THE MODULATORY ROLE OF SELECTIVE ATTENTION ON P50 SENSORY GATING AND EVENT RELATED BETA ACTIVITY IN SCHIZOPHRENIA

by

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Abstract

Sensory gating refers the central nervous system's capacity to filter redundant sensory information. Deficient auditory sensory gating abilities have been documented in individuals with schizophrenia and may contribute to some of the sensory and perceptual disturbances associated with this disorder. When using event-related potentials (ERP) to investigate the phenomenon of sensory gating, traditional dual-click paradigms focus on the attenuation in P50 amplitude to the second click (S2) compared to the first click (S1). While long believed to be pre-attentional, recent findings have suggested that this phenomenon can be modulated by selective attention. A standard dual-click task and two modified dual-click tasks that required participants to attend to either S1 or S2 were used to examine the effect of selective attention on S1 or S2 P50 amplitude in (n=25) participants with schizophrenia and (n=24) healthy controls. Results reveal that attending to S1 increases P50 amplitude to S1 for healthy controls but not for the schizophrenia group. There were no increases to S2 P50 amplitude for either group when attending to S2. Subsequently there were also no differences for either group to the S1-S2 difference scores when attending to S1 or S2. Wavelet analysis of event-related Beta-1 frequency activity revealed that controls were able to augment their Beta-1 response to S1 when attending to S1 but not their Beta-1 response to S2-when attending to S2. The schizophrenia group did not show increased Beta-1 activity when attending to S1 but did show increased Beta-1 activity to S2 when attending to S1 and when attending to S2. The different pattern of Beta-1 activity in controls and individuals with schizophrenia might reflect an underlying deficiency that individuals with schizophrenia have in processing salient auditory information. Furthermore, these results are consistent within the context

of selective attention deficiencies that are commonly reported in individuals with schizophrenia.

Preface

This research was conducted at the Clinical Cognitive Neuroscience Laboratory located in the Psychology department at UBC. The data presented in this manuscript was collected as a subset of two larger research protocols overseen by Dr Colleen Brenner that were approved by the UBC Behavioural Research Ethics Board (H10-00570 & H10-01210). Graduate student collaborators include Amy Burns, Season Johnson and Samuel Rumak. I was responsible for designing the protocol, conducting clinical interviews and assisting with EEG data collection. I was also responsible for processing and analyzing the majority of the data and was responsible for the preparation of this manuscript.

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To my loved ones…

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Schizophrenia is a debilitating mental illness that is characterized by unusual sensory experiences ranging from distorted auditory and visual perception during the early stages (Cutting & Dunn, 1986) to persistent hallucinations experienced by those with chronic schizophrenia (Phillipson & Harris, 1985). These dysfunctional sensory processes (ie. sound processing in the auditory cortex) may in turn impair higher-level perceptual processes (ie. discriminating between two auditory tones with different sound properties) (Javitt, 2009), which may lead to cognitive processing deficits (ie. working memory, executive control) (Howard et al. 2003; Williams & Boksa, 2010). Those with schizophrenia exhibit a heterogeneous array of cognitive deficits (attention, memory, learning, conceptualization, organization, planning, self-monitoring, and flexibility of thinking) that are present at the onset of the illness and for the most part have proven to be refractory to anti-psychotic medications (Rund, 1998; Twamley, Jeste & Bellack, 2003; Palmer, Dawes, & Heaton, 2009; Potkin et al., 2009). The poor functional outcomes associated with persistent cognitive deficits results in an economic burden in Canada. In 2004 the estimated cost was nearly seven billion dollars, with approximately 70% of these costs reflecting lost productivity in the workforce (Goeree et al., 2005). It is critical to understand the nature of these functional impairments as it is becoming increasingly clear that there is an interplay between bottom-up sensory processes and top-down cognitive functions.

Sensory gating is a broad term for a number of processes that allow the human brain to filter sensory information. The central nervous system is continuously

bombarded with input from all of its sensory modalities. In order for the brain to process and make sense of this information, mechanisms are in place to prevent it from being overwhelmed with information (Cromwell, Mears, Wan & Boutros, 2008). The auditory sensory gating deficit in schizophrenia is thought to be an aberration in the mechanism by which redundant auditory information is filtered to prevent overload (Patterson et al., 2008; Javitt, 2009). This particular deficit is believed to be related to a number of cognitive and functional deficits observed in those with schizophrenia (Cullum et al., 1993; Potter et al. , 2006; Yadon, et al., 2009; Williams & Boksa, 2010).

Event-related potentials (ERPs), in conjunction with the auditory dual click paradigm, are the most common tool utilized to assess sensory gating impairments in schizophrenia. The ERP component that has been the primary focus of most studies is the P50. The P50 is a positively deflected waveform that occurs roughly 50ms after the presentation of an auditory stimulus (Freedman et al., 1987; Rosburg, Boutros, & Ford, 2008; Brockhaus-Dumke et al., 2008). When a healthy individual is presented with two auditory clicks spaced 500 ms apart, the P50 waveform after S2 will typically be smaller when compared to the P50 after S1. This measurement of auditory sensory gating has traditionally been expressed as a ratio of S2/S1 (so that lower ratio scores reflect a greater attenuation of the S2 response) however more recent studies have found that the difference score (S1-S2) is a more reliable metric (Smith, Boutros & Swartzkopf, 1994; Cadenhead, Light, Geyer & Braff, 2000; Rentzsch, Jockers-Scherübl, Boutros & Gallinat, 2008).

