difference
Hz	Hertz
ms	Millisecond
NVLH	Neonatal Ventral Hippocampus Lesion
fMRI	Functional Magnetic Resonance Imaging

MRI	Magnetic Resonance Imaging
STG	Superior Temporal Gyrus
PFC	Prefrontal Cortex
CA3	Carbonic Anhydrase III
α 7 nAChR	Alpha7-Nicotinic Acetylcholine Receptor
GABA	Gamma Aminobutyric Acid
CHRNA7	Cholinergic Receptor, Nicotinic, Alpha Polypeptide 7
PANSS	Positive and Negative Syndrome Scale
SD	Standard Deviation
SCID-IV	The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders IV
dB SPL	Decibels of Sound Pressure Level
s	Seconds
HEOG	Horizontal Eye Movements
VEOG	Vertical Eye Movements
kΩ	Kiloohm
Ag–AgCl	Silver Chloride Electrode
μV	Microvolts
SPSS	Statistical Package for the Social Sciences
LSD	Fisher's Lease Significant Difference

ABSTRACT OF THE THESIS

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by

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Sensory gating is a process in which the brain's response to irrelevant and repetitive stimuli is inhibited. Poor P50 gating in those with schizophrenia is typically measured by the ratio or difference score of the event-related potential (ERP) amplitudes in response to a paired click paradigm. Failure to suppress the ERP in response to the second click is thought to reflect a faulty inhibitory system. Oscillatory activity during the inter-click interval in the beta (20-30 Hz) and gamma (30-50 Hz) frequency bands may reflect inhibitory processes initiated by the first click. Paired-auditory stimuli were presented to 131 participants with schizophrenia and 196 healthy controls. P50 ERP amplitude as well as averaged- and single-trial beta (20-30 Hz) and gamma (30-50 Hz) frequency power during the inter-click interval were measured from the CZ electrode site. Data were analyzed using a series of ANOVAs and regression models. The statistical analyses provide evidence that patients with schizophrenia exhibited less evoked beta and gamma power across the delay interval, particularly at the 0-100 ms time point, in response to S1. We found that evoked beta and gamma responses early during the 500 ms delay interval (0-100 ms) are critical in determining the S1 amplitude and

extent of P50 gating across the delay interval for both healthy controls and individuals with schizophrenia. Our findings also support a disruption in “gating in” processes in those with schizophrenia. The investigation of oscillatory activity at different time points during the inter-click interval may provide a new framework for studying the mechanisms that support sensory inhibition, and may help researchers and clinicians develop future cognitive training protocols.

CHAPTER ONE

INTRODUCTION

The central nervous system (CNS) integrates and processes sensory information from different parts of the body in response to environmental changes (Miller & Lane, 2000). A major component of sensory processing is the CNS's ability to adaptively inhibit irrelevant sensory input from the environment, known as "sensory gating" (Venables, 1963). Sensory gating serves as a protective mechanism that regulates the brain's sensitivity to incoming stimuli from "flooding" the higher cortical centers, known as "gating out" (Bunney et al., 1999; Clementz, Blumenfeld, & Cobb, 1997a; Freedman et al., 1987a; Venables, 1960). Sensory gating out prevents humans from being overwhelmed by redundant sensory stimulation, which allows humans to attend and respond to only salient and novel environmental stimuli, known as "gating in" (Adler, Pachtman, Franks, Pecevich, Waldo, & Freedman, 1982; Braff & Geyer, 1990; Braff, Swerdlow, & Geyer, 1994). Individuals with schizophrenia exhibit deficits in sensory gating, which may contribute to the sensory and cognitive disturbances associated with the disorder. While sensory gating is well characterized, neural mechanisms underlying such abilities remain unclear. The current study utilizes electroencephalography (EEG) to investigate the biological basis of sensory gating in healthy controls and individuals with schizophrenia.

The structure of this review will first address the sensory gating phenomenon and common electrophysiological methods of examining sensory gating within electroencephalography research, followed by current neurobiological mechanisms underlying normal and abnormal auditory gating as examined in healthy controls and

patients with schizophrenia. Descriptions of ERPs, neural oscillations, and specific brain regions as they relate to this phenomenon are provided. Thereafter, the relationship between ERPs and oscillatory dynamics recorded during sensory gating, cognition, and certain clinical symptoms are reviewed. Finally, a brief discussion of the future directions in sensory gating research and its important implications for the development of novel diagnostic tools and treatments are provided.

The Sensory Gating Paradigm

A common electrophysiological method of examining sensory gating involves comparing event-related potentials to repeated auditory stimuli using a paired-click or conditioning-testing paradigm (Eccles, 1969). These ERPs consist of a series of brain wave recordings from electrodes placed on the scalp during auditory stimulation (Santos et al., 2010). In response to brief non-startling sounds, humans exhibit a P50 ERP, which is the most positive deflection appearing approximately 50ms post-presentation of an auditory stimulus. The N100 is a negative ERP peaking between 75 and 150ms (Adler et al 1982; Boutros & Belger 1999; Grunwald et al., 2003). The P50 and the N100 are common measures of sensory gating, as these ERP components habituate to repetitive auditory stimuli in healthy and psychopathological populations. Recording P50 gating is proven optimal at the central (Cz) and frontal-central (FCz) sites of the scalp (Clementz, Geyer, & Braff, 1998). The Cz site, in particular, appears to be the most optimal site for discriminating healthy subjects from psychopathological groups, such as those with schizophrenia (Clementz & Blumenfeld, 2001; Clementz et al., 1998b; Freedman et al., 1997). Micouland-Franchi et al., 2014; Nagamoto et al., 1989; Waldo & Freedman, 1986).

As stated above, sensory gating is commonly measured using a paired-click paradigm. This paradigm includes two identical auditory clicks presented twice with a 500ms interstimulus interval (Hu et al., 2012; Freedman et al., 1987b). The first click is typically referred to as the S1 or "conditioning stimulus (C)," and the second click is commonly referred to as the S2 or "testing stimulus (T)." The terms "conditioning" and "testing" refer to the paradigm because the first stimulus is hypothesized to elicit the response to the target as well as relevant inhibitory mechanisms that suppress the brain's response to the second click (Olincy et al., 2010). In healthy subjects, researchers examining various interstimulus intervals (ISI) within the paired click paradigm have shown that the mechanism responsible for suppression of the second stimulus is most likely activated during the 500 ms ISI after auditory stimulus presentation. Longer intervals failed to effectively suppress the test response and appear more variable (Bak, Rostrup, Larsson, Glenthoi, & Oranje, 2014; Braff & Judd, 1987; Colpitts, Mayeno, & Gaglioardi, 1981; Dolu, Suer, & Ozesmi, 2001; Rentzsh et al., 2008). Effective gating has been found to decrease as ISI increases up to 1000 ms (Nagamoto et al. 1991; Fruhstorfer, Soveri, & Jarvilehto, 1970). While we know that a 500 ms ISI appears to be the most effective timing to activate the gating mechanism responsible for an attenuated S2 P50 amplitude, the physiological nature of this gating mechanism remains unknown. Researchers hypothesize that inhibitory activity builds during the delay period between the paired auditory stimuli, and that the testing stimulus is used to test the extent to which an individual can suppress or gate the S2 following exposure to S1 (Potter et al., 2006). When healthy individuals are exposed to pairs of repeated auditory stimuli, the P50 wave evoked by S2 is significantly lower in amplitude relative to the amplitude that is evoked

by the S1 (Fruhstorfer et al., 1970; Devrim-Ucok, Keskin-Ergen, & Ucok, 2008, Boutros, Korzyukov, Jansen, Feingold, & Bell, 2004a). More specifically, the S2 P50 amplitude typically decreases by over 60% relative to the S1 P50 amplitude (Moxon, Gerhardt, Gulinello, & Adler, 2003a).

P50 sensory gating is typically measured in two ways. The first method quantifies the ERP amplitudes in response to S1 and S2 as a ratio, where the average amplitude of the P50 response to S2 is divided by the average amplitude of the P50 response to the first click (e.g., S2/S1, gating ratio). The second method quantifies the amplitude difference between S1 and S2 (e.g., S1-S2; Smith, Boutros, & Schwarzkopf, 1994). Strong gating is defined by a S2/S1 ratio closer to 0, with healthy individuals commonly scoring below .50. A large amplitude difference also indicates normal or more effective sensory gating. In contrast, a high gating ratio indicates poor P50 suppression (Adler et al., 2004; Freedman et al. 1987a, Freedman et al., 2000; Patterson et al., 2008; Potter et al., 2006; Waldo et al., 1991). Poor sensory gating is defined by an elevated S2/S1 ratio closer to 1, and a small S2-S1 amplitude difference (Clementz, Geyer, & Braff, 1997a; Jin, Potkin, Patterson, Sandman, Hetrick, & Bunney, 1997). The computation of both the S2/S1 P50 ratio and S1-S2 P50 amplitude difference score is a more psychometrically reliable index of capturing P50 suppression (Smith, Boutors, & Schwarzopf, 1994).

Similar to the P50 literature of healthy subjects, the N100 waveform also exhibits a maximal pattern of S1 to S2 suppression when an ISI of 500 ms is used (Brenner et al., 2009; Kisley & Cornwell, 2006). Healthy individuals also show a decrement in the N100 S2/S1 ratio due to a smaller S2 amplitude compared to the S1 amplitude in addition to a large S2 and S1 amplitude difference; this reflects normal sensory gating processes (Hu

et al., 2012; Javitt et al., 2009). The N100 is a measure of auditory sensory perception that is also related to later attention processes (O'Donnell et al., 2004).

Neural Oscillatory Activity and Sensory Gating

Neural oscillations are defined as rhythmic shifting of neuronal populations between high and low excitability states, and can be classified by its frequency in cycles per second or Hertz (Hz) (Schroeder, Lakatos, Kajikawa, Partan, & Puce, 2008). In response to environmental sensory stimuli, a neuron or population of neurons can change the frequency at which it fires, depending on the summation of excitatory postsynaptic activity in neurons (Siegel, Donner, & Engel, 2012). Oscillatory activity that is spontaneous is referred to as *induced oscillations*, and involves evaluation of single-trials in lieu of averaged responses, because their latency varies from trial to trial. Induced oscillations preserves activity that is not time-locked to the stimulus. Compared to induced oscillations, *evoked oscillations* are strictly phase-locked to the onset of the stimulus and are measured by stimulus-triggered averages of responses**.**

Several studies on synchronized neural oscillations have demonstrated the contributions of oscillatory activity to auditory sensory processing in healthy participants and in patients with schizophrenia. Using time-frequency analysis, studies have found that the auditory stimulus used to elicit P50 ERPs also evoke oscillatory activity in a wide spectrum of frequency bands (Brenner et al., 2009; Hong, Summerfelt, McMahon, Thaker, & Buchanan, 2004; Hong et al., 2008; Jansen, Agarwal, Hegde, & Boutros, 2003; Jansen, Hegde and Boutros, 2004; Makeig et al., 2002; Makeig, Debener, Onton and Delorme, 2004; Singer, 1999; Senkowski, Schneider, Foxe, & Engel, 2008; Smucney et al., 2013; Uhlhaas and Singer, 2010). In human literature, oscillatory activity is

typically subdivided in five frequency bands: delta- (0–3 Hz), theta- (4–7 Hz), alpha- (8–12 Hz), beta- (13–30 Hz), and gamma-band (30–200 Hz). Oscillatory activity in the beta and gamma frequency bands have been found to represent different aspects of auditory information processing (Kopell, Ermentrout, Whittington, & Traub, 2000; Pantev, 1995; Traub, Jefferys, & Whittington, 1999b; Uhlhaus et al., 2008). For example, gamma oscillations are associated with local sensory integration of stimuli to form an object or scene, immediate stimuli registration (Eckhorn et al., 1988; Tallon-Baudry and Bertrand, 1999) and memory formation (Csicsvari, Jamieson, Wise, & Buzsaki, 2003; Gruber & Muller, 2005; Herrmann, Lenz, Junge, Busche, & Maess, 2004). In contrast, beta oscillations are associated with salience detection, encoding, and consolidation of sensory information over long distances across cortical regions (Bibig et al., 2001; Brenner et al., 2009; Haenschel, Baldeweg, Croft, Whittington, & Gruzelier, 2000; Kisley & Cornwell, 2006; Kopell et al., 2000; Leiberg et al., 2006; Hong, Summerfelt, McMahon, Thaker, & Buchanan, 2004a; Traub et al., 1999a; Uhlhaas et al., 2008; Siegel et al., 2012). For example, beta band responses to S1 are shown to predict subsequent P50 amplitudes to S2, indicating a role in stimulus encoding (Hong et al., 2004).

Several studies have also examined the gamma-to-beta frequency shift phenomenon in neuronal networks as observed on the human scalp using ERPs in response to a single click auditory stimulus (Haenschel et al., 2000; Hong et al., 2004; 2008a). For example, Hong and colleagues (2004) found that averaged gamma frequency was followed by beta frequency in healthy controls and patients with schizophrenia post-S1. Hong et al. (2004) demonstrated that the latency for frequency shift in the scalp occurred about 60-120 ms after S1 for both patient and controls; however, other studies

have found that this frequency change occurs at approximately 200 ms when induced by tetanic stimulation in hippocampal slices of rats (Traub, Whittington, Buhl, Jeffrys, & Faulkner, 1999a; Bibbig et al., 2001; Whittington, Traub, & Jeffreys, 1995) and in human EEG recordings (Haenschel et al., 2000; Hong et al., 2004). Induced gamma activity is found to begin within the same time frame as the P50 and N100 ERPs (Trautner et al., 2006). Haenschel and colleagues (2000) also found that an evoked gamma band was followed by a beta band response, but only when the auditory stimulus suddenly changed, providing further evidence that beta oscillations reflect stimulus salience detection and possibly attention switching.

Sensory Gating Deficit and Schizophrenia

P50 Gating Event-Related Potentials in Schizophrenia

Dysfunction in sensory gating has been demonstrated in a number of psychiatric disorders; however, it has been largely examined in schizophrenia for approximately three decades (Franks, Adler, Waldo, Alpert, & Freedman, 1983; Adler et al., 1982; Boutros et al., 2004). Extensive literature examining sensory gating deficits in the paired-click paradigm have generally found that both the P50 and N100 ERP sensory gating ratios are higher among patients with schizophrenia compared to healthy subjects, suggesting poor auditory gating mechanisms (Adler et al., 1982; Clementz, Geyer, & Braff, 1997b; Freedman, Adler, Waldo, Pachtman, & Franks, 1983; Freedman et al., 1996; Boutros et al., 1999; Javitt, 2009; Patterson et al., 2000; Boutros, Overall, Zouridakis, 1991a, 1992; Boutros et al., 2004; Braff & Geyer, 1990; Light, Geyer, Clementz, Cadenhead & Braff, 2000; Myles-Worsley, 2002; Clementz et al., 1998, 2003; Hong et al., 2004; Budnick, &Braff, 1992; Olincy et al., 2010; Ringel et al., 2004;

Johannesen, Kieffaber, O'Donnel, Shekhar, Evans, & Hetrick, 2005; Nagamoto, Adler, Waldo, Griffith, & Freedman, 1991; Price et al., 2006; Brockhaus-Dumke et al., 2008a; Jansen, Hu, & Boutros, 2010; Bak et al. 2014; Siegel, Waldo, Mizner, Adler, & Freedman, 1984). Thus, heightened response to the second auditory stimulus in patients with schizophrenia conceptually demonstrates a deficient or ineffective inhibitory mechanism where patients are more distracted by redundant and irrelevant environmental stimuli (Smucney et al., 2013). Although healthy subjects demonstrate effective suppression of S2, they still hear the second sound. The role of sensory gating is not to filter out all sounds from reaching the cortical centers. Rather, the purpose of sensory gating is to dampen the signal of unimportant stimuli so that humans may differentially attend to relevant stimuli (Turetsky, Calkins, Light, Olincy, Radant, & Swerdlow, 2007). Findings of decreased P50 and N100 ERP attenuation has been one of the most robust findings in schizophrenia research (Turetsky et al., 2007).