Individuals with schizophrenia show a lesser degree of attenuation of S2. This is thought to be related to the filtering of redundant auditory information as is described by

sensory gating theories (Adler et al., 1982). The suppression of the P50 in response to repetitive stimuli was originally conceptualized as an automatic process that occurs before the information is consciously processed (Freedman et al., 1996; Smith et al., 2010). Because auditory P50 attenuation is often expressed as a ratio of S2/S1 the larger ratio observed in patients could be the result of less suppression of the S2 amplitude or a smaller S1 amplitude.

In addition to analyzing the P50 ERPs, it is also possible to examine the oscillatory activity in various frequency bands that occurs during the dual click paradigm. This approach may allow for greater specificity in identifying the neural mechanisms associated with sensory gating. This process allows one to quantify the contributions of oscillatory activity within specific frequency bands to the overall waveform (Johannesen et al., 2005; Uhlhaas, Haenschel, Nikolic, & Singer, 2008). Furthermore, examining the activity in the various frequency bands reveals some interesting temporal components that are not apparent in the ERP analysis. Of particular interest is the temporal sequence of the evoked phase-locked beta-1 (12 - 20 Hz) and gamma (30 - 50 hz) oscillatory activity that is present within the same time window as the P50 caused by S1 (Haenschel et al., 2000). Frequency analysis of the suppressed S2 P50 has revealed that there is a significant reduction in Beta-1 activity compared to what is seen in response to S1 and this appears to be the reason for the attenuated S2 P50 ERP (Kisley & Cornwell, 2006).

There has been some debate as to whether the poorly attenuated waveforms in schizophrenic patients are the result of a failure to filter-out or a failure to encode sensory information. Research by Brenner and colleagues (2009) demonstrated that the response to S1 was also diminished in patients with schizophrenia, indicating a role of initial

sensory encoding deficits in sensory gating. This has been demonstrated in other auditory dual click studies (Ghissolfi et al.,2004) but not all (Gjini, Arfken, & Boutros, 2010). The study by Brenner and colleagues also revealed that in response to salient pairs of auditory stimuli, schizophrenic participants exhibited less phase-locked Beta-1 activity after the onset of S1 compared to healthy controls. Interestingly, research by Hong and colleagues (2004) reported that Beta-1 activity following S1 was inversely correlated with the amplitude of the P50 ERP amplitude in response to S2 in schizophrenia patients. Unfortunately, there are only a few studies that have explored the role of oscillatory EEG activity for the P50 dual click paradigm in schizophrenic patients.

Most of what is known about the relationship between oscillatory activity and the S2/S1 score has been gleaned from healthy samples. In one such sample, Hong and colleagues (2008) found that non-phase locked alpha (5-12 Hz) and beta-1 activity 25 - 150ms after S1 to be strong predictors of the S2/S1 ratio score. They also found evidence that Beta-1 activity occurring 151-250ms after S1 accounted for additional variation in the ratio score. There was no relationship between oscillatory activity at any frequency occurring 250-400ms and the ratio score. Others have also found no relationship between oscillatory activity occurring 250-400ms time window and the S2/S1 ratio but have reported a decrease in non-phase-locked Beta-1 activity in this time window compared to baseline Beta-1 activity (Kisley & Cornwell, 2006). Given that the above findings came from healthy samples, it is yet to be seen if these relationships are also present in schizophrenic samples.

Furthermore, very few studies have investigated the role that attention has on auditory P50 gating in schizophrenic samples. The P50 gating phenomenon was

originally conceptualized to be a pre-attentive automatic phenomenon in which the response to S1 triggered inhibitory mechanisms that served to attenuate the response to the second click. The non-attenuated responses to S2 in those with schizophrenia were thought to reflect a faulty inhibitory process (Braff & Light, 2004; Freedman et al., 1996; Jerger, Biggins & Fein, 1992). Recent research has shown that manipulating attentional resources either by changing the properties of the stimuli themselves (i.e. intensity of the clicks) or the context in which they are perceived (i.e. rare versus common stimuli) can affect P50 amplitudes. These studies indicate that the P50 ratio and difference scores can in fact be manipulated based on the attentional focus of the task (Brenner et al., 2009; Moura, Trinanes-Pego & Carrillo-de-la-Pena, 2010).

Despite the assertion that the P50 gating phenomenon is pre-attentional, there is evidence to suggest that selective attention can modulate early auditory processing. ERP and Magnetoencephalography (MEG) source localization studies on healthy individuals have shown that paying selective attention to auditory stimuli can augment waveforms originating from the supra temporal plane of the auditory cortex that occur as early as 20ms post stimulus (Woldorff & Hillyard, 1991; Woldorff et al., 1993). Other fMRI research has shown a distinction in regional activation for auditory stimulus driven attention and selective attention in the auditory cortex (Rinne et al.,2007). Furthermore, Petkov and colleagues (2004) used fMRI surface mapping to image the auditory cortex while participants underwent an auditory selective attention task. They reported that stimulus driven attentional activations were predominant in right the mesial auditory cortex whereas selective attention activations were predominant in the left lateral auditory cortex. Interestingly, reduced MRI volumetric measurements in these areas of the

auditory cortex have been associated with a longer duration of illness and more positive symptoms in schizophrenic patients (Crespo-Facorro, 2004). Yee and colleagues (2010) have provided evidence that selective attention may compensate for the deficits seen in those with schizophrenia on an auditory P50 dual-click task. Their study showed that by selectively attending to S1, schizophrenic participants had greater P50 suppression at S2. Furthermore, the altered S2/S1 P50 ratio score in chronic schizophrenic patients appeared to be driven by increases of the P50 amplitude at S1 and not by suppression of S2. The malleability of the P50 component to the influence of conscious attentional control suggests that the sensory gating phenomenon is the product of distinct but interacting neural systems. It has been speculated that the superior temporal gyrus (STG), region CA3 of the hippocampus, the dorsolateral prefrontal cortex (DLPFC) and the thalamus play a fundamental role in the generation and suppression of P50 ERPs. Evidence in support of the distinct but interacting neural systems has come from a source localization study by Williams, Nuetcherlein, Subotnik & Yee (2010). This study revealed that the gating ratios in schizophrenia patients correlate positively with activity in the DLPFC whereas the ratios in healthy controls correlate positively with activity in the hippocampus.

It would appear that dysfunction in different brain structures may account for the gating deficits in schizophrenia, but it is not clear how having patients selectively attend to target stimuli is compensating for the deficit. An examination of the frequency components that contribute to the attentional modulation of P50 gating may help explain this. As mentioned above, phase locked Beta-1 oscillations make significant contributions to the S1 P50 waveform and the subsequent suppression of S2 is largely driven by a

reduction in Beta-1 activity. Activity in this frequency range has been tied to the evaluation and encoding of novel and salient stimuli (Traub et al., 1999; Haenschel et al., 2000; Kisley & Cornwell, 2006) and Beta activity has been associated with variable responses to above-threshold auditory stimuli due to drowsiness (Makeig & Jung, 1996). Furthermore, it has been suggested that selective attention to an auditory stimulus increases synchronization of beta oscillations and when averaged this increased phase locked activity would result in augmented ERP waveforms. Together, these findings suggest that aberrant stimulus driven salience detection (as ostensibly represented by beta range activity) may play a role in the sensory gating deficits observed in those with schizophrenia.

This research utilized electroencephalographic (EEG) and a series of auditory dual-click tasks to investigate auditory sensory gating deficits in schizophrenia. This study investigated the modulation of auditory sensory gating by examining the impact of selective attention on the resulting waveforms and their constituent oscillatory activity. In light of the confusion surrounding the actual effects of attention on the P50 sensory gating, this research first aimed to verify whether selectively attending to either the first or second stimulus in the auditory paired-click paradigm impacted sensory gating. Secondly, we explored the components of sensory gating to determine whether there are differential effects of attention on S1 and S2 in healthy and schizophrenia groups. To examine the impact of attention on different components of the P50 response, three different paradigms were presented. The first was the typical dual-click paradigm to serve as a baseline. The second was a modification of the basic dual-click paradigm that required participants to make distinctions based on the intensity of the auditory stimuli

that was intended to allocate selective attention to the first stimulus. The third was a modification to the basic paradigm that required participants to distinguish between the number of clicks which was intended to allocate selective attention to the second stimulus. We investigated whether participants with schizophrenia, with known deficits in selective attention on complex neuropsychological tasks, demonstrated comparable modulation of the P50 response as the healthy control group. We also examined the impact of selective attention on the oscillatory activity within different frequency bands, with particular emphasis on the beta-1 (12-20 Hz) band.

We hypothesized that in the baseline condition schizophrenia patients would demonstrate decreased sensory gating which will be reflected in a smaller difference S1-S2 score when compared to healthy controls. Furthermore, schizophrenia patients will exhibit less Beta-1 activity than controls at S1 and more Beta-1 activity at S2 compared to healthy controls. In the intensity condition, it is hypothesized that directing attention to the first stimulus will increase S1 P50 amplitude for both the schizophrenia group and the control group with respect to the baseline condition, however the magnitude of change will be greater for the control group. There should be no change in magnitude for either group at S2. We expect that this will result in an increased S1-S2 P50 gating score for both groups but this increase should be greater for the schizophrenic group. Furthermore, it is expected that directing attention to S1 will increase Beta-1 activity for both groups, but more so for the control group. In the number condition, we do not expect that directing attention to the second stimulus will impact S1 P50 amplitude, however we do expect an increase in the amplitude of the S2 P50 response for schizophrenia group and the control group, however the magnitude of change will be greater for the control group.

This increased S2 amplitude should result in a decreased S1-S2 for both groups, but more so for the control group. There should be no change in Beta-1 activity at S1 for either group. However, Beta-1 will increase for the control group at S2 but not the schizophrenia group

Method

Research Design

This study utilized a non-equivalent 2 x 3 mixed-factorial design with conditition (baseline, intensity and number) as the within-subject factor and diagnosis (schizophrenia and healthy control) as the between subject factor. The dependant variables examined for the ERP analysis were the amplitudes of the P50 ERP to S1 and the P50 ERP to S2, the S1-S2 P50 amplitude difference score. The wavelet analysis looked at Beta-1 activity following S1 and S2. The P50 ERP waveforms will be extracted from averaged EEG data. Beta-1 spectral power will be derived from an offline transformation of raw EEG data.