The Consortium on Genetics of Schizophrenia is the largest study to examine P50 auditory gating in healthy community members, patients with schizophrenia, and their non-psychotic relatives (Olincy et al., 2010). In this study, Olincy and colleagues (2010) found that approximately 40% of patients' first-degree relatives had poor P50 gating comparable to their affected family members. Relatives showed significantly larger gating ratios and smaller S1-S2 difference scores than healthy community controls. Moreover, Siegel et al. (1984) found that half of first-degree relatives (e.g., at least one parent) demonstrated poor inhibition of the P50 wave, as reflected in an abnormal S2/S1 ratio. Unmedicated patients with schizophrenia and their biological relatives had larger S2 P50 amplitudes relative to healthy controls. However, patients had worse P50 gating

than their relatives, who had worse inhibition than the healthy controls (Siegel et al., 1984). Interestingly, Siegel et al., (1984) found that relatives who had an abnormal gating ratio presented with normal P50 S1 amplitudes, whereas individuals with schizophrenia who have similarly elevated gating ratios did not. Individuals with schizophrenia generated a smaller S1 amplitude response compared to their first-degree relatives. Results from this study suggest that P50 gating deficits can occur in the absence of overt psychosis. In addition, although first-degree relatives share a certain degree of sensory gating deficit that is similar to those with schizophrenia (e.g., poor inhibition of the S2 P50 amplitude), they do not share a secondary marker that is associated with the manifestation of clinical symptoms (Siegel et al., 1984).

Other studies of first-degree relatives of patients with schizophrenia further corroborate the hypothesis that abnormal P50 gating may be a possible endophenotype (Adler, Hoffer, Griffith, Waldo, & Freedman, 1992; Clementz, Geyer, & Braff, 1998; Louchart-de la Chapelle et al., 2005; Myles-Worsley, 2002; Siegel et al., 1984; Waldo, Adler, & Freedman, 1988, 1995; Waldo et al., 1991). However, the idea of abnormal gating being a viable endophenotype remains unclear, as some studies have not found P50 gating deficits in patients with schizophrenia nor their unaffected first-degree relatives (Arnfred, Chen, Glenthoj, & Hemmingsen, 2003; de Wilde, Bour, Dingemans, Koelman, & Linszen, 2007; Brenner et al., 2009; Jin et al., 1998; Kathmann & Engel, 1990; Turetsky, Bilker, Siegel, Kohler, & Gur, 2009). Genes have been identified that may be involved in the illness, but have not been widely nor consistently replicated (Freedman et al., 2003).

Genetic studies on neural oscillations and auditory sensory gating have advocated the use of beta and gamma frequencies as endophenotypes for schizophrenia. A study by Hong and colleagues (2004b) showed that reduced gamma band activity is also observed in first-degree relatives of patients with schizophrenia. Furthermore, gamma deficits appear to exist in first-episode patients (Gallinat, Winterer, Herrmann, & Senkowski, 2004; Spencer, Salisbury, Shenton, & McCarley, 2008; Symond, Harris, Gordon, & Williams, 2005). However, results from Hall and colleagues (2011) show that neither gamma or beta gating are abnormal in relatives, and that relatives did not differ significantly from controls.

Although the P50 sensory gating deficit is considered an endophenotype in some studies, this deficit is not specific to schizophrenia, and is also found in schizotypal personality disorder, bipolar disorder, Huntington's disease, and Autism Spectrum Disorder (Magnee, Oranje, Engeland, Kahn, & Kemner, 2009). Early problems in P50 suppression have been found to relate to positive symptoms, such as perceptual anomalies and magical ideation in patients with a diagnosis of schizotypal personality disorder (Croft, Lee, Bertolot, & Gruzelier, 2001; Cadenhead, Light, Geyer, & Braff, 2000; Jin et al., 1998). Patients with acute mania have also demonstrated deficits in P50 suppression (Adler et al., 1982). However, P50 gating deficits tend to normalize upon remission of manic symptoms, while these same deficits are more persistent in patients with schizophrenia (Franks et al., 1983). Together, these studies suggest that further research is needed to determine the status of P50 gating and neural oscillations in the beta and gamma frequency ranges as an endophenotype for schizophrenia.

Mechanisms of P50 Sensory Gating

Although a large number of studies have sought to determine the factors that contribute to sensory gating scores among healthy and pathological populations, the mechanistic underpinnings that lead to sensory gating remain unknown (Brockhaus-Dumke et al., 2008; Brenner et al., 2009). Many studies have traditionally examined sensory gating and its disturbance in schizophrenia in terms of deficits in suppression or "gating out" extraneous information. These studies all suggest sensory gating deficits in schizophrenia, in which a larger gating ratio and/or a small S1-S2 difference value are thought to reflect a lack of suppression of the second auditory stimulus. However, more recent studies have increasingly demonstrated that sensory gating deficits are not only limited to gating out stimuli (represented by suppression of the S2 response), but may in part be due to abnormalities in the response to S1 as well (Smith, Grant, Fisher, Borracci, Labelle, & Knott, 2013). Three etiological hypotheses of reduced sensory gating have surfaced in the literature that have distinctively highlighted the roles of the S1 amplitude, S2 amplitude, and the combined effect of both.

Sensory "Gating Out" Mechanism

One explanation for poor sensory gating is that the S2 response amplitude is not suppressed in the presence of a normal S1 amplitude, which indicate poor "gating out" (Brenner et al., 2009). Poor suppression of the S2 response indicates a reduced ability to habituate or inhibit the brain's response to repeated and irrelevant auditory stimuli. It has also been hypothesized to indicate a deficit in the brain's ability to activate the inhibitory processes responsible for suppressing the response to the second click. This results in a failure to 'gate out' the irrelevant and redundant auditory stimulation that is the S2 (Adler

et al., 1982; Clementz et al., 1997b; Freedman et al., 1987; Olincy et al., 2010; Turetsky et al., 2007; Smucney et al., 2013). Many studies have determined that the lack of suppression to the second stimulus is a core determinant of an elevated gating ratio score (Chang, Arfken, Sangal, & Boutros, 2011; Clementz et al., 1998; Clementz et al., 1997b; Freedman et al., 1987; Jin et al., 1997; Smith et al., 2010). Past studies by Clementz et al. (1997) show no group difference in S1amplitude responses, but found that patients had a significantly larger P50 S2 amplitude (worse P50 suppression) than healthy controls. Studies that have specifically questioned the importance of the S1 amplitudes have indicated that poor sensory gating—as indicated by a large S2/S1 ratio—is not related to the S1 amplitude response, but rather the S2 amplitude (Clementz, Geyer, & Braff, 1997; Jin et al., 1997). In examination of healthy subjects, Fuerst and colleagues (2007) corroborate previous findings by demonstrating that the S1 amplitude is not significantly correlated with nor is it predictive of the gating ratio.

In a most recent meta-analysis of the P50 sensory gating literature by Chang and colleagues (2011), the authors found that 38 out of 58 studies yielded results that support a smaller mean S1 amplitude in schizophrenia patients. However, the authors found more consistent support across 52 out of 58 studies for a larger mean S2 amplitude and S2/S1 ratio in schizophrenia patients compared to healthy subjects. Based on these findings, they concluded that deficits in S2 gating are not contingent upon patients' ability to register the first auditory stimulus (e.g., an abnormal S1 response to novel auditory stimuli), as the effect size of the S2 amplitude and P50 gating ratio is much larger in patients with schizophrenia compared to healthy controls (Chang et al., 2011).

Findings from extensive P50 literature indicate that abnormal P50 gating (S2 responses) in patients with schizophrenia may better elucidate the mechanisms of change in reference to the brain's response from S1 to S2 stimuli between healthy and schizophrenia groups than S1 alone. Together, these studies continue to raise the question of whether the P50 S1 amplitude is a candidate for a schizophrenia endophenotype. More research with large patient samples is needed to better clarify the contribution of the S1 amplitude in the P50 gating process, as it seems that S1 alone is not sufficient in explaining poor suppression of S2 in patients with schizophrenia (Chang et al., 2011). Moreover, because the majority of P50 gating literature has utilized the S2/S1 gating ratio as the dominant measure of sensory gating, the authors strongly suggest the use of the S1-S2 amplitude difference measure along with the gating ratio in order to provide a more comprehensive examination of sensory gating deficits in schizophrenia (Chang et al., 2011).

Sensory "Gating In" Mechanism

The second explanation for poor sensory gating is that the response to S1 is abnormally small in the presence of a normal S2 amplitude, which indicates poor "gating in" (Blumenfeld & Clementz, 2001; Boutros, Zouridakis, & Overall, 1991b; Brenner et al., 2009; Brockhaus-Dumke et al. 2008; Clementz et al., 2003; Clementz & Blumenfeld, 2001; Jansen et al., 2004; Jin et al., 1997; Johannesen et al., 2005; Smith et al., 2010; Vohs et al., 2009; Zouridakis, Boutros, & Jansen, 1997). Response to the first auditory stimulus is proposed to be an important determinant of sensory gating, as it is driven by attention and encoding processes that activate an inhibitory mechanism to suppress the brain's response to the second stimulus (e.g., subsequent irrelevant and repeated sounds).

This “gating in” process is associated with Venable's (1964) seminal proposal that involuntary attention is what normally allows the brain to focus on sounds of interest, so that humans are not drawn to trivial environmental sounds. Healthy subjects generally have a larger response to the first stimulus, reflecting the brain's ability to attend to novel and salient auditory changes in the environment. This in turn, facilitates the filtering of subsequent extraneous information (Blumenfeld & Clementz, 2001; Boutros, Zouridakis, & Overall, 1991; Clementz & Blumenfeld, 2001; Jin et al., 1998; Johannesen et al., 2005). In contrast, a small S1 response indicates failure of the nervous system to register and/or attend to the first auditory stimulus, which contributes to poor sensory gating (Brenner et al., 2009).

Similarly, researchers have also found a decreased N100 amplitude in response to S1 in patients with schizophrenia (Clementz et al., 2001; Clementz et al., 2003; Boutros et al., 2004; Jansen et al., 2004; Smith et al., 2010). Smith and colleagues (2010) specifically demonstrated that the N100 ratio score group differences were due to a smaller S1 response in patients with schizophrenia, and reflected a deficit in attention and encoding processes of auditory information rather than the ability to filter unimportant information. Brockhaus-Dumke and colleagues (2008) found that the S1-S2 difference was highly correlated with the P50 and N100 S1 amplitudes, but weakly with the S2 amplitudes, which reflects an impairment in stimulus attention and registration. Furthermore, Johannesen et al. (2005) noticed a small S1 response in the presence of a normal S2 response, which led to an elevated P50 gating ratio among schizophrenia patients. A small S1 amplitude is conceptually driven by the brain’s failure to register and/or attend to the S1 auditory stimulus, which creates difficulty in discriminating

and/or responding to novel, changing, and specific stimuli and is related to "gating in" processes (Brenner et al., 2009; Brockhaus-Dumke et al. 2008a; Smith et al., 2010). Both of these theorized etiologies of sensory gating abnormalities are in line with Boutros and colleagues' (1999) statement that ERPs, which are elicited using the paired-click paradigm, reflect the nervous system's abilities to 1) screen out unnecessary information from the environment, which is measured by ERP amplitude to S2 compared to S1; and 2) 'gate in' novel, salient, and changing information, which is measured by ERP response amplitudes to S1.

Studies on animals have further provided support for the sensory "gating in" literature. Rodents are often used in P50 research, as they share similar ERP components and characteristics with human P50 ERPs during the paired-click procedure (Adler, Rose, & Freedman, 1986; Boutros, Bonnet, Milana, & Liu, 1997; Mears, Klein, & Cromwell, 2006; Miyazato, Skinner, Crews, Williams, & Garcia-Rill, 2000; Phillips, Ehrlichman, & Siegel, 2007; Stevens, Nagamoto, Johnson, Adams, Rose, 1998). The N40 ERP in rodents, which is a negative deflection after 40ms post-stimulus onset, is considered to be analogous to the human P50 ERP by many researchers (Boutros, Zouridakis, & Overall, 1991b; Stevens et al., 1997, Boutros, Uretski, Berntson, & Bornstein, 1994; Boutros & Kwan, 1998; Stevens, Fuller, & Rose, 1991; Stevens, Meltzer, & Rose, 1995). Similar to how sensory gating is measured in humans, the S2/S1 gating ratio is also used to reflect sensory gating efficacy in rodents (Vohs et al., 2009). Lesions in the frontal (Korzyukov et al., 2007; Weisser, Weisbrod, Roegrig, Rupp, Schroeder, & Scherg, 2001) and hippocampal regions (Freedman, Waldo, Brickford-Winner, & Nagamoto, 1991; Moxon, Gerhardt, & Adler, 2003b) have been found to impact sensory gating in both humans and

rodents. Damage to the ventral hippocampus in rodents leads to the emergence of "schizophrenia-like" symptoms and behaviors and may mimic the developmental pathogenesis of schizophrenia as these rodents transition into adulthood. These symptoms include increased sensitivity to the environment and deficits in working memory and inhibition (Lipska, Swerdlow, Geyer, Jaskiw, Braff, & Weinberger, 1995; Chambers, Moor, McEvoy, & Levin, 1996; Al-Amin, Weinberger, & Lipska, 2000; Le Pen & Moreau, 2002). In rats with neonatal ventral hippocampus lesion (NVLH), Vohs and colleagues (2009) found a reduced S1 response but failed to detect gating ratio deficits. The authors credited this gating ratio discrepancy to the lack of pharmacological manipulations in rats, as the rats were not affected by psychotropic medications as patients with schizophrenia oftentimes are. These results are similar to those found in other studies that have consistently reported S1-mediated gating deficits in schizophrenia with humans and rat models (Boutros et al., 1997; DeBruin, Ellenbrock, van Luijtelaar, 2001; Mekeig, 1993).

Combined Sensory Gating In and Gating Out Mechanisms

The third possible explanation for poor sensory gating is that there may be an unidentified relationship between the S1 and S2 responses, in which both the response to both S1 and S2 amplitudes are impaired. Although attention to sensory stimuli and inhibitory processes are often viewed as distinct processes involving separate brain networks (Posner, 2004), these two systems can also interact and may not function independently from one another (Gjini, Arfken, & Boutros, 2010). For example, attention to sensory stimuli may be affected by inhibitory mechanisms, and vice versa, through both bottom-up and top-down processes (Hillyard, Vogel, & Luck, 1998; Hu et al., 2012;

Posner, 2004; Woldorff et al., 1993; Yee et al., 2010). Given that the response to S1 is hypothetically linked to the activation of neuronal gating mechanisms that inhibit the response to S2, a relationship between the two systems is likely. More specifically, it is theorized that once the first stimulus in a paired-click procedure is detected, subsequent stimuli are predictable and lose their relevance, making the sensory information subject to be "gated out" (Hu et al., 2012).

Several studies have found support for a combined sensory gating in and gating out mechanism, in which deficits in one domain can damage aspects of the other. A study by Yee and colleagues (2010), demonstrated the effects of P50 amplitude to S1 on P50 amplitude to S2 in patients with chronic and recent-onset schizophrenia when attention is manipulated. In this study, when chronic and recent-onset schizophrenia patients were told to direct voluntary attention toward the first sound, the chronic patient group showed an enhanced P50 response to S1 and an improved sensory gating ratio that was comparable to those of healthy subjects. The recent-onset schizophrenia group showed reduced P50 response to S2 and improved sensory gating; however, the S1 amplitude did not differ from baseline. Thus, manipulation and control of early attention can possibly have a modulatory influence on P50 gating of the second stimulus, suggesting that gating deficits in schizophrenia can be improved without the use of pharmacological interventions. In a study examining whether response variability and incompleteness is associated with P50 and N100 gating deficits, Jansen and colleagues (2010) found that gating deficits in schizophrenia are due to both an inconsistent S1 response (e.g., higher trial-to-trial S1 response latency variability or fewer S1 complete responses containing P50 and N100 ERPs) and a reduced attenuation response to S2 in patients with

schizophrenia relative to healthy controls. However, smaller S2 than S1 responses were noticed in both patients and healthy controls following complete S1 responses (Jansen, Hu, & Boutros, 2010). Due to existing debates in the sensory gating literature regarding the etiology of an elevated gating ratio, it is thus fundamental for prospective sensory gating research that are utilizing the paired-click paradigm to test both the gating out (e.g., the degree of attenuation from S1 to S2) and gating in (e.g., abnormal S1 amplitude response) processes. The present study will further examine the gating in and gating out mechanisms underlying the sensory gating phenomenon.

Neural Oscillatory Activity and Sensory Gating in Schizophrenia

Several investigations have demonstrated the relationship between abnormal oscillatory activity, ERP amplitudes, and the psychopathology of schizophrenia (Andreasen, Nopoulos, O'Leary, Miller, Wassink, & Flaum, 1999; Andreasen, 2000; Senkowski and Gallinat, 2015; Uhlhaas et al., 2008). Oscillatory abnormalities have been identified among patients with schizophrenia, specifically in the gamma- (Clementz, Blumenfeld, & Cobb, 1997a; Johannesen et al., 2005; Hall et al., 2011) and beta-band oscillations after presentation of the first auditory stimulus **(**Clementz and Blumenfeld 2001; Hall et al., 2011; Hong et al., 2008; Uhlhaas & Singer, 2010). Oscillatory activity within both the gamma (35-45 Hz) and beta (13-30 Hz) frequency range has been found to contribute to auditory P50 ERP responses in the time-frequency domain (Haenschel et al. 2000).

Gamma Band Activity and P50 S1/S2 Amplitudes

Many studies have examined gamma-band activity in patients with schizophrenia,

and have provided evidence for the presence of abnormal gamma oscillations (Uhlhaas et al., 2008). Researchers have demonstrated reduced gamma band activity after presentation of the first stimulus in patients with schizophrenia within the P50 (55-60 ms) time window (Basar, Rosen, Basar-Eroglu, & Greitschus, 1987; Clementz & Blumenfeld, 2001; Clementz, Blumenfeld, & Cobb, 1997a; Hall et al., 2011; Johannesen et al., 2005). When comparing auditory gamma activity to P50 ERPs, Basar and colleagues (1987) reported that the gamma band activity temporally and morphologically overlapped with ERP components. Researchers have also found significant positive correlations between gamma power to S1 and P50 S2 amplitudes in healthy controls (Hall et al., 2011) as well as patients (Hong et al., 2004). Hong et al. (2004) hypothesize that gamma's positive relationship to S2 amplitude in patients may be due to the hyperexcitability of neural substrates, which in turn, leads to poor P50 gating (Adler, Freedman, Ross, Olincy, & Waldo, 1999). Thus, the more excitable the post-S1 gamma response, the lesser the S2 suppression. Hall and colleagues (2011) provide further support by finding reduced gamma power to S1 stimuli and reduced beta power to S2 stimuli in patients compared to controls.

These results lead us to propose that S1 P50 responses and evoked gamma activity reflect the same phenomenon, and that gamma band activity is associated with stimulus onset (Crone, Boatman, Gordon, & Hao, 2001; Basar et al., 1987; Clementz et al., 1997a; Clementz & Bloomenfeld, 2001; Kopell et al., 1999). Although the S1 P50 ERP and gamma band activity appear to overlap in the time-frequency domain and may potentially explain ERP abnormalities within schizophrenia, results have been inconsistent (Brenner et al., 2009; Brockhaus-Dumke et al., 2008). Some studies have

also found no significant difference between healthy and patients in the gamma band response in auditory sensory gating (Brenner et al., 2009; Clementz et al., 1997; Clementz & Blumenfeld, 2001; Hong et al., 2008).

Beta Band Activity and P50 S1/S2 Amplitudes

Beta activity in relation to schizophrenia has been less explored in comparison with gamma band activity. Hall et al. (2011) found reduced beta power to S2 in several brain regions in patients compared to healthy controls in addition to finding that post-S1 beta power was significantly associated with the P50 S2 amplitude in healthy controls, but not patients. Hong and colleagues (2004) observed the gamma-to-beta shift in response to the first stimulus in the paired-click paradigm and found that beta (14-26 Hz) oscillations negatively contributed to the S2 amplitude when examined together with gamma (30-50 Hz) oscillations within the gamma-to-beta shift in patients with schizophrenia, suggesting that less P50 gating is associated with post-S1 beta amplitude (Hall et al., 2011). Together, averaged beta and gamma oscillations explained approximately 59% of the S2 variance in schizophrenia patients (Hong et al., 2004).

Correlations Between Beta Activity and Event-Related Potentials

Hong and colleagues (2004) did not find significant correlations between beta activity and P50 S1 or S2 amplitudes, suggesting that the negative contribution of beta to S2 may occur only in the context of gamma/beta oscillation in patients with schizophrenia. However, whether a “coupling mechanism” of gamma/beta oscillation or the individual frequencies themselves is associated with the S2 amplitude in patients remains unclear (Hong et al., 2004). Although gamma/beta oscillations were observed in

healthy controls, both frequencies were positively but non-significantly related to the S2 amplitude. Beta oscillations have also been shown to contribute to the N100 amplitude (Kisley & Cornwell, 2006). No significant interactions were found between gamma and beta frequencies in the control and patient groups (Hong et al., 2004).

Frequency Bands, Delay Interval Time Points, and P50 Gating

In a follow-up study, Hong and colleagues (2008) identified the time- and frequency-specific oscillatory components contributing to sensory gating using a paired-click paradigm with only healthy subjects. The authors examined alpha and theta (5-12 hz), beta (12-20 hz), low gamma (20-40 hz), and high gamma (40-85 hz) within single trials of 500 ms EEG that were separated into four distinct 125 ms time points (-100-25, 26-150, 151-275, and 276-400 ms). For low gamma (20-40 hz), time points 26-150 ms, 151-275 ms, and 276-400 ms had increased power compared to baseline (0-25 ms). For beta (12-29 hz), power increased at 26-150 ms and 151-275 ms, but returned to a baseline level at 276-400 ms before the onset of S2. The authors found a persistent beta oscillatory response from 26-375 ms within the inter-click interval. Kisley and Cornwell (2006) found an observable reduction in induced beta activity within the 200-500 ms delay window in healthy controls. At time points 26-150 ms and 151-275 ms, the P50 gating ratio was significantly associated with beta oscillatory EEG activity**,** but not gamma or alpha/theta frequencies (Hong et al., 2008).

Hong and colleagues (2008) also found significant correlations between the S2 P50 amplitude and beta power at 26-150 ms, but not with alpha or gamma in healthy controls. This is consistent with other studies that have found a correlation between

reduction in beta band activity to the first click and abnormality in P50 gating measures in patients (Hall et al., 2011; Hong et al., 2004), suggesting that beta in response to S1, but not other frequencies, affected the S2 P50 amplitude and P50 ratio in a similar way and is indicative of a neural process associated with the strength of sensory gating (Hong et al. 2008). The results of Hong et al. (2008)'s study demonstrated that the effect of single-trial beta response on P50 gating may approximately span a 300 ms window in healthy subjects; however, the relationship remains unclear in patients with schizophrenia.

The results of these studies support the idea that both gamma and beta power contribute to the generation of P50 ERPs. The results of research on spectral frequency demonstrate that within the wide spectrum of frequency bands, a beta frequency band appears most relevant in determining the degree of auditory gating in humans, such that a larger beta response to S1 predicted stronger S2 P50 amplitude attenuation and P50 gating scores. This finding is consistent with the notion that the beta frequency band may be involved in saliency processing, which is considered higher level neural processing of sensory information (Bibbig et al., 2001; Faulkner, Traub et al., 1999a; Kopell et al., 2000; Konigqt & Singer, 1997; von Stein, Rappelsberger, Sarnthei, & Petsche, 1999).

Neurobiology of P50 Sensory Gating

Sensory gating is most effectively demonstrated using various neurophysiological (EEG) and neuroimaging (fMRI, MRI) measures that trace the flow of sensory input from sensory organs through the brainstem and subcortical regions (e.g., hippocampus and thalamus), and into higher cortical brain regions (e.g., primary auditory cortex). The primary auditory cortex plays a critical role in further decoding pitch, intensity and sound

location. The hippocampus plays an important role in auditory processing by deciding the significance of a sound and enabling the generation of a memory trace after the presentation of an auditory stimulus. When a repeated sound is heard, it is compared to the memory trace of the first and is inhibited by hippocampal neurons, as it contains no new information (Cromwell et al., 2008; Zouridakis and Boutros 1992).

These same techniques have been used in several studies to identify the sources involved in sensory gating deficits in patients with schizophrenia (Knott, Millar, & Fisher, 2009; Mathiak, Ackermann, Rapp, Mathiak, Shergill, Riecker, & Kircher, 2011; Mayer et al., 2009, 2013; Oranje, Geyer, Bocker, Leon, Verbaten, 2006; Reite, Teale, Zimmerman, Davis, Whalen, & Edrich, 1988; Thoma et al., 2003; Tregellas et al., 2007). Results from neuroimaging studies are consistent in finding reduced suppression of auditory stimuli in auditory cortices (Mathiak et al., 2011). This relationship is consistent with the developmental trajectory of the auditory cortex, as the auditory cortex is fully matured in late human development. Hence, the auditory system is vulnerable to disruption even in late adolescence and early adulthood—a period in which symptoms of schizophrenia typically appear (Javitt & Freedman, 2014). Similarly, it has been found that sensory deficits are undetected until adolescence, which is around the time course of the onset of schizophrenia (Schultze-Lutter. Ruhrmann, Picker, Reventlow, Brockhaus-Dumke, & Klosterkotter, 2007; Schultze-Lutter. Addington, Ruhrmann, & Klosterkotter, 2007).

Many studies have shown that several brain regions are involved in P50 gating, such as the hippocampus (Adler et al., 1992, 1998; Bak et al., 2014; Braff & Light, 2004; Boutros et al., 2005; Callaway, 1970; Goff, Williamson, VanGilder, Allison, & Fisher,

1980; Grunwald et al., 2003; Wilson, Babb, Halgren, Wang, & Crandall, 1984; Yee et al., 2010; Waldo et al., 1994), thalamus (Carlsson, 1988; Carlsson and Carlsson, 1990), superior temporal gyrus (STG; Knott et al., 2009; Korzyukov et al., 2007; Oranje et al., 2006; Reite et al., 1988; Thoma et al., 2003), medial temporal lobe (Simons & Spiers, 2003), and frontal lobe (Jensen, Oranje, Wienberg, & Glenthoj, 2008; Korzyukov et al., 2007; Oranje et al., 2006; Weisser et al., 2001;Vleck, Bob, & Roboch, 2014), specifically the prefrontal cortex (PFC) that is related to the selection, engagement, monitoring, and inhibition of stimuli (Simons & Spiers, 2003; Grunwald et al., 2003; Knight et al., 1989). These results suggest that a distributed neural network is involved in generating the P50 response and sensory gating (Williams et al., 2012).

Animal studies have provided insight into the basic neural mechanisms of sensory gating. Similar to findings in the human literature, the hippocampus may serve an important role in sensory gating as the generator of cerebral evoked responses (Callaway, 1970). Many animal investigations have demonstrated that the CA3 (Carbonic Anhydrase III) region of the hippocampus of the rat analogue is specifically associated with P50 gating (Adler et al., 1998; Bickford-Wimer et al., 1990; Freedman et al., 1996; Luntz-Leybman, Bickford, & Freedman, 1992; Speck, Dim, & Mercer, 1966). The CA3 region consists of many alpha7-nicotinic receptors, which plays a significant role in activating CA3 interneurons (Luntz-Leybman et al., 1992; Bickford-Wimer et al., 1990). CA3 interneurons release and activate the inhibitory neurotransmitter gamma aminobutyric acid (GABA) to transiently prevent subsequent neurotransmitters, such as the excitatory neurotransmitter glutamate, from being released so that the neurons do not receive as much excitatory input from the second stimulus; hence, showing a diminished neural

response (Escaplez, Hirsch, Khazipov, Ben-Ari, & Bernard, 1997; Homayoun & Moghaddam, 2007; Klausberger & Somogyi, 2008; Korzyukov et al., 2007; Krause, Hoffmann, & Hajos, 2003; Miller & Freedman, 1993; Seamans, Gorelova, Durstewitz, & Yang, 2001; Weisser et al., 2001).

A large number of studies on the neurobiology of schizophrenia have focused on the sensory gating dysfunction of the prefrontal cortex, hippocampus, and thalamus. The hippocampus has been identified as the site of inhibitory processing in schizophrenia patients (Bak et al., 2011; Grunwald et al., 2003). Reduced volume and over-activation of the hippocampus during the presentation of an auditory stimuli has been found to underlie gating deficits in schizophrenia (Bak et al., 2014; Thoma et al., 2008; Tregellas, Ellis, Shatti, Du, & Rojas, 2009; Wolf et al., 2008). Several human and animal investigations have demonstrated that sensory gating depends on the alpha7-nicotinic receptor's activation of inhibitory neuron functions in the hippocampus **(**Freedman et al. 1994), and that patients with schizophrenia have a mutation in the alpha7-nicotinic receptor gene on chromosome 16q14 locus of CHRNA7. Abnormality of the alpha7-nicotinic receptor results in the failure to activate the inhibitory neurotransmitter GABA to prevent the excitatory neurotransmitter glutamate from being released in response to the repeated stimulus, which leads to hippocampal hyperexcitability (Bickford-Wimer et al., 1990; Freedman, Hall, Adler, & Leonard, 1995; Freedman et al., 1997, 2003, 2014; Luntz-Leybman et al., 1992; Stevens et al., 1996; Young & Geyer, 2013).