Participants

A total of 25 participants were included in the schizophrenia group (18 female; mean age 33.2) and 24 were included in the healthy control group (16 female; mean age 29.3). Originally 36 individuals with schizophrenia or schizoaffective disorder and 35 controls from the community were invited to take part in this study after partaking in a brief telephone eligibility screen. Participants in the schizophrenia group were recruited from various community run peer support and vocational training centers. Diagnostic status for all participants was confirmed using the Structured Clinical Interview for the DSM-IV (American Psychiatric Association [DSM-IV-TR], 2000), which was administered by trained graduate students. Participants were excluded from the study if they reported a history of a head injury, a loss of consciousness for more than 5 minutes, learning disability, hearing impairment, or if they consumed alcohol or recreational

substances within the 24-hour period preceding the onset of the study. Of the 36 individuals recruited for the schizophrenia group, 11 were excluded reducing the total of number of participants in this group to 25. Eight of these individuals were excluded because they met criteria for one of the above mentioned exclusion criteria. Two individuals were excluded because they did not have enough correct trials (at least 70 out of 82) on one or more of the experimental tasks. One individual was excluded because of technical difficulties with the EEG equipment. Of the 35 healthy controls invited to participate, 11 were excluded leaving a total of 24 in this group. Of these, four were excluded because they did not pass the exclusion criteria. Four were excluded because of poor performance on the experimental tasks and three were excluded due to technical difficulties at the time of EEG recording. During the study all participants were asked to refrain from smoking 40 prior to the onset of EEG testing to minimize potential acute effects of nicotine on ERP amplitudes (Adler, Hoffer, Wiser, & Freedman, 1993). Data was also collected on participants' current prescription medication use (type and dose) so that analyses could be conducted to rule out any effect of typical or atypical anti-psychotic medications (Nagamoto et al., 1996). Written consent was obtained from all participants in accordance with the policies of the University of British Columbia Behavioural Research Ethics Board.

Procedure

The procedure for the EEG tasks closely resembled the one described in Yee et al. (2010). Participants completed three different auditory tasks, a baseline task and two attention tasks (intensity and number). The attention tasks were partially counterbalanced to eliminate possible order effects, although the baseline task was always presented first

so that participants were not inadvertently selectively attending to either S1 or S2 during the baseline task.

During the baseline task EEG acquisition participants were seated comfortably and presented with 82 trials of binaural stimuli while focusing on a fixation cross on a computer monitor. Auditory stimuli were pairs (S1 and S2) of 3 ms, 90 dB SPL1000 Hz tones, with a 500 ms inter-stimulus interval and a variable inter-trial interval ranging between 2.5 and 4.5s. All auditory stimuli were presented through insert earphones (Etymotic Research, Elk Grove Village, Ill).

The Intensity task was similar to the baseline task except that there were additional auditory stimuli added in order to direct the participant's attention to the first click (S1) of the 90 db SPL dual-click pairs. This task involved four types of auditory stimuli that were presented to the participant in a random order. In addition to the 82 pairs 90 dB SPL (high intensity) clicks described in the baseline task, there were 26 pairs of 80 dB SPL (low intensity) clicks. Participants were also presented with 26 single 90 dB SPL (high intensity) clicks and 26 single 80 dB SPL (low intensity) clicks. Participants were asked to respond as quickly as possible to high intensity stimuli (both double and single clicks) via a button press and to ignore all low intensity clicks.

The Number task used the same stimuli described in the Intensity task however the instructions were changed in order to direct attention to the second click (S2) of the 90 dB SPL (high intensity) pairs. Participants were asked to respond as quickly as possible whenever they heard a double-click (both high-intensity and low-intensity) and to ignore all single clicks.

Data Acquisition

Raw electroencephalographic (EEG) data was collected with a Brain Products Quick Amp 72 amplifier from 32 recording sites (1000 Hz A/D rate; 0.10 Hz high pass, 200 Hz low pass; gain = 10 K; average reference; impedances ≤ 10 kΩ) using sintered Ag–AgCl electrodes.

P50 Peak Measurement

To quantify the amplitude of the P50 peak at S1 and S2 for each task, raw EEG data at electrode site Cz was segmented from -100 ms to 400 ms after stimulus onset. The segments were then baseline corrected and ocular artifacts were removed (Gratton, Coles, & Donchin, 1983). Trials with values exceeding ± 100 μV were excluded from the analysis. A 10–50 Hz (24 dB/octave) band-pass filter was applied to single trials and the filtered segments were averaged prior to peak detection. Peak amplitude was defined as the difference between the most positive peak and the maximum deflection of the preceding trough that falls within 35 to 85 ms after the onset of the first stimulus in a pair. The equivalent waveform response to the second tone in the pair will be defined as the highest amplitude peak (measured trough to peak) that falls within ± 15 ms of the time the S1 P50 peak was measured after the first tone. In the baseline task all 82 trials were used for signal averaging. Only trials in which the participants made a correct response were used for signal averaging in the intensity and number tasks., participants who had less than 70 out of 82 possible correct responses on either the intensity or number tasks were excluded from the analysis on the basis that that there would not be enough trials for adequate signal averaging.