Further support for hippocampal nicotinic receptor involvement in sensory gating has also been indicated through pharmacological studies, in which nicotine (e.g., cigarette smoking) is shown to temporarily reverse gating deficits by stimulating the alpha7-

nicotnic receptors (Adler et al., 1993; Adler et al., 1998; Erwin, Erwin, Turetsky, Moberg, Gur, & Gur, 1998; Waldo, Cawthra, & Adler, 1994; Freedman et al., 1997; Leonard et al., 1998; Myles-Worseley et al., 1999; Freedman et al., 2001). Many studies have consistently shown that Clozapine, an atypical neuroleptic, normalizes P50 inhibition in schizophrenia patients and mice (Nagamoto et al., 1996; Simosky, Stevens, Adler, & Freedman, 2002). Clozapine is a nicotinic agonist that has been found to increase the activation of alpha-7 receptors indirectly through the release of acetylcholine in the hippocampus; hence, exerting a restorative effect on sensory gating.

In addition to having reduced nicotinic receptors, patients with schizophrenia also seem to have an overabundance of cortical and subcortical presynaptic and postsynaptic dopaminergic receptors in the brain, especially in the auditory cortex (Lewis, Campbell, Foote, Goldstein, & Morrison, 1987; Mattysse, 1978; Seeman et al., 1984; Stevens, 1979). Dopamine's overinvolvement in sensory gating is still unknown; however, it is hypothesized that too much dopamine makes neurons hypersensitive to their synaptic inputs, which then causes a lack of neuronal synchrony to produce a large action potential. The lack of synchronous activity is said to be responsible for the production of a smaller P50 wave, especially in unmedicated schizophrenia patients (Freedman et al., 1987a). The dopamine system's dysfunction is consistent with the hypofrontality hypothesis in the pathophysiology of schizophrenia, which proposes that increased dopamine activity induces a decrement of frontal activity with the loss of inhibitory mechanisms in patients, as shown on patients' working memory performance (Braff & Geyer, 1990).

Recent studies are now examining oscillatory activity across a broad range of frequencies to gain greater understanding of how sensory gating deficits are related to neuronal dynamics in schizophrenia. Based on the proposed roles that gamma- and beta-band activity play in auditory gating, it is likely that these frequency ranges involve complex interactions between inhibitory, excitatory, and cholinergic neurotransmitter systems (Smucney et al., 2013). Animal studies investigating neuronal oscillations associated with auditory sensory gating and nicotinic α 7 nAChRs using wild type (normal) and α 7 heterozygote (schizophrenia, decreased expression of α 7 nAChR) mice have found that gating of beta (15-26 Hz) and gamma (30-150 Hz) power was decreased in the α 7 heterozygote mice compared to wild type mice similar to human studies, in which patients have decreased beta and gamma gating power compared to healthy controls (Adams, Yonchek, Zheng, Collins, & Stevens, 2008; Smucney et al., 2013), suggesting that P50 gating deficits are associated with neural oscillations in the high frequency ranges and deficits in nicotinic receptors. A deficit in α 7 receptor expression would result in a reduction of GABA, which is relevant in the generation of high frequency oscillations and local synchronization, and promote cortical hyper-excitability (Bartos, Vida, & Jonas, 2007; Draguhn, Traub, Schmitz, & Jefferys, 1998; Traub, Bibbig, LeBeau, Buhl, & Whittington, 2004; Fukuda, Kosaka, Singer, & Galuske, 2006; Nase, Singer, Monyer, & Engel, 2003; Uhlhaas & Singer, 2013). The loss of GABAergic interneurons signaling onto excitatory neurons to curtail their firing is hypothesized to impair the generation of synchronous high frequency oscillations, such as that within the gamma frequency, thus leading to a dysfunction in the inhibitory neurotransmitter systems to attenuate the repeated stimuli (Cobb, Buhl, Halasy, Paulsen, & Somogyi,

1995; Gandal, Edgar, Klook, & Siegel, 2012; Sohal,, Zhang, Yizhar, & Diesseroth, 2009; Wang & Buzsaki, 1996).

P50 Gating and Cognition

Measures of sensory gating (e.g., S2 amplitude and gating ratio) associate with distinct cognitive domains. Toyomaki and colleagues (2015) found a significant association between executive functioning and P50 ratio, as well as sustained attention and S2 amplitude. As the S2 response and P50 ratio seem to engage in different neurophysiological processes, Toyomaki and colleague's (2015) finding is not surprising. Studies that examine varying attention load and distraction in healthy and psychopathological subjects provide the strongest evidence of a relationship between P50 ERPs and cognition (e.g., pre-attention) within sensory information processing (Brockhaus-Dumke et al., 2008a; Potter et al., 2006). In particular, the P50 ERP may serve as a measure of pre-attention (Brockhaus-Dumke et al., 2008a; Erwin et al., 1998; Cullum, Harris, Waldo, Smernoff, & Nagamoto, 1993). Pre-attention is largely referred to as an automatic and multi-layered sensory information-processing system that continuously monitors the environment (gating in) in order to distinguish trivial from salient sensory cues, which then helps facilitate gating out processes (Geyer & Braff, 1987). In Sokolov's (1963) seminal work, the author described this basic aspect of attention as an "orienting response to mild, information-laden stimuli." Upon distinction between important and unimportant stimuli, it is assumed that a more controlled attention-dependent process that involves the allocation of attentional resources to the novel and/or salient stimulus is involved (Braff & Light, 2004). Illuminating the physiological characterization of this process is the focus of the current study.

Deficits in attention, saliency detection, and sensory processing have all been found in patients with schizophrenia (Boutros et al., 2004; Javitt, Doneshka, Zylberman, Riter, & Vaughan, 1993; Clementz & Blumenfeld, 2001; Jeon and Polich, 2001; Turetsky et al., 2008). Manipulation of attention has also been found to improve P50 gating in patients with schizophrenia, but not healthy controls (Yee et al., 2010). Yee and colleagues (2010) demonstrated that voluntary attention towards the first stimulus results in improvement of P50 suppression in patients—this is known as the compensatory attention model (Yee et al., 2010). Interestingly, when patients' attention was directed towards S2, attention to the S1 was disrupted and deficits in P50 gating worsened. This may be due to an already impaired P50 gating mechanism and patients' vulnerability to distractions (Yee et al., 2010).

Many P50 and N100 investigations also link the ERP components of sensory gating to other neurocognitive domains, such as processing speed (Potter et al., 2006; Cullum et al., 1993; Sanchez-Morla, Santos, Aparicio, Garcia-Jimenez, Soria, & Arango, 2013) and working memory (Erwin et al., 1998; Cullum et al., 1993; Lijffijt et al., 2009; Potter et al., 2006), which are aspects of executive functioning (Braff, Stone, Callaway, Geyer, Glick, & Bali, 1978; Cullum et al., 1993; Erwin et al., 1998; Kurtz, 2005; Sánchez-Morla et al., 2009; Reichenberg, 2010; Toyomaki et al., 2015). A study of healthy individuals found associations between the N100 amplitude to S1 and ratio scores on a working memory task. No relationship was found between N100 amplitudes to S2 and working memory, indicating that working memory may be more closely related to pre-attention than inhibition (Lijffijt et al., 2009; Smith et al., 2010). Although aspects of executive function have been linked to measures of sensory gating, some studies have

yielded mixed results (Erwin et al., 1998; Thoma et al., 2003; Miller & Canive, 2004). Thus, the relationship between working memory, executive functioning, and P50 suppression remain unclear as some authors found poorer performance in working memory and executive tests in relation to P50 deficits, while others have not. Studies that have shown a positive correlation between executive functioning and sensory gating suggest that poor sensory gating may lead to impairment of the brain's ability to selectively attend, process, and store information, relating to attention and executive functions (Braff and Geyer 1990; Grunwald et al., 2003).

A large number of researchers have examined neural oscillations during cognitive tasks and have found gamma- and beta-band activity to be involved in a wide range of cognitive domains, such as such as attention, maintenance of information in working memory, executive control, and perceptual processing (Haenschel et al., 2009; Minzenberg, Firl, Yoon, Gomes, Reinking, & Carter; Ford, Roach, Faustman, Mathalon, 2008; Hirano et al., 2008; Tallon-Baudry, Bertrand, & Peronnet, Pernier, 1998; Uhlhaas & Singer, 2013). Researchers also demonstrate that a reduction in gamma band activity observed in patients with schizophrenia relative to controls is associated with working memory (Basar-Eroglu, Brand, Hildebrandt, Kedzior, Mathes, &Schmiedt, 2007; Kissler, Muller, Fehr, Rockstroh, & Elbert, 2000; Gonzalez-Hernandez, Cedeno, Pita-Alcorta, Galan, Aubert, Figueredo-Rodriguez, 2003) and inhibition (Cho, Konecky, & Carter, 2006; Haenschel, Uhlhaas, & Singer, 2007). Studies have primarily focused on gamma band oscillations; however, beta-band oscillations has been shown for auditory sensory processing. For example, Brenner and colleagues (2009) demonstrated patients with schizophrenia showed less evoked beta 1 power (12-20 Hz) in response to salient or rare

stimuli at S1 relative to health controls. The authors observed greater beta 2 (30-50 Hz) activity in response to rare stimuli at S1 compared to S2 for both controls and patients. These results indicate abnormal auditory processing during the initial stages of stimulus evaluation and saliency detection as reflected by reduced attenuation of beta 1 power in response to the rare stimuli pairs within the delay interval between S1 to S2, suggesting poor gating in patients. Furthermore, the N100 amplitude to S1 positively correlated with beta 1 power to S2 in both standard and rare auditory stimuli.

P50 Amplitudes and its Clinical Correlates

Sensory gating deficits have been implicated to underlie the development of positive (Smith et al., 2013; Freedman et al., 1987a) and negative symptoms (Ringel et al., 2004; Louchart-de la Chapelle et al., 2005; Thoma et al., 2005). Smith and colleagues (2013) found a correlation between the P50 gating ratio and the severity of active auditory verbal hallucinations experienced by schizophrenia patients (Smith et al., 2013). In a study of patients' feelings of strangeness to auditory stimuli, Micoulaud-franchi and colleagues (2011) found that familiar environmental sounds (e.g., animals or ocean waves) and abstract sounds (e.g., sound transformations) were perceived differently in patients and healthy control groups. Patients with schizophrenia evaluated abstract sounds as more familiar and everyday environmental sounds as less familiar and more invasive compared to healthy controls. The authors found a negative correlation between familiarity ratings for abstract sounds and the S1 amplitude, and a positive correlation between the P50 gating ratio and invasive ratings of familiar environmental sounds. These results suggest dysfunctions in both sensory gating in and out, in which patients inadvertently attach an important meaning to an otherwise insignificant sound and "gate

in" the novel abstract sound, and perceive familiar everyday environmental sounds as more invasive or overwhelming due to feeling inundated by these sounds (gating out) relative to controls (Micoulaud-franchi et al., 2011; Cicero, Kerns, & McCarthy, 2010; Kapur, 2003). Abnormalities in the N100 has also been specifically linked to positive symptoms of thought disorder and negative symptoms of alogia (e.g., inability to speak) (Turetsky et al., 2009).

Patients with prominent positive symptoms have been found to be especially vulnerable to auditory distractions (Green & Walker, 1986; Walker & Harvey, 1986). In a recent study examining the impact of distracting environmental sounds on performance of an auditory attention task, Smucney and colleagues (2013) found that patients with schizophrenia had greater reaction time on the attention task and made more errors of commission (e.g., pressing the spacebar when no response was needed) and errors of omission (e.g., forgetting to press spacebar during all numbers except for '3') than healthy controls. Schizophrenia patients also had a larger gating ratio, which positively correlated with noise-induced changes in reaction time on the task while the control group did not. These findings suggest that patients may be more sensitive to and have more difficulty overcoming distracting environmental noises than controls. The increase in reaction time on a particular task may be driven by a deficit in information processing of sounds, in which schizophrenia patients allocate greater amounts of processing resources to distracting auditory stimuli than do healthy individuals. As a result, this may ultimately lead patients to feel flooded with auditory stimuli due to deficits in their ability to 'gate out' irrelevant and distracting stimuli (Smucney et al., 2013).

Several studies have found associations between abnormal gamma- and beta-band

oscillations and negative and positive symptoms of schizophrenia (Hamm, Gilmore, Picchetti, Sponheim, & Clementz, 2011; Gandal et al., 2012; Kiel, Romero, Balz, Henjes, & Senkowski, 2016). Many of these studies have examined gamma band activity in particular and have demonstrated that disruption in gamma band activity is associated with various symptoms in schizophrenia, such as hallucinations, disorganization, and psychomotor poverty (Gallinat et al., 2004; Lee, Williams, Breakspear, & Gordon, 2003a; 2003b; Behrendt & Young, 2004; Reulbach, Bleich, Maih ouml fner, Kornhuber, & Sperling, 2007; Spencer et al., 2004). For example, Spencer and colleagues (2009) found that reduced gamma synchrony was positively correlated with the severity of auditory verbal hallucinations in patients with schizophrenia. Kiel and colleagues (2016) found that reduced gamma band amplitude and gamma band sensory gating was correlated with higher positive symptoms. Johannesen and colleagues (2008) reported reduced evoked gamma band (20-50 Hz) activity to S1 and gamma activity suppression was associated with patients who endorse higher ratings of subjective perceptual disturbance compared to perceptually normal schizophrenia subgroups and healthy controls. Gallinat and colleagues (2004) have also found a positive correlation between the degree of reduction in gamma band activity to both the positive symptom and the duration of illness in an auditory oddball paradigm.

In addition to positive symptomology, reduced gamma band activity has been found in contribution to the negative symptomology and severity of schizophrenia (Lee et al., 2008b). Lee and colleagues (2003) found that increased phase synchrony in response to targets (high tones) in an auditory oddball paradigm, which tested each participant's ability to distinguish between rare (task-irrelevant) stimuli from frequent (task-relevant)

stimuli within a series of tones, was positively correlated with increased positive symptoms while negative symptoms correlated with a decrease in gamma band activity in patients with chronic schizophrenia. However, research is inconsistent, as other studies demonstrate that gamma power and coherence are preserved in patients with primary negative symptoms (Bucci, Mucci, Merlotti, Volpe, & Galderisi, 2007). In regards to beta activity, Spencer and colleagues (2003) demonstrated that the phase-locking in the beta-band range was related to symptom severity in schizophrenia, indicating that lower frequencies of evoked oscillations are associated with more severe symptomatology. Smucny and colleagues (2013) found that less evoked beta-band power gating in the paired-click paradigm was associated to severity of negative symptoms in schizophrenia. Taken together, reduced gamma- and beta-band power may reflect the inability to suppress irrelevant auditory sensory information in patients with schizophrenia.