Spectral Frequency Power

The quantification of the frequency activity involved segmenting raw EEG into 1000 ms epochs with a 500 ms baseline. The segments underwent the same ocular correction, artifact rejection and baseline correction procedures used in processing the ERPs, described above. Time-varying spectral power was computed for the 12-20 Hz frequency band. Average ERP signals were convolved using a complex Morlet's wavelet (1-60Hz, c=5.0, 60 steps).

To identify the latency windows for the extraction of peak power in the beta-1 (12-20 Hz) frequency band, the raw EEG for the twenty-four healthy control participants included in the analyses was segmented from −100 to 500 ms and averaged across trials. Spectral power over time within the 12-20 Hz frequency range was plotted using the Frequency Extraction function of Brain Vision Analyzer software (Brain Products, Munich, Germany). The latency of the point at which 12-20 Hz power is the greatest was recorded for each healthy control participant and the average latency. (± 1.5 standard deviations) was used as the time-window for which power from the Morlet time frequency matrix was extracted (Brenner et al., 2009).

Statistical Analyses

For all electrophysiological dependant variables, statistical outliers were identified separately for each group utilizing inter-quartile ranges (Brenner, Edwards, Carroll, Kieffaber, & Hetrick, 2004). To investigate differences between the groups on the sensory gating metric, a Oneway ANOVA was run on the S1-S2 P50 scores at baseline. To investigate sensory gating performance, separate repeated measures ANOVA analyses were run for P50 amplitude and Beta-1 activity for S1, S2 and S1-S2

across all three tasks (baseline, intensity and number) and between diagnostic groups (schizophrenia and healthy controls). To investigate significant results and interesting trends in the preceding analyses, fully within-subject repeated measure ANOVAs were conducted for each group separately.

Results

Demographic Information

Demographic information for age, gender, ethnicity and handedness is presented in Table 1. Groups did not differ significantly on any of these variables and none of these variables correlated with the electrophysiological variables examined in this study.

Patient data including age of onset, duration of illness, medication type, dose and current psychosis symptom scores were collected are presented in Table 2 and Table 3. Age of onset and duration of illness showed no significant correlation with any of the electrophysiological dependant variables. None of the healthy controls were taking psychiatric medications at the time of testing. With the exception of one individual in the schizophrenia group, all were taking either typical or atypical antipsychotic medications at the time of participation in this study. For those individuals on antipsychotic medications, Chlorpromazine equivalents (CPZ) were calculated based upon their self-report daily dose. CPZ scores did not correlate with any of the electrophysiological variables. However, CPZ did have a significant positive correlation with the reaction times in the Intensity condition, r=0.619, p=0.003 and a marginally significant correlation with the reaction time in the Number condition, r=0.429. p=0.052.

Scores from the Positive and Negative Sydrome Scale (PANSS) are reported in Table 2.3. The PANSS Total, Positive subscale, or Negative subscale scores did not correlate with any of the electrophysiological dependant variables. The general symptom scores did correlate with the S1-S2 P50 ERP score for the Intensity condition r=0.467, p=0.021. Furthermore, there was a significant correlation r=0.490, p=0.015 with reaction time in the Number condition.

Behavioural Data

Behavioural data for the selective attention tasks are presented in Table 4. Oneway ANOVAs comparing reaction time and the number of correct trials for each task revealed that participants with schizophrenia had significantly slower reaction times in the intensity condition compared to controls, $F(1,47)= 5.739$, p=.021 and marginally slower reaction times in the number task, $F(1,47)= 3.145$, p=.083. Reaction Times for each task did not correlate with any of the electrophysiological dependant variables for either group. Furthermore, groups did not differ on the number of correct trials for either the intensity or the number task and the number of correct trials did not correlate with any of the dependant measures.

ERP Analyses

P50 ERP latencies of S1 and S2 did not differ for schizophrenia participants and controls for the Baseline, Intensity or Number conditions (See Table 5).

Data for S1-S2 P50 difference scores are presented in Table 6. A Oneway ANOVA comparing the S1-S2 P50 difference scores at baseline for each group revealed that schizophrenia participants (M=0.65 SD=0.92) and controls (M=.38 SD=1.06), did

not differ significantly from one another, $F(1,47)=.940$ $p=0.337$. An examination of the magnitude of S1-S2 P50 differences at baseline (Cohen's $d=0.28$) revealed a small effect size.

A repeated measures ANOVA comparing P50 S1-S2 difference scores with the two diagnostic groups as a between subjects factor and the three tasks as a within-subjects factor revealed no task by diagnosis interaction, $F(2,94) =1.206$ $p=0.304$ $\eta_\rho^2 =0.025$ and no main effect of task, $F(2,94)=1.587$, $p=0.304$, $\eta_\rho^2=0.025$.

Data for S1 and S2 P50 amplitudes are presented in Table 7. A repeated measures ANOVA comparing S1 P50 amplitudes with the two diagnostic groups as a between subjects factor and the three tasks as a within-subjects factor revealed a marginal main effect of task, $F(2,94)=2.503$ $p=0.087$ $\eta_\rho^2=0.051$. To follow-up this finding, fully-within ANOVAs comparing S1 P50 amplitudes across the three tasks for each diagnostic group separately revealed that this effect was driven by increased S1 P50 amplitudes for healthy controls in the intensity condition, $F(2,46)=2.80$ $p=0.071$, $\eta_\rho^2=0.108$. S1 P50 amplitudes across the three tasks did not differ for the schizophrenia group, $F(2,48)=.33$ $p=.721$ $\eta_\rho^2 =0.014$. A repeated measures ANOVA comparing S2 P50 amplitudes with the two diagnostic groups as a between subjects factor and the three tasks as a within-subjects factor revealed no significant diagnosis by task interactions and no main effect of task.