Many researchers examining different subtypes of schizophrenia have found an association between P50 gating deficits in particular subgroups of schizophrenia patients (Jin et al., 1998). For example, although both primarily negative and non-negative symptomatic chronic schizophrenia patients have shown higher P50 ratios than healthy comparisons (Santos et al., 2010), studies have shown that patients with prominent negative symptoms have significantly longer latencies of P50 response to S1 and S2 (Louchart-de la Chapelle et al., 2005; Adler, Waldo, Tatcher, Cawthra, Baker, & Freedman, 1990; Boutros et al., 2004). Total scores on the Positive and Negative Syndrome Scale (PANSS) scores have also been found to significantly correlate with a higher gating ratio (Ringel et al., 2004). Patients with a disorganized subtype of schizophrenia have also shown less suppression in the dual click paradigm than healthy

controls (Ringel et al., 2004). A study by Brockhaus-Dumke and colleagues (2008b), found that P50 and N100 suppression ERP measures (e.g., gating ratio and S1-S2 difference score) differed significantly between schizophrenia subgroups and healthy subjects, with unmedicated chronic individuals with schizophrenia displaying the lowest amount of suppression. In comparison to healthy subjects, significant deficits of the P50 ratio and the N100 S1-S2 amplitude difference index was found in prodromal and first-episode subjects, yet these gating deficits were not as prominent as in the chronic group. At-risk subjects who did not transition to psychosis did not differ in N100 gating indices relative to healthy subjects, yet this group still displayed significant impairments in P50 suppression. Many studies have yielded similar conclusions of sensory gating impairments in the early stages of schizophrenia that become worse in the chronic stages (Patterson et al., 2008; Siegal et al., 1984; Yee et al., 2010). These results provide evidence that disruptions in sensory gating, particularly in auditory information processing, can occur during the early stages of the illness, which may increasingly worsen with illness progression (Myles-Worsley, Ord, Blailes, Ngiralmau, &Freedman, 2004; Hong et al., 2009).

Limitations of Current Literature

Failure to suppress the ERP in response to the second click is thought to reflect a faulty inhibitory system. Oscillatory activity during the inter-click interval, which might reflect inhibitory processes initiated by the first click, are not well characterized. A study by Hong and colleagues (2008) is the only report to date that has examined spectral frequency in relation to ERP components and P50 gating within distinct time points across the 500 ms inter-click interval in order to elucidate the role of oscillations in

auditory gating. The authors provided evidence for the contribution of beta (13-29 Hz) frequency to P50 gating at time points 26-150 ms and 151-275 ms, and the S2 response amplitude at the 26-150 ms time point within the delay interval. Gamma activity did not significantly contribute to either ERP components. The results from Hong et al. (2008)'s study highlight the critical role of the beta response in determining the extent of P50 gating and subsequent S2 amplitude suppression. However, the authors' main limitation is their small sample size (n=104) and examination of only healthy controls. Hence, it is possible that with a larger sample size that includes both patients with schizophrenia and healthy controls, as is the case in this proposed study, group differences in gamma and beta spectral activities may be detected.

Aims and Hypotheses

In the present study, we aim to examine ERPs to the first and second stimulus and possible suppression mechanisms via averaged and single-trial beta (20-30 Hz) and gamma (30-50 Hz) frequency power during the inter-click interval, in order to elucidate the relationship between oscillatory band activity, P50 amplitudes, and P50 gating in relation to auditory sensory gating and its disturbance in schizophrenia. We will also further examine the gating in and gating out mechanisms underlying the sensory gating phenomenon by investigating oscillatory activity at different time points during the delay interval in order to provide timing information about the mechanisms that support sensory inhibition. Few studies have used two different approaches (averaged and single-trial evoked potentials and ERPs) to analyze auditory suppression in a paired-stimulus paradigm in schizophrenia patients and healthy controls, with specific attention on the

delay period (200-500 ms)—which consists of oscillatory activity after the ERP deflections returned to baseline—post-S1 P50 and N100 ERP. We hypothesized that aberrant information processing during the delay interval, as reflected in the gamma and beta neural oscillations after S1 in schizophrenia, contributes to poor auditory sensory gating.

Hypothesis 1: Patients with schizophrenia will exhibit lower P50 ERP difference scores and higher gating ratio scores than healthy controls.

Hypothesis 2: Paired auditory stimuli induces both gamma and beta oscillatory responses during the delay interval (0-500 ms) in both healthy controls and patients with schizophrenia. However, gamma and beta activity will significantly differ between groups, such that schizophrenia patients will exhibit less single-trial and averaged evoked gamma power early in the delay interval (0-200 ms) and less evoked and induced beta power across the inter-click interval (0-500 ms) compared to healthy controls.

Hypothesis 3: Finally, the single-trial and averaged beta oscillatory responses following the first auditory stimulus (S1) and N100 (e.g., 200-300 ms) will be significantly correlated to the P50 ratio and difference scores and S2 amplitude, suggesting that beta activity is critical for sensory gating subsequent S2 responses in both healthy controls and patients with schizophrenia.

CHAPTER TWO

METHODS

Participants

The participants were 327 individuals (140 females, mean age = 37 ranging in age from 18 to 55, SD = 11), including patients meeting criteria for schizophrenia (N = 118) or schizoaffective disorder (N = 13; 45 females, mean age = 40) based on *The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders IV* (SCID-IV, 1994), and 196 unrelated healthy subjects (95 females, mean age = 35, SD = 10.8) who were paid $10 per hour to participate in the study. The SCID-IV was used to exclude healthy subjects with any Axis I or Axis II disorders. None of the healthy subjects had a family history of psychoses nor met criteria for alcohol dependence within the past 2 years or substance abuse within 6 months prior to testing. Exclusion criteria included participants above the age of 55, head injury, learning disability, hearing impairment, verbal IQ less than 70, and alcohol or illicit substance use within 24 hour prior to testing. Participants were not permitted to smoke during the 40 min preceding testing, thus minimizing possible acute effects of nicotine on ERP amplitudes (Adler et al., 1993). The number of individuals who smoked cigarettes within 24 h of testing significantly differed between groups ($p < .00$), although did not significantly correlate to any electrophysiological variable except for S1 amplitude ($p < .05$). There were significant differences between patients and healthy controls on age ($p = .03$, $\chi^2 = .07$), highest level of education completed ($p = .04$, $\chi^2 = .00$.), and gender ($p = .00$, $\chi^2 = .01$). However, crosstab analyses revealed no significant relationships in age, highest level of education completed, and gender to any electrophysiological variables ($ps > .05$). All patients were

recruited through inpatient and outpatient programs at Larue Carter Hospital in Indianapolis, Indiana. Healthy controls were recruited through local advertisements. Each subject gave informed written consent approved by the Indiana University Bloomington Institutional Review Board.

Procedures

Subjects were seated in a dimly-lit, sound-attenuated room, and asked to relax, keep their eyes open, avoid movements including eye movements and listen to one-hundred and thirty pairs of click stimuli (S1 and S2) that were presented binaurally through a pair of ear inserts. The auditory stimuli consisted of two standard click pairs of the same peak intensity of 81 dB SPL, and broadband square waves of 3 ms duration (85% probability; N = 110 trials). Stimuli were presented against a 58 dB SPL white-noise background. The interpair interval varied randomly between 7 and 11 s (mean = 9 s) with a 500 ms interclick interval between S1 and S2 (see Figure 1). Eye movements were recorded from electrodes placed at the outer and inner corners of both eyes for the horizontal eye movements (HEOG), and above and below the right eye (VEOG) for the vertical movements. Recordings were visually monitored**.**

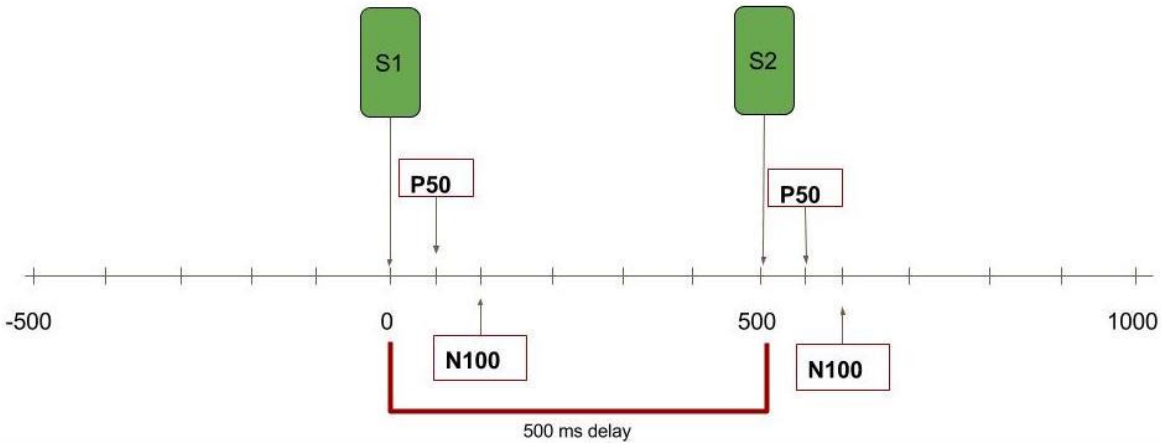

Figure 1. Paired-click paradigm to examine sensory gating in healthy controls and patients with schizophrenia. Data was segmented into 1500 ms trials. Event related-potential components (P50 and N100) were recording in response to both auditory stimuli. Gamma and beta activity were measured during the 500ms delay interval for each condition.

EEG Recordings and Data Processing

Electroencephalographic activity was recorded from 29 recording sites and referenced to the nose using Brain Vision Analyzer software (Brain Products, Munich, Germany). Data was continuously recorded at a sampling rate of 1000 Hz (0.10 Hz high pass and 499 Hz low pass; gain=10 K) using sintered Ag–AgCl electrodes. All electrode impedances were less than or equal to 10 kΩ. To be consistent with the literature, the central channel (CZ) was used for data analysis because it provides the most prominent P50 gating (Clementz, Geyer, & Braff, 1998; Freedman et al., 1997; Nagamoto et al., 1989).

ERP Peak Measurement

A 10—50 Hz bandpass filter with 24 octave slope was applied to raw data for P50 and N100 ERP analyses. Ocular correction was applied using the Gratton-Coles method

(Gratton et al., 1983). Data was segmented (−50 to 250 ms), baseline corrected, and remaining trials with values greater than ±100 μV were excluded prior to averaging. The S1 P50 response window was set to 30 to 80 ms. P50 responses to the second click at Cz were segmented (450 to 750 ms). The same filtering procedure was applied to the S2 response, with the S2 response window set to 30 to 80 ms after the onset of S2 for each subject. The strength of P50 gating was defined by the S2/S1 P50 ratio and S1-S2 P50 difference score. The amplitude of the N100 response was defined as the most negative deflection within 60 to 180 ms after stimulus presentation (referenced to baseline). A semi-automatic peak detection computer algorithm was used to identify both P50 and N100 peaks, troughs, amplitudes, and latencies.

Gamma/Beta Oscillations in Delay Interval

Raw EEG data were segmented into 1500 ms trials. A complex Morlet wavelet was run over the entire averaged waveform to calculate evoked spectral power from 10-60 Hz in 50 steps (c = 6), with 300 ms baseline correction. Averaged beta (20-30 Hz) and gamma (30-50 Hz) power were evaluated within seven distinct time intervals (0-100 ms, 100-200 ms, 200-300 ms, 300-400 ms, 400-500 ms, 0-500 ms, 200-500 ms) of 100 ms length from channel CZ to extract the temporal features of the gamma- and beta-frequency bands (see Figures 2 and 3). For single trial analysis, the same complex Morlet wavelet was run over the data for all 110 single trials, and then averaged. Induced spectral power will be evaluated in the same 100 ms time bins during the inter-stimulus interval as evoked power.

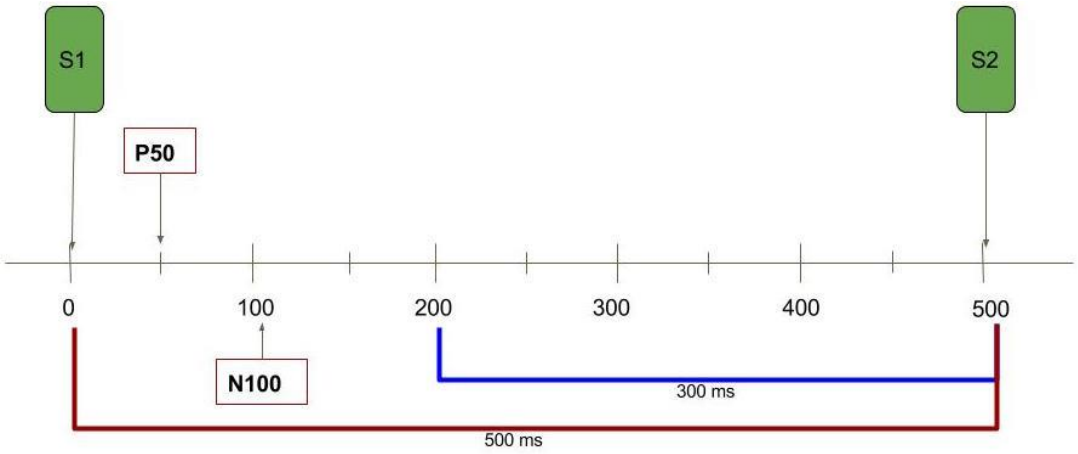

Figure 2. Gamma and beta activity were measured at 200-500 ms (300 ms) and throughout the 500 ms delay interval as demonstrated by the u-shaped connectors.

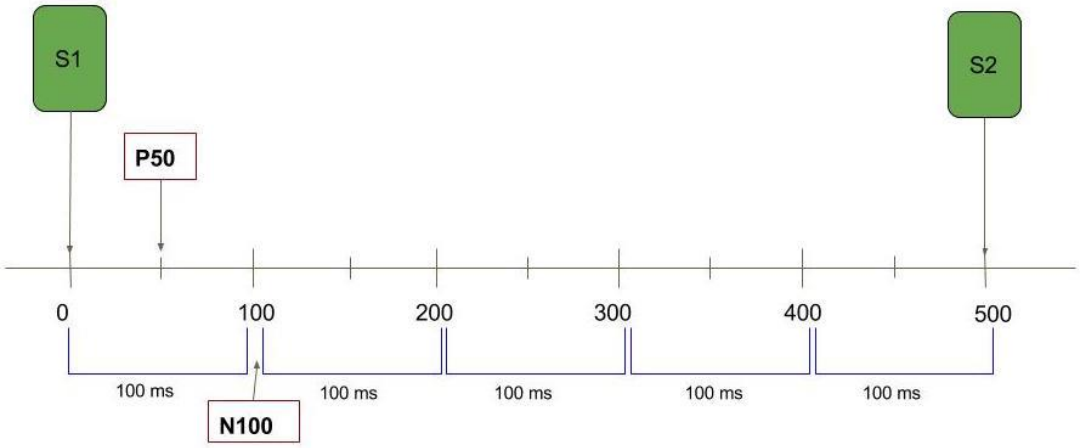

Figure 3. The delay interval was divided into five 100 ms time points as demonstrated by the u-shaped connectors on the timeline. Averaged gamma and beta power were measured within the 100 ms time points of the 500 ms delay interval.

Statistical Analysis

Data were transformed to normalize the distribution if it is found to be non-normal. However, ANOVAs are not sensitive to moderate deviations from normality (Glass, Peckham, & Sander, 1972; Harwell, Rubinstein, Hayes, & Olds, 1992; Lix, Keselman, & Keselman, 1996). To elucidate whether healthy controls and patients with

schizophrenia show different P50 S1 and S2 amplitudes, within- and between-group comparisons were conducted using a Repeated measures ANOVA, with Group (healthy vs. schizophrenia patients) as the between-subjects factor and Stimulus (S1 vs. S2) as a within-subjects factor. Independent samples t-test were used to compare P50 gating, as measured by the P50 gating ratio (S2/S1) and difference (S1-S2) scores between groups (healthy vs. patients with schizophrenia).

A 5x2 Repeated measures ANOVA were computed to test time-frequency interactions on oscillatory responses within the beta (20-30 Hz) and gamma (30-50 Hz) frequency ranges, with Group (healthy vs. schizophrenia patients) as the between-subjects factor and the 5 time points (0-100 ms, 100-200 ms, 200-300 ms, 300-400 ms, 400-500 ms) as within-subjects factors. Two separate independent samples t-test were used to determine whether there is a significant difference between oscillatory activity within the 200-500 ms and 0-500 time points between groups (healthy vs. patients with schizophrenia) at each frequency band (beta and gamma). Greenhouse Geiser correction were reported due to violations of sphericity.

The question of whether post-S1 gamma and/or beta components contribute to P50 gating (S2/S1 P50 ratio, S1-S2 P50 difference) were addressed in a multiple linear regression framework, in which a P50 gating measure served as the dependent variable and post-S1 oscillatory activity within the five time points (0-100 ms, 100-200ms, 200-300 ms, 300-400 ms, 400-500 ms) served as the independent variables. Beta- and gamma-bands were tested separately in the multiple regression equation. Analyses were also performed for each group (healthy vs. schizophrenia) separately. Separate multiple linear regression analyses were used to examine whether post-S1 gamma and/or beta

components contribute to the S1 amplitude, in which the S1 amplitude served as the dependent variable and oscillatory activity within the five time points will serve as the independent variables. Analyses were also performed for each group (healthy vs. schizophrenia) and each frequency band (gamma, beta) separately. The same analyses were used to test whether beta and gamma activity contribute to the S2 amplitude. A total of sixteen multiple linear regression analyses were computed.

Four separate simple linear regression analyses were used to predict the contribution of oscillatory activity within the 200-500 ms time point to P50 gating (S2/S1 P50 ratio, S1-S2 difference), with the time point serving as the independent variable and P50 gating measure as the dependent variable. Analyses were performed separately for each group (healthy vs. schizophrenia). Four additional separate simple linear regressions were used to predict the contribution of oscillatory activity within the 200-500 ms time point to P50 amplitude (S1, S2), with the time point serving as the independent variable and the P50 amplitude as the dependent variable. Analyses were performed separately for each group (healthy vs. schizophrenia). The same 8 simple linear regressions analyses were used to test whether the delay interval time point 0-500 ms contributes to P50 gating and the P50 amplitudes, with 0-500 ms serving as the independent variable. A total of sixteen simple linear regression analyses were computed. All statistical analyses were done using SPSS version 23.0.

CHAPTER THREE

RESULTS

In support of our first hypothesis, an independent samples t-test revealed a significant difference in P50 gating ratio and P50 difference scores between patients with schizophrenia and healthy controls, such that patients with schizophrenia have a higher P50 ratio and lower P50 difference scores than healthy controls [$t(315) = -4.728$, $p < .001$, $r^2 = .56$; $t(323) = 7.195$, $p < .001$, $r^2 = 1.31$, respectively]. In addition, an independent samples t-test partially support our second hypothesis and revealed significant group differences in beta activity throughout the entire 500ms inter-click interval, such that beta activity was larger in the healthy control group compared to the schizophrenia group, $t(311) = 2.913$, $p < .05$, $r^2 = .21$. Results for all independent samples t-tests did not differ between averaged- and single-trial analyses. Results for significant simple linear regression (see Tables 1 and 2) and multiple linear regression analyses (see Tables 3 and 4) are presented in tables below. Due to violations of collinearity, results of multiple regression analyses for beta activity at the five 100 ms time points predicting P50 gating and P50 amplitudes are not interpreted.

Table 1. Results of Simple Linear Regression Analyses: Evoked and Induced Gamma during the 500ms Delay Interval Predicting P50 Gating and P50 Amplitudes

Predictor Variable	Healthy Control	Schizophrenia
P50 Ratio		
b	-0.57	-0.015
	(0.002)	(0.064)
B	-0.039	-0.002
	(0.020)	(0.143)
t	-0.551	-0.026
	(0.285)	(1.638)
p-value	>0.050	>0.050
	(>0.050)	(>0.050)
R^2_{adj}	-0.004	-0.008
	(-0.005)	(0.013)
P50 Difference		
b	3.138	2.230
	(0.073)	(0.008)
B	0.413	0.348
	(0.138)	(0.021)
t	6.300	4.183
	(1.935)	(0.239)
p-value	**<0.001**	**<0.001**
	(>0.050)	(>0.050)
R^2_{adj}	0.166	0.114
	(0.014)	(-0.007)
S1 P50 Amplitude		
b	5.299	3.482
	(0.088)	(0.009)
B	0.561	0.455
	(0.137)	(0.021)
t	9.412	5.757
	(1.929)	(0.237)
p-value	**<0.001**	**<0.001**
	(>0.050)	(>0.050)
R^2_{adj}	0.311	0.201
	(0.014)	(-0.007)
S2 P50 Amplitude		
b	2.178	0.847
	(0.005)	(0.004)
B	0.505	0.265
	(0.018)	(0.017)
t	8.167	3.121
	(0.245)	(1.890)
p-value	**<0.001**	**<0.050**
	(>0.050)	(>0.050)
R^2_{adj}	0.251	0.063
	(-0.005)	(-0.008)

Note: Bolded P-values indicate significance. Values in parentheses ( ) indicate results from single-trial analyses.

Table 2. Results of Simple Linear Regression Analyses: Evoked and Induced Beta during the 500ms Delay Interval Predicting P50 Gating and P50 Amplitudes

Predictor Variable	Healthy Control	Schizophrenia
P50 Ratio		
b	-0.135	-0.021
	(-0.005)	(0.066)
B	-0.143	-0.005
	(-0.059)	(0.150)
t	-2.021	-0.054
	(-0.819)	(1.720)
p	**<0.050**	>0.050
	(>0.050)	(>0.050)
R^2_{adj}	0.015	-0.008
	(-0.002)	(0.015)
P50 Difference		
b	3.390	3.065
	(0.092)	(0.004)
B	0.615	0.552
	(0.199)	(0.011)
t	10.876	7.488
	(2.833)	(0.125)
p	**<0.001**	**<0.001**
	(<0.050)	(>0.050)
R^2_{adj}	0.376	0.299
	(0.035)	(-0.008)
S1 P50 Amplitude		
b	4.325	3.497
	(0.093)	(0.100)
B	0.664	0.543
	(0.172)	(0.023)
t	12.332	7.314
	(2.436)	(0.258)
p	**<0.001**	**<0.001**
	(<0.050)	(>0.050)
R^2_{adj}	0.438	0.289
	(0.025)	(-0.007)
S2 P50 Amplitude		
b	1.031	0.322
	(0.011)	(0.014)
B	0.366	0.146
	(0.049)	(0.067)
t	5.498	1.673
	(0.679)	(0.754)
p	**<0.001**	>0.050
	(>0.050)	(>0.050)
R^2_{adj}	0.130	0.014
	(-0.003)	(-0.003)

Note: Bolded P-values indicate significance. Values in parantheses ( ) indicate results from single-trial analyses.

Table 3. Results of Multiple Linear Regression Analyses: Evoked and Induced Gamma at Five 100ms Time Points Predicting P50 Gating and P50 Amplitudes

	P50 Difference					S1 P50 Amplitude					S2 P50 Amplitude				
Predictor Variable	*b*	*B*	*t*	*p*	R^2_{adj}	*b*	*B*	*t*	*p*	R^2_{adj}	*b*	*B*	*t*	*p*	R^2_{adj}
Healthy Control					0.165					0.332					0.263
					(0.074)					(0.124)					(0.079)
Time 1: 0-100ms	82.003	0.485	5.027	**<0.001**		140.972	0.674	7.804	**<0.001**		58.441	0.596	6.795	**<0.001**	
	(15.015)	(0.348)	(3.869)	**(<0.001)**		(23.477)	(0.436)	(4.798)	**(<0.001)**		(7.768)	(0.342)	(4.300)	**(<0.001)**	
Time 2: 100-200ms	-109.925	-0.084	-0.808	>0.050		-212.97	-0.131	-1.414	>0.050		-105.11	-0.132	-1.408	>0.050	
	(-0.685)	(-0.016)	(-0.123)	(>0.050)		(-1.297)	(-0.025)	(-0.171)	(>0.050)		(-2.186)	(-0.123)	(-0.919)	(>0.050)	
Time 3: 200-300ms	37.524	0.018	0.231	>0.050		33.547	0.013	0.186	>0.050		1.320	0.001	0.014	>0.050	
	(-10.051)	(-0.248)	(-1.824)	(>0.050)		(-10.799)	(-0.208)	(-1.384)	(>0.050)		(0.615)	(0.029)	(0.200)	(>0.050)	
Time 4: 300-400ms	-58.942	-0.028	-0.339	>0.050		124.749	0.047	0.648	>0.050		188.653	0.146	1.923	>0.050	
	(0.709)	(0.017)	(0.106)	(>0.050)		(-7.473)	(-0.142)	(-0.723)	(>0.050)		(-5.171)	(-0.223)	(-1.446)	(>0.050)	
Time 5: 400-500ms	59.041	0.026	0.347	>0.050		-30.969	-0.011	-0.164	>0.050		-94.658	-0.069	-0.982	>0.050	
	(7.797)	(0.232)	(1.784)	(>0.050)		(12.170)	(0.284)	(1.733)	(>0.050)		(2.921)	(0.159)	(1.161)	(>0.050)	
Schizophrenia					0.309					0.448					0.071
					(0.038)					(0.048)					(-)
Time 1: 0-100ms	98.415	0.608	7.749	**<0.001**		141.719	0.755	10.095	**<0.001**		24.718	0.335	3.567	**<0.010**	
	(9.965)	(0.356)	(2.530)	(>0.050)		(14.037)	(0.421)	(3.004)	(>0.050)		-	-	-	-	
Time 2: 100-200ms	-95.810	-0.107	-1.344	>0.050		-231.040	-0.183	-2.203	**<0.050**		-19.783	-0.044	-0.449	>0.050	
	(-2.946)	(-0.111)	(-0.675)	(>0.050)		(-3.295)	(-0.104)	(-0.636)	(>0.050)		-	-	-	-	
Time 3: 200-300ms	-149.904	-0.109	-1.185	>0.050		-221.280	-0.136	-1.628	>0.050		-78.907	-0.091	-0.861	>0.050	
	(-0.467)	(-0.021)	(-0.099)	(>0.050)		(-3.665)	(-0.137)	(-0.653)	(>0.050)		-	-	-	-	
Time 4: 300-400ms	73.380	0.050	0.582	>0.050		296.526	0.158	2.012	**<0.050**		59.737	0.058	0.465	>0.050	
	(-4.928)	(-0.163)	(-0.857)	(>0.050)		(-4.799)	(-0.133)	(-0.704)	(>0.050)		-	-	-	-	
Time 5: 400-500ms	-169.464	-0.137	-1.706	>0.050		-231.19	-0.161	-2.216	**<0.050**		42.562	0.044	0.392	>0.050	
	(-2.488)	(-0.079)	(-0.603)	(>0.050)		(-1.944)	(-0.052)	(-0.397)	(>0.050)		-	-	-	-	

Note: Bolded P-values indicate significance. Values in parantheses ( ) indicate results for single-trial analyses. Hyphens (-) indicate violations of collinearity (VIF > 10; Tolerance < .10).

Table 4. Results of Multiple Linear Regression Analyses: Evoked and Induced Beta at Five 100ms Time Points Predicting P50 Gating and P50 Amplitudes

	P50 Difference					S1 P50 Amplitude					S2 P50 Amplitude				
Predictor Variable	*b*	*B*	*t*	*p*	R^2_{adj}	*b*	*B*	*t*	*p*	R^2_{adj}	*b*	*B*	*t*	*p*	R^2_{adj}
Healthy Control					0.415					0.545					0.150
					-										
Time 1: 0-100ms	107.375	0.718	10.259	**<0.001**		133.171	0.782	11.653	**<0.001**		31.711	0.432	4.729	**<0.001**	
Time 2: 100-200ms	-63.628	-0.151	-2.039	**<0.050**		-33.875	-0.071	-1.006	>0.050		-7.667	-0.034	-0.363	>0.050	
Time 3: 200-300ms	138.794	0.080	1.219	>0.050		113.407	0.050	0.881	>0.050		-167.12	-0.152	-1.951	>0.050	
Time 4: 300-400ms	-108.943	-0.044	-0.691	>0.050		-72.604	-0.024	-0.419	>0.050		49.996	0.038	0.478	>0.050	
Time 5: 400-500ms	106.326	0.047	0.818	>0.050		-98.631	-0.030	-0.557	>0.050		-128.429	-0.085	-1.172	>0.050	
Schizophrenia					0.325					0.351					0.019
Time 1: 0-100ms	83.243	0.591	6,299	**<0.001**		102.678	0.641	6.676	**<0.001**		8.804	0.172	1.522	>0.050	
Time 2: 100-200ms	1.344	0.003	0.027	>0.050		-23.241	-0.042	-0.399	>0.050		2.516	0.010	0.078	>0.050	
Time 3: 200-300ms	-130.813	-0.109	-1.059	>0.050		-72.433	-0.046	-0.515	>0.050		90.718	0.122	1.093	>0.050	
Time 4: 300-400ms	215.776	0.150	1.371	>0.050		140.191	0.072	0.761	>0.050		-32.300	-0.033	-0.287	>0.050	
Time 5: 400-500ms	-183.643	-0.106	-1.169	>0.050		-101.711	-0.036	-0.446	>0.050		106.536	0.077	0.787	>0.050	

Note: Bolded P-values indicate significance. Results from single-trial analyses are not presented due to violated assumptions of collinearity (VIF > 10; Tolerance < .10).

A Repeated Measures analysis of variance (ANOVA) with group (healthy control vs. schizophrenia) as the between-subjects factor and Stimulus (S1 vs. S2) as the within subjects factor revealed a main effect of stimulus for both averaged-trial analyses [$F(1, 323) = 276.197$, $p < .001$)], indicating that P50 amplitude in response to S1 was larger than that in response to S2, regardless of group. In addition, there was also a significant main effect of Group [$F(1, 323) = 26.795$, $p < .001$)], indicating that P50 amplitudes in general were larger in the healthy control group compared to the schizophrenia group. Finally, there was a group x stimulus interaction [$F(1, 323) = 112.737$, $p < .001$)], indicating that P50 amplitude to S1 was larger in the healthy control group than the schizophrenia group, but the P50 amplitude to S2 did not differ between groups. Single-trial analyses yielded consistent findings.