Wavelet Analyses

Data concerning the time windows used for exporting the oscillatory wavelet information is summarized in Table 8 and data for S1 and S2 Beta-1 activity can be found in Table 9 and Table 10. A Oneway ANOVA comparing S1 Beta-1 activity at baseline

for the schizophrenia group (*M*=14.99 *SD*=12.84) and the control group (*M*=9.37 *SD*=8.70) revealed that the groups did not differ from each other, $F(1,43)=2.50$ $p=0.121$. However, the magnitude of S1 Beta-1 difference between the groups at baseline (Cohen's *d*=0.51) revealed a medium effect size. A Oneway ANOVA comparing S2 Beta-1 activity at baseline for the schizophrenia group (*M*=4.57 *SD*=5.01) and the control group (*M*=3.70 *SD*=2.49) did not differ from each other, $F(1,41)=2.18$ $p=.148$. The magnitude of S2 Beta-1 difference between the groups at baseline (Cohen's *d*=-0.22) revealed a small effect size.

A repeated measures ANOVA comparing S1 Beta-1 activity with the two diagnostic groups as a between subjects factor and the three tasks as a within-subjects factor revealed a marginal diagnosis by task interaction, $F(2,86)=2.79$ $p=.067$ $\eta_\rho^2=.061$. To follow-up this finding, fully-within ANOVAs comparing S1 Beta-1 activity across the three tasks for each group separately revealed significant differences among the tasks for the control group, $F(2,40)=4.95$, $p=.012$ $\eta_\rho^2=.198$. Pair-wise comparisons revealed that S1 Beta-1 activity in intensity condition (*M*= 14.48 *SD*=14.14) was significantly greater than both the baseline (*M*=9.75 *SD*=8.66) and number condition (*M*=8.87 *SD*=7.10). For the schizophrenia group participants S1 Beta-1 activity did not vary across the three tasks, $F(2,46)=.595$ $p=.60$ $\eta_\rho^2=.025$.

A repeated measures ANOVA comparing S2 Beta-1 activity with the two diagnostic groups as a between subjects factor and the three tasks as a within-subjects factor - after adjusting the degrees of freedom for a violation of sphericity using a Greenhouse-Geisser correction - revealed a significant main effect of task,

$F(1.54,63.12)=3.70$ $p=.029$ $\eta_p^2=.083$. To follow-up this finding, fully-within ANOVAs comparing S2 Beta-1 activity across the three tasks for each diagnostic group separately revealed no significant differences among the tasks for the control group. For the participants with schizophrenia, S2 Beta-1 activity differed across the tasks, $F(1.257,26.39)=5.22$ $p=.024$ $\eta_p^2=.20$. Pairwise comparisons revealed that for these participants, S2 Beta-1 activity in both the Intensity condition ($M= 5.55$ $SD=4.28$) and Number condition (M = 9.03 SD = 9.76) was significantly greater than baseline ($M=4.57$ $SD=5.01$)

Discussion

This purpose of this study was to investigate the role that selective attention plays in modulating auditory sensory gating in individuals with schizophrenia. To this end, we compared a schizophrenia group and a control group on a commonly used electrophysiological measure of auditory sensory gating, the S1-S2 P50 difference score, while they completed a passive dual-click task and two modified versions of the task that had participants direct their attention to either the first or second click in the dual-click pair. We also looked at the P50 response to each click individually as there is evidence that suggests the attenuation effect represented by the S1-S2 score may be governed by distinct neural mechanisms and thus attention may play a differential role in modulating the amplitudes of each component (Williams, Nuetcherlein, Subotnik & Yee, 2010). In addition to looking at P50 scores we looked at event-related oscillatory activity in the Beta-1 (12-20Hz) frequency range following each click, as activity in this range has been shown to be related to auditory gating scores and to processes related selective attention (Johannesen et al., 2005).

The S1-S2 P50 difference score is thought to represent the attenuation of redundant sensory information. Individuals with schizophrenia are thought to have a diminished capacity to filter out redundant sensory information and this may contribute to some of the sensory processing difficulties often associated with this disorder (Light & Braff, 2000). As such, it was expected that participants with schizophrenia would show less attenuation of their P50 response to the second-click in the baseline task compared to participants in the healthy control group. Surprisingly, this was not found in this current study. Our results revealed that the S1-S2 scores in the patient sample were slightly

greater than controls, albeit the effect was small and insignificant. The P50 sensory gating deficit is a well-documented phenomenon that has been observed in this clinical population and in their first-degree relatives (Heinrichs, 2004). However, some studies have failed to find such differences (Kathman & Engel, 1990; de Wilde et al., 2007).