A Repeated Measures analysis of variance (ANOVA) was used to analyze group differences in oscillatory responses within the beta frequency range, with group (healthy control vs. schizophrenia) as the between-subjects factor and the five 100 ms time points (0-100 ms, 100-200ms, 200-300 ms, 300-400 ms, 400-500 ms) as within-subjects factors. Mauchly's Test of Sphericity indicated that the assumption had been violated for both averaged- and single-trial analyses, $X^2(9) = 1596.777$, $p < 0.001$; $X^2(9) = 345.259$, $p < 0.001$, respectively. Averaged- and single-trial analyses revealed a main effect of beta activity at the five 100 ms time points [$F(1.264, 357.743) = 195.728$, $p < .001$; $F(2.448, 741.866) = 87.816$, $p < .001$, respectively). Based on LSD post-hoc analyses, Time 1 (0-100ms) beta activity significantly differed from beta activity all other 100 ms time points for both averaged- and single-trial analyses (all ps $< .001$). Time 2 (100-200ms) significantly differed from all other 100ms time points for both averaged- and single-trial

analyses (all *p*s < .001). Time 3 (200-300ms) significantly differed from time points 1, 2, and 4 for both averaged- and single-trial analyses (*p*s <.05), but did not differ from time 5 (400-500ms; *p* >.05). Time 4 (300-400) significantly differed from time points 1, 2, and 3 (*p*s < .05), but did not differ from time 5 for averaged-trial analyses (*p* >.05). In contrast, single-trial analyses revealed that Time 4 significantly differed from all other 100ms time points (*ps* < .05). In addition, these analyses revealed a significant main effect of group for averaged trial analyses [$F(1, 283) = 7.784$, $p < .05$)], indicating that evoked beta at all 100 ms time points was larger in the healthy control group compared to the schizophrenia group. Finally, there was a group x 100 ms time points interaction for averaged-trial analyses [$F(1.264, 357.743) = 5.137$, $p < .05$)]. In the averaged-trial analyses, beta at time 1 (0-100ms) was larger in the healthy control group than the schizophrenia group, but this difference was not found in all other time points between groups. Single-trial analyses did not reveal a significant main effect of group nor a group x 100 ms time points interaction (*ps* > .05).

A Repeated Measures analysis of variance (ANOVA) was used to analyze group differences on oscillatory responses within the gamma frequency range, with group (healthy control vs. schizophrenia) as the between-subjects factor and the five 100 ms time points (0-100 ms, 100-200ms, 200-300 ms, 300-400 ms, 400-500 ms) as within-subjects factors. Mauchly's Test of Sphericity indicated that the assumption had been violated for both averaged- and single-trial analyses, $X^2(9) = 2638.06$, $p < 0.001$; $X^2(9) = 146.411$, $p < 0.001$, respectively. These analyses revealed that there was a main effect of gamma activity at the five 100 ms time points [$F(1.049, 297.919) = 198.827$, $p < .001$; $F(3.168, 959.935) = 59.198$, $p < .001$, respectively). Based on LSD post-hoc analysis,

Time 1 (0-100ms) gamma activity significantly differed from gamma activity during all other 100 ms time points for both averaged- and single-trial analyses (all *p*s < .001). Time 2 (100-200ms) significantly differed from all other 100ms time points for averaged- trial analysis (all *p*s < .001), but only significantly differed from Time 1 in the single-trial analysis ($p < .001$). Time 3 (200-300ms) significantly differed from time points 1 and 2 (*p*s < .001), but did not differ from time points 4 and 5 in the averaged-trial analysis (400-500ms; $p > .05$). In contrast, Time 3 significantly differed from Time 1 and Time 4 in the single-trial analysis (*ps* < .05). Time 4 (300-400) significantly differed from time points 1 and 2 (*p*s < .001), but did not differ from time points 4 and 5 in the averaged-trial analysis (*p*>.05). In contrast, Time 4 significantly differed from Time 1 and Time 3 in the single-trial analysis (*ps* < .05). The averaged-trial analyses also revealed a significant main effect of group [$F(1, 284) = 5.828$, $p < .05$)], indicating that gamma at all 100 ms time points was larger in the healthy control group compared to the schizophrenia group. Finally, there was a group x 100 ms time points interaction in the averaged-trial analyses [$F(1.049, 297.919) = 4.101$, $p < .05$)]. Gamma at time 1 (0-100ms) was larger in the healthy control group than the schizophrenia group, but this difference was not found in all other time points between groups. Single-trial analyses did not reveal a significant main effect of group nor a group x 100 ms time points interaction (*ps* > .05).

CHAPTER FOUR

DISCUSSION

Sensory gating is part of a complex information processing system that allows humans to attend to salient environmental stimuli and pre-attentively filter unimportant and repetitive sensory information (Freedman et al., 1987; Geyer & Braff, 1987; Venables, 1964). Due to existing debates in the sensory gating literature regarding the etiology of poor P50 gating, the mechanisms that drive this process are not yet identified. In particular, it is unclear whether abnormal gating ratios and amplitude difference scores in patients with schizophrenia reflect dysfunctions in registration/encoding (gating in), gating/filtering (gating out), or both (Blumenfeld & Clementz, 2001; Boutros & Belger, 1999; Clementz et al., 1997; Clementz & Blumenfeld, 2001; Edgar et aI., 2008; Hall et al., 2010; Hong et al., 2004; Jin et al., 1997; Johannesen et al., 2005; Popov et al. 2011). The mechanism of auditory sensory gating is typically understood in a conditioning framework, in which the first stimulus activates an inhibitory neural mechanism that acts to suppress the repeated stimuli (Adler et al., 1982). Thus, it is proposed that the brain's failure to suppress S2 is most likely caused by neurobiological events occurring after S1 but before S2 within the inter-click interval (Hong et al., 2004). The current study used the paired-click paradigm to examine oscillatory activity within the gamma and beta bands across and within distinct time points of the delay interval to examine the physiological basis behind this conditioning mechanism, as well as test both gating out (e.g., the degree of attenuation from S1 to S2) and gating in (e.g., abnormal S1 amplitude response) processes in a sample of patients with schizophrenia and healthy controls (Eccles, 1969).

Findings of Current Study

To our knowledge, this is the first reported study that has examined oscillatory activity and event-related potentials by using two different approaches (averaged-trial analyses and single-trial analyses) to evaluate the contribution of oscillatory components to sensory gating within specific time windows of the inter-click interval. The use of both approaches provides a more comprehensive measure of auditory processing than the analysis of averaged evoked potentials alone (Hong et al., 2004). In support of our first hypothesis and consistent with previous sensory gating literature, we found that individuals with schizophrenia had worse P50 inhibition compared to healthy controls, as reflected by an elevated P50 gating ratio and reduced P50 difference score. Our results suggest a deficit in the suppression of irrelevant auditory stimuli in individuals with schizophrenia and is in agreement with extensive research on P50 gating (Adler et al., 1982; Clementz et al., 1997b; Freedman, et al., 1983; Freedman et al., 1996; Boutros et al., 1999; Javitt, 2009; Boutros et al., 2004; Braff & Geyer, 1990; Light et al., 2000; Clementz et al., 1998, 2003; Olincy et al., 2010; Ringel et al., 2004; Johannesen et al., 2005; Brockhaus-Dumke et al., 2008a; Jansen et al., 2010; Bak et al. 2014; Siegel et al., 1984).

In addition, we found that patients with schizophrenia demonstrated an abnormally smaller S1 response, but not S2 response, compared to healthy controls. This finding is inconsistent with a large number of studies that traditionally support a "gating out" etiology of P50 gating, as reflected in poor suppression of the S2 amplitude in the presence of a normal S1 response in individuals with schizophrenia (Chang, Arfken, Sangal, & Boutros, 2011; Clementz et al., 1998; Clementz et al., 1997b; Freedman et al.,

1987; Jin et al., 1997; Smith et al., 2010). Our findings corroborate studies that have yielded considerable evidence for a "gating in" etiology of poor auditory sensory gating in patients with schizophrenia (Blumenfeld & Clementz, 2001; Boutros, Zouridakis, & Overall, 1991b; Brenner et al., 2009; Brockhaus-Dumke et al. 2008; Clementz et al., 2003; Clementz & Blumenfeld, 2001; Jansen et al., 2004; Jin et al., 1997; Johannesen et al., 2005; Smith et al., 2010; Vohs et al., 2009; Zouridakis, Boutros, & Jansen, 1997). We propose that deficits in P50 gating are contingent upon patients' inability to register or attend to the salient and novel stimuli, and that a small S1 response in patients with schizophrenia may better elucidate the mechanisms of change in reference to the brain's response from S1 to S2 stimuli between healthy and schizophrenia groups.

Our study measured oscillatory activity within the beta (20-30 Hz) and gamma (30-50 Hz) frequency ranges and their relationship to P50 amplitudes and gating measures. Delay interval activity was assessed in three ways: 1) within 0-500 ms to obtain a measure of total delay activity, 2) within 200-500 ms to obtain a measure of oscillatory activity after the ERP deflections returned to baseline, and 3) within 100 ms time windows to obtain more detailed timing information of delay interval activity. As observed in prior studies, we found that the auditory stimulus used to evoke the P50 ERP also induced both gamma and beta oscillatory responses in humans (Hong et al., 2008). In support of our second hypothesis, we found that individuals with schizophrenia exhibited less evoked and induced beta activity in response to the initial click stimulus (S1) throughout the 500 ms delay interval. These results are in agreement with Hong and colleagues' (2004) study, which reported reduced beta oscillatory response to S1 within the inter-click interval. We also found that beta activity contributed to auditory P50 ERP

responses in the time-frequency domain (Haenschel et al. 2000). In particular, we found that greater evoked and induced beta activity throughout the 500 ms delay interval was associated with increased attention to the S1 (larger S1 P50 amplitudes), more efficient gating (higher P50 difference scores and lower P50 ratio), and S2 suppression (larger S2 P50 amplitude) for healthy controls. Similar results were found for individuals with schizophrenia, but only for evoked, not induced beta activity and beta activity within the 500 ms delay interval did not contribute to the S2 amplitude (see Table 2). One hypothesis for our nonsignificant induced beta finding may be that the single-trial technique that our study employed for feature extraction and classification was subject to higher trial-to-trial S1 response latency variability (Jansen et al., 2010).

Our present findings of beta activity's association with ERPs are in agreement with evidence suggesting that oscillations in the beta frequency band, which is thought to be involved in stimulus salience and spatially distributing and encoding sensory information across distant cortical regions, is critical to help prevent both individuals with schizophrenia and healthy controls to discriminate important from unimportant stimuli and prevent repeated stimuli from being consciously processed (Smucny et al., 2013). Our results for healthy controls are consistent with findings from Hong et al. (2004)'s study, in that beta positively contributed to the S2 amplitude in healthy controls. However, unlike Hong and colleagues (2004), we did not find a significant relationship between beta and the S2 response nor that the beta frequency response was inversely correlated to the S2 amplitude in patients. This discrepant finding may be due to differences in the context of gamma and beta oscillations. Hong et al. (2004) examined gamma and beta oscillations within the context of a gamma-to-beta shift phenomenon,

while we did not investigate the timing of these oscillatory transitions. According to Hong et al. (2004), beta's negative contribution to the S1 amplitude occurred only in the context of the gamma-to-beta shift, rather than independently. Hence, a coupling mechanism of gamma and beta oscillatory activity may be the driving force to the S2 suppression in healthy controls. Based on our findings, higher oscillatory activity within the beta frequency band is predictive of increased attention and registration to salient auditory stimuli and more efficient gating in healthy subjects. The discrepancy in beta's contribution to the S2 suppression (S2 amplitude) between groups may suggest that in patients with schizophrenia a reduced S1 response may induce less beta activity that does not account for patients' response to S2.

In regards to evoked or induced gamma activity across the 500 ms delay interval, our findings did not yield any group differences. This finding is consistent with studies that have also found no significant difference between healthy controls and patients with schizophrenia in the gamma band response in auditory sensory gating (Brenner et al., 2009; Clementz et al., 1997; Clementz & Blumenfeld, 2001; Hong et al., 2008). However, it is discordant with previous human and animal studies examining gamma and beta oscillations, which have found reduced gamma oscillations in individuals with schizophrenia by using two standard click pairs of the same peak intensity of 92 dB in human studies (Haenschel et al., 2000; Hall et al., 2011) and intensive repetitive tetanic stimulation with rat models to cortically evoke gamma activity (Traub et al., 1999a). It is possible that the relatively lower stimuli peak intensity used in our study (81 dB) may not be as optimal in detecting group differences in gamma band activity (Hong et al., 2004).

For both healthy controls and individuals with schizophrenia, the relationship between gamma activity and ERP components was positive, such that greater evoked (not induced) gamma activity across the delay interval was associated with larger S1 and S2 P50 amplitudes and higher P50 difference scores (see Table 1). These findings are in agreement with past studies that have found significant positive correlations between gamma power to S1 and P50 S2 amplitudes in healthy controls (Hall et al., 2011) as well as patients (Hong et al., 2004). However, our finding that increased gamma activity is associated with a larger S2 amplitude in both healthy subjects and patients with schizophrenia is inconsistent with Hong et al. (2004)'s finding of a positive relationship only observed in patients. The authors hypothesized that the positive relationship between gamma and S2 is what leads to poor suppression of the S2 seen in patients and attribute the cause to the hyperexictability of neural substrates conveyed through the loss of nicotinic inhibitory interneurons that is found in individuals with schizophrenia (Smucny et al., 2013; Uhlhaas & Singer, 2013). Although this hypothesis may explain an unattenuated S2 response in patients, it does not hold true for healthy controls, as healthy subjects are able to efficiently suppress the S2 (as reflected in a smaller S2 response relative to the S1). Future studies are needed to clarify this relationship to further detect whether there are group differences.

The lack of identified group differences in gamma activity across the delay interval in our results may suggest that the role in which the gamma band plays in its contribution to P50 gating across the delay interval is similar for both healthy subjects and patients with schizophrenia. Also, because we did not find that induced gamma activity across the delay interval contributed to the ERP components (see Table 1), one

hypothesis may be that although single-trial EEG offers a way to examine spontaneous and preserved gamma activity that is not time-locked to the stimulus, the fact that the latency varies from trial-to-trial may produce an unfavorable ratio between signal (ERP) and noise (all non-phase-locked neural activity as well as to non-neural artifacts as interfering) that makes it difficult to distinguish between signals of interest to interfering noise (Blankertz, Lemm, Treder, Haufe, & Muller, 2010).