While there has been only a limited number of studies conducted on P50 gating deficits in recent onset schizophrenia, some studies have suggested that individuals with recent onset schizophrenia to not manifest auditory sensory gating deficits to the same degree as those who have lived with the illness longer periods of time (Bachmann et al., 2010; Yee et al., 2010). While the sample used in this study was relatively young, with an average of 12.9 years of illness, we did not see a significant correlation between the P50 S1-S2 scores at baseline.

Other research has suggested that anti-psychotic medications may restore auditory sensory gating to levels indistinguishable from healthy controls (Yee, Nuechterlein, Morris & White, 1998). Most of the participants in our patient sample were on anti-psychotic medication. Although, chlorpromazine equivalency scores did not correlate with S1-S2 difference scores at baseline, participants in the patient group were taking a variety of different anti-psychotic medications. Unfortunately, the mechanisms of action of the various anti-psychotic medications are not well understood and thus it is difficult to rule out the potential effects of anti-psychotics based upon chlorpromazine equivalents alone. More research is necessary to examine the effects of specific drugs on P50 sensory gating.

Nicotine has also been shown to have a restorative effect on P50 sensory gating (Chen et al., 2011; Brinkmeyer et al., 2011). While participants were not permitted to smoke for at least 45 minutes prior to data acquisition, detailed data on the participants overall smoking habits was not collected in this study therefore we were unable to explore potential differences in P50 gating scores between smokers and non-smokers. Furthermore, approximately 70-80% of individuals with schizophrenia report smoking cigarettes on a regular basis, which is significantly higher than the general population (McEvoy & Brown, 1999). Given the possibility that nicotine may exert a corrective effect on the P50 gating metric and the likelihood that there were more smokers in our patient group, our lack of data with respect to the smoking habits of our sample makes it difficult to rule this out as a possible confounding factor.

General arousal has also been shown to influence sensory gating indices (Makeig & Jung, 1996). Some studies that have examined electrophysiological indices of arousal while looking at P50 sensory gating have shown that decreased alertness results in increased S1 amplitudes (Griskova-Bulanova et al., 2011). Given that most of our patient group was taking antipsychotic medication, which has been known to cause drowsiness, it is plausible that this could account for the seemingly normal gating in our patient group at baseline. Anti-psychotic medication has also been shown to slow down behavioral responses (Yee, Nuechterlein, Morris & White, 1998). This was reflected in this study by the fact that individuals in the schizophrenia group who were taking larger doses of antipsychotic medication also tended to have slower behavioral response times.

It was expected that directing attention to the first stimulus would increase S1 P50 amplitude for both the schizophrenia group and the control group with respect to the

baseline condition, but more so for the control group, and that there would be no effect on S2 amplitude. These hypotheses were partially confirmed. The schizophrenia group did not show any change to their S1 P50 amplitude when attending to the first stimulus compared to baseline whereas the healthy control group showed a marginal increase. This finding may suggest an increased capacity for selective attention in healthy individuals, which in turn enables them to modulate their response to the first stimulus. As expected, both groups showed no changes to the P50 amplitude following the second stimulus. This partially confirms the finding by Yee et al. (2010), which revealed attending to the first stimulus increased the S1 P50 for healthy controls. Chronic patients showed increased S1 P50 amplitudes when attending to the first stimulus whereas recent onset patients showed no change in S1 amplitude but instead exhibited decreased S2 amplitude.

It was expected that directing attention to the second stimulus in the number condition would result in increased S2 amplitudes for the control group but not the schizophrenia group and would have no effect on S1 amplitudes for either group. Contrary to expectation, S2 P50 amplitudes did not change with respect to baseline for either group when attending to the second stimulus. As expected, S1 amplitudes did not increase for either group when attending to the second stimulus. This is in contrast to findings by Yee et al. (2010) that show increased S2 P50 amplitudes for healthy controls when attending to the second stimulus. Furthermore their results revealed increased S1 and S2 amplitudes for individuals with chronic schizophrenia when attending to the second stimulus, while recent onset patients showed reduced S1 amplitudes.

It was expected that directing attention to the first stimulus would increase the S1-S2 gating score for both groups, but to a larger extent in the control group. Furthermore it

was expected that directing attention to the second stimulus would result in a decreased S1-S2 score for the control group but result in no change for the schizophrenia group. However, contrary to expectations the difference score did not change with respect to baseline whether they were attending to the first or second stimulus.

At baseline, it was hypothesized that schizophrenia patients would exhibit less S1 beta-1 activity and more S2 beta-1 activity compared to the healthy control group. However, there were no significant differences between the groups for S1 or S2. This finding is similar to what was seen in the ERP data at baseline. It is worthwhile to note that while groups did not differ significantly in Beta-1 power at S1, the patient group showed a trend towards greater S1 Beta-1 than controls, which resulted in a medium effect size (Cohen's d = .51). While relatively few studies have compared S1 Beta-1 activity between patients and controls the few studies that exist show effect sizes ranging from virtually zero effect (Brenner et al., 2009) or small effect size (Hong et al., 2004) to medium effect size (Hall, Taylor, Salisbury & Levy, 2010) favouring greater S1 Beta-1 in control groups. It is evident that more studies need to be conducted to gain a clearer understanding of this phenomenon, but given the opposite pattern of results at baseline in our sample it might be wise to interpret these results with caution and to consider alternative explanations as to why the patient group is exhibiting greater S1 Beta-1 at baseline (ie. chronicity of illness, nicotine consumption, medication and arousal levels).