In examination of induced or evoked gamma- and beta-band activity in the 200-500 ms time point, we also did not find group differences between individuals with schizophrenia and healthy controls. Gamma and beta at the 200-500 ms time point were also not related to P50 amplitudes and measures of P50 gating. Previous studies have shown an observable reduction in induced beta activity within the 200-500 ms delay window in healthy controls (Kisley & Cornwell, 2006) and that beta returned to a baseline level at 276-400 ms before the onset of S2 (Hong et al., 2004). A return to baseline level in beta activity within the 200-500 ms time window in healthy controls may explain why there is not a significant relationship between beta activity, P50 responses, and gating measures. However, this does not explain the present results for patients. This finding seems to suggest that oscillatory activity early, rather than later, in the 500 ms delay interval (0-200 ms) may be driving the inhibitory mechanism within the paired-click paradigm for both patients and healthy controls.

The abovementioned results suggest that oscillatory activity within the gamma- and beta –frequency bands across the entire delay interval has significant influence on P50 amplitudes and gating in both healthy controls and patients with schizophrenia. Hence, the next question that we aimed to answer concerns the specific temporal origins

of when during this 500 ms delay interval is oscillatory activity within the gamma- and beta-frequency range related to P50 inhibition, and whether there are group differences in the physiological basis and timing for this type of conditioning. In order to identify such specific temporal information, we divided the 500 ms delay interval into five distinct 100 ms time points. We consistently found that evoked and induced gamma activity at the 0-100 ms time point was significantly predictive of P50 amplitudes and the extent of P50 gating (P50 difference scores) for healthy controls. The same pattern emerged for patients; however, only for evoked gamma activity at the 0-100 ms time point. For both groups, the higher the activation of evoked gamma activity during the first 100 ms after the initial click, the more subjects in both groups were able to attend to the novel click and efficiently filter the repeated click (see Table 3). Our finding that evoked gamma at the 0-100 ms time point is associated to S1 amplitude is in concert with studies on the gamma-to-beta frequency shift phenomenon, which propose that gamma frequency appears within the P50 and N100 time window and may be temporally and morphologically overlap with these ERP components (Basar et al., 1987; Clementz & Blumenfeld, 2001; Clementz, Blumenfeld, & Cobb, 1997a; Hall et al., 2011; Johannesen et al., 2005). Our findings lead us to propose that S1 P50 responses and evoked gamma activity reflect a similar phenomenon, and that gamma band activity is associated with stimulus onset (Crone, Boatman, Gordon, & Hao, 2001; Basar et al., 1987; Clementz et al., 1997a; Clementz & Bloomenfeld, 2001; Kopell et al., 1999). The relationship between the S1 P50 amplitude and evoked gamma at the five 100 ms time points was less clear in patients compared to healthy controls, as evoked gamma at 100-200 ms, 300-400 ms, and 400-500 ms also predicted S1 amplitude, but in different directions. Future

studies are needed to clarify the relationship between evoked gamma and S1 amplitude to identify whether early gamma activity within the delay interval is critical in determining patients' capacity to detect novel and salient auditory stimuli. Interestingly, we did not find any significant relationships between induced gamma activity at all five 100 ms time points and sensory gating nor P50 amplitudes for patients (see Table 3). One hypothesis may be that the single-trial technique that our study employed for feature extraction and classification was subject to higher variability in the classification accuracy both between subjects and within subjects (Blankertz et al., 2010). Future studies are needed to examine the differences in predictive power between evoked versus induced gamma activity in its association with P50 amplitudes and gating in patients and healthy controls.

Partially consistent with our second hypothesis that proposed reduced gamma activity early in the delay interval for patients, we found that evoked gamma activity at the 0-100 ms time point, and not at any other time point, was significantly reduced in patients with schizophrenia relative to healthy controls. However, we did not find any group differences in induced gamma activity during any of the five 100 ms time points. Evoked gamma at the 0-100 ms time window of the delay interval reflects tightly time-locked activity that leads to an ERP. Since healthy controls and patients differ in evoked gamma activity within this time point, it is reasonable to assume that patients with schizophrenia did not produce the magnitude of response and/or were not time-locked to the same extent as healthy controls. A lack of difference in induced gamma activity at 0-100 ms indicates that the overall magnitude of non-time-locked activity was the same between groups. Hence, it is only when the non-time-locked events are removed by averaging the single trials, as is in evoked oscillatory activity, that a finding of group

difference is demonstrated. Our discrepant results related to group differences between evoked and induced gamma activity during each 100 ms time point of the delay interval needs further clarification from future studies. It is difficult to understand changes in gamma activity due to several factors that can affect it, such as subjects' motivation and behavioral state (attention and degree of arousal).

Gamma-band oscillations play an important role in dynamically selecting neurons that communicate information about auditory sensory inputs effectively and integrating stimuli to form a memory trace of an auditory perception (Uhlhaas & Singer, 2008). Given the importance of gamma in neural coding and integration of a sensory input, reduced gamma oscillations found in patients would lead to confused messages that may reverberate throughout the delay interval (Lisman & Buzsaki, 2008). Diminished evoked gamma band activity that we observed early in auditory stimulus processing in association with a small S1 response to the initial click found in our patients may reflect an impairment in basic auditory memory functions necessary to form an auditory sensory memory trace of the stimuli that allows humans to compare the repeated sound to the memory trace of the first stimuli, and then recruit the same assembly of neurons to activate the inhibitory mechanism in order to suppress the repeated click (Cromwell et al., 2008; Csicsvari et al., 2003; Freedman et al., 1987; Gruber & Muller, 2005; Herrmann et al., 2004; Uhlhaas et al., 2011; Zouridakis and Boutros 1992).

In examination of beta activity within the five 100 ms time points of the delay interval, our findings do not support our third hypothesis that evoked and induced beta responses within the 200-300 ms time point after presentation of the initial click would significantly correlate with P50 gating measures and the P50 S2 amplitude. Similar to our

findings in the gamma band, evoked beta activity early in the delay interval (0-100 ms and 100-200 ms time points) was significantly and positively associated with P50 amplitudes and P50 gating for healthy controls, such that greater evoked beta activity at the 0-100 ms and 100-200 ms time points was associated with larger P50 amplitudes and more efficient P50 gating as measured by the P50 difference score (see Table 4). In disagreement with our results, Hong et al. (2008) found that induced beta power early in the delay interval at 26-150 ms significantly and negatively contributed to P50 gating for healthy controls. In addition, Hong et al. (2008) also found a significant association between induced beta at the 151-275 ms time window to be significantly associated with the P50 gating ratio, while we did not yield similar findings in the 200-300 ms time point for either evoked or induced beta. This difference may be due to the fact that the authors examined beta activity within the context of a gamma-to-beta shift phenomenon. In patients, we found that evoked (not induced) beta activity at the 0-100 ms time point contributed to the S1 amplitude and P50 difference scores (but not S2 amplitude as it did in healthy controls), such that greater beta activity during the first 100 ms of the delay interval is predictive of greater attention to stimuli saliency (larger S1 P50 response) and the strength of sensory gating (see Table 4). Hall and colleagues (2010) also found that post-S1 beta power was not significantly associated with the P50 S2 amplitude in patients.

In regards to group differences in beta activity within each 100 ms time point, we found that evoked beta activity at the 0-100 ms, but not at other time points, was significantly lower in patients with schizophrenia compared to healthy controls. In an animal study of the neonatal ventral hippocampus lesion (NVLH) rat analogue, Vohs et

al. (2009) also found a reduction in the beta frequency band within the first 55 ms after S1 in addition to an attenuated S1 and lack of S2 suppression resulting in deficient beta band gating. Because beta oscillations are associated with salience detection, stimulus encoding, and consolidation of sensory information over long distances across cortical regions, reduced evoked beta band responses to S1, especially early in the delay interval in patients may curtail inhibitory processes that lead to overall poor suppression scores (Bibig et al., 2001; Haenschel et al., 2000; Kisley & Cornwell, 2006; Kopell et al., 2000; Leiberg et al., 2006; Hong et al., 2004a; Traub et al., 1999a; Uhlhaas et al., 2008; Siegel et al., 2012). In addition, the diminished time-locked beta band activity in patients may also explain deficiencies in the encoding of S1, as proposed by Hong and colleagues (2004).

It is important to note that the P50 difference score appears to be a better quantitative indicator of P50 gating than the P50 gating ratio in our study, as oscillatory beta and gamma activity consistently yielded significant relationships with the P50 difference scores of both patients and controls, but not P50 gating ratio. This psychometric finding is supported by recent P50 literature that strongly suggest the use of the S1-S2 amplitude difference measure over the more dominant measure of sensory gating ratio, as it provides a more comprehensive examination of sensory gating deficits in schizophrenia (see review by Chang et al., 2011). Our findings that evoked beta and gamma activity are consistently predictive of both the P50 difference score and S1 amplitude in patients and healthy controls is in line with research from Brockhaus-Dumke and colleagues (2008), in which they have found that the S1-S2 difference was highly correlated with the P50 S1 amplitude, but weakly with the S2 amplitudes.

Limitations

A number of possible limitations in the current study should be considered. First, our study is cross-sectional; thus, may not be generalizable to all patients. Second, we did not examine the duration of illness in the present sample. Past researchers have found that the P50 deficit may be less pronounced in early courses of the illness (de Wilde et al., 2007; Yee et al., 2010). Third, although the control group had equivalent representation of males and females, the patient group was predominantly male. Fourth, there may be undetected confounding effects due to nicotine use. Cigarette smoking is shown to transiently normalize auditory sensory gating deficits in patients with schizophrenia (Adler et al., 1993). Reduction in α-7 nAChRs is also found to modulate beta and gamma frequency ranges in patients and mice model (Smucney et al., 2013). Fifth, the majority of participants were taking antipsychotic medication, which may contribute to a reduced group difference, as atypical antipsychotics have been shown to normalize the P50 ratio in the typical dual-click paradigm by indirectly acting on the nicotinic receptor (Light et al., 2000; Nagamoto et al., 1996; 1999). An atypical antipsychotic known as clozapine, in particularly, is shown to improve P50 ratios (Nagamoto et al., 1996; Simosky et al., 2002). Sixth, we did not separate patients by subtype in our sample, although patients were diagnosed with either schizophrenia or schizoaffective disorder. Attention and arousal were also not controlled for in the present study; hence, it cannot be determined whether changes to the P50 amplitudes and gating over time are associated with repeated utilization of the P50 network, or whether they are a more general result of decreasing arousal levels (Croft et al., 2001). Lastly, due to problems with multicollinearity in our regression analyses, particularly in the beta frequency band at the five 100 ms time points, we were not able to report comprehensive results regarding the contributing role

of beta activity at each 100 ms time points on P50 amplitudes and sensory gating measures.

Conclusions and Implications

Overall, the results of the present study demonstrates that in addition to ERP amplitude responses (e.g., S1 amplitude), the brain's oscillatory responses in the beta (20-30 Hz) and gamma (30-50 Hz) frequency bands within the early time window of the delay interval are also shown to be major contributors to sensory gating. More specifically, greater beta and gamma frequency responses to S1 in the first 100 ms during the 500 ms inter-click interval appears to be the most critical period in predicting the strength of auditory sensory gating for both patients and healthy controls. In addition, greater activation of gamma activity within the early time points of the delay interval contributed to S2 amplitude suppression in both patients and healthy controls. Our findings extend previous literature by examining oscillatory activity within the gamma and beta frequency bands within the 500 ms inter-click interval in more detail than has previously been reported in the literature (Hong et al., 2004; 2008). Specifically, we were able to identify specific timing of when oscillatory activity in response to S1 contributes to P50 gating, and find support for the sensory "gating in" etiology. These findings suggest that failure to attend to S1 and aberrant beta and gamma, especially as it relates to stimulus encoding and registration within the first 100 ms after S1 presentation, may be considered a primary mechanism underlying sensory processing abnormalities in schizophrenia. These results also suggest that patients and healthy controls have the same gating mechanism that is activated in between S1 and S2; however, this inhibitory mechanism is not as efficient in patients as it is in healthy controls.

The present findings of smaller evoked beta- and gamma-band responses to the first auditory stimulus in patients suggests that this reduced interplay may influence the efficiency of encoding/consolidation of auditory information, sensory integration, and active memory formation within the delay interval, which may influence the brain's ability to attend to important stimuli (S1) and ultimately leave the brain vulnerable to information overflow (poor P50 gating; Freedman et al., 1987a; Kopell et al., 2000; Hong et al 2004b; Ringel et al., 2004; Uhlhaas et al., 2006). Several animal studies have demonstrated the important role of nicotinic receptors in gating of P50 ERPs by showing that deficits extend to beta-and gamma-frequency ranges in patients (Adams et al., 2008; Adler et al., 1998; Bickford-Wimer et al., 1990; Callaway, 1970; Freedman et al., 1996; Luntz-Leybman, Bickford, & Freedman, 1992; Smucney et al., 2013; Speck et al., 1966). In the adult hippocampus, nicotinic receptors are primarily located on inhibitory interneurons. When activated, these receptors induce GABA release, an inhibitory neurotransmitter that prevents excitatory neurons, such as glutamate, from being released so that the neurons do not receive as much excitatory input from the second stimulus. Hence, the brain responds less to repeated stimuli (Cobb et al., 1995; Gandal et al., 2012; Sohal et al., 2009; Wang & Buzsaki, 1996). Reductions in nicotinic receptor expression would thus reduce GABAergic neurotransmitters and lead to hyperexcitability. On a network level, the loss of GABAergic interneurons and this change in excitability may be related to a decrease in oscillatory power. Decreased beta and gamma power to S1 in patients may therefore reflect a general increase in cortical excitability that decreases patients' ability to encode/detect saliency (reduced beta) and integrate local auditory

input to form a memory trace (reduced gamma; Traub et al., 1999a; Kopell et al., 2000; Traub, Jeffreys, Whittington, 1999b; Bibbig et al., 2001).

In conclusion, oscillatory activities during the interclick-interval serve a critical function in auditory information processing in the central nervous system. Our findings that impairments in processing the initial auditory stimulus and observations of reduced beta and gamma activity in patients within the early temporal time frame of the ERP components potentially affect stimulus encoding, memory processes, and overall auditory information processing may help researchers and clinicians develop cognitive training protocols that aim to improve patients' attention and registration of important sounds. Our finding of a gating in etiology also emphasizes the importance of directing early attention toward novel and salient auditory stimuli, which in turn may facilitate effective auditory sensory gating (Yee et al., 2011). Thus, it may be beneficial for future interventions to help patients practice discriminating, directing voluntary attention, and controlling their attention to salient sounds in the environment, which may help to subsequently filter out distracting sensory information, normalize P50 gating, and overall improve the processing of repeated sounds (Popov, 2011). In a study by Popov (2011), the author found that cognitive training related to discriminatory training which comprised of 60-minute daily sessions within 20 consecutive workdays, increased (normalized) evoked gamma (60–80 Hz) response time-locked to the first click in SZ patients, which was associated with the normalization of P50 ratio. Thus, training effects on gamma activity (indicating improved S1 encoding) may have influenced training effects on the subsequent brain state, indicated P50 ratio normalization, reflecting improved processing of the paired clicks. The investigation of oscillatory activity using

averaged- and single-trial analyses at different time points during the inter-click interval provides researchers with specific timing information about the mechanisms that support sensory inhibition may also further provide a comprehensive link between oscillatory activities and sensory gating within a novel framework that allows for future experimental models of auditory sensory gating.

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