It was expected that directing attention to the first stimulus would increase S1 Beta-1 activity for both groups but more so for the control group and would have no effect on S2 Beta-1 activity for either group. As expected, results for the healthy controls revealed that attending to the first stimulus resulted in increased S1 beta-1 activity and no

change to S2 beta-1 activity. However, contrary to expectation, schizophrenic participants did not show any change to S1 but instead showed a significant increase to S2 Beta-1 amplitude when selectively attending to the first stimulus. It was expected that directing attention to the second stimulus would result in increased S2 beta-1 activity for both groups, but to a greater extent in the healthy control group. It was expected that there would be no effect on S1 beta-1 activity for either group. Contrary to expectation, participants in the control group did not show increased S2 Beta-1 activity when attending to the second stimulus whereas participants in the schizophrenia group did. As expected, neither the control or schizophrenia group had increased S1 beta-1 activity while paying attention to the second stimulus. It would appear that healthy controls and individuals with schizophrenia differ with respect to beta-1 activity when allocating attentional resources to the second stimulus.

Given that healthy controls show increased S1 Beta-1, but not S2 Beta-1 activity when attending to the first stimulus, it seems that they have the capacity to selectively attend to the stimuli. However, it would appear when healthy controls attend to the second stimuli, the S2 Beta-1 response is suppressed by an intact gating mechanism activated after processing the first stimuli. This seems to support the idea that there may be distinct but interacting mechanisms responsible for this phenomenon (Williams, Nuetcherlein, Subotnik & Yee, 2010). Contrary to the pattern shown in healthy controls, individuals with schizophrenia do not show increased S1 beta-1 activity when attending to the first stimulus, which may mean that they are not able to allocate attentional resources to augment the response to the first click. It does seem that they can augment the response to the second click whereas healthy controls do not. However, when

schizophrenic participants selectively attended to the first click this also resulted in increased Beta-1 activity in response to the second click. It is possible that this is due to deficient functioning in the gating mechanism that is supposed to be activated by the first click. There are a number of studies that implicate the response to the first click as being at least partially responsible for sensory gating deficiencies (Brenner et al., 2009; Moura, Trinanes-Pego & Carrillo-de-la-Pena, 2010). This may be related to a reduced capacity to process input auditory information as opposed to filtering redundant auditory information (Yee et al., 2010). Furthermore, if Beta-1 activity reflects attentional processes it would seem that when attempting to attend to the first stimulus, individuals with schizophrenia are inadvertently allocating resources to the second stimuli. This finding would be consistent with attentional processing deficiencies that have been documented in individuals with schizophrenia (Palmer, Dawes & Heaton, 2009).

Overall, the results of the ERP measures of sensory gating did not reflect the expected modulation of the P50 ERP components. However, we did find differences in beta oscillatory activity. Beta oscillatory activity likely reflects the entire P50-N1-P2 complex. Therefore, when it comes to measures of selective attention, we may need to measure more than just the P50 response (which some have linked to early sensory registration whereas the N1 and P2 have been linked to attention and more complex stimulus processing)(Boutros et al., 2004). Based upon the results of this study, it would appear that schizophrenia patients and healthy controls differ when allocating attention to either the first or second stimuli of an auditory dual-click task. Whereas selective attention to the first stimulus augments the Beta-1 activity in response to the first stimulus for healthy controls, individuals with schizophrenia did not show this effect. Instead,

individuals with schizophrenia show an augmented Beta-1 response to the second click when they are attending to S1 or S2. This finding is consistent with the idea that the P50 gating deficiencies may be related to an inability to gate-in the salient auditory information. Furthermore, these findings are also consistent with selective attention deficits commonly observed in schizophrenia.

This study was limited by relatively small sample sizes that may have reduced the ability to detect between-group differences in such a design. Furthermore, the schizophrenic participants in this study contained mostly recent-onset patients and as previously discussed there have been a few that do not show sensory gating deficits in recent-onset patients (Kathman & Engel, 1990; de Wilde et al., 2007). Yee and colleagues (2010), demonstrated that recent-onset and chronic schizophrenia patients differed with respect to how the modulated their P50 response when attending to either the first or second stimuli of the dual-click pair. Future studies may be better able to detect such changes by looking at chronic and recent-onset patients separately. Another improvement on this study would be to include a measure of general arousal, as arousal has been shown to affect electrophysiological responses in dual-click paradigms (Griskova-Bulanova, 2011). Finally, while this study did take measures to reduce the intake of nicotine immediately prior to EEG acquisition, more detailed information about participant smoking habits would be necessary to completely rule out the effects of nicotine.

This study utilized a relatively novel approach to the understanding of auditory sensory gating deficits in schizophrenia. Relatively few studies have looked at the role that selective attention might play in modulating a phenomenon that has long been

viewed as pre-attentive (Jerger, Biggins & Fein, 1992). Furthermore, using oscillatory activity to examine the interplay between attention and sensory gating provides a more detailed look at the brain activity that contributes to this phenomenon, as amplitude and latency of ERP components only provide a small amount of information compared to the overall complex waveform (Johannesen et al., 2005; Uhlhaas, Haenschel, Nikolic, & Singer, 2008). Future research of auditory sensory gating that examines oscillatory activity from various frequency bands will provide a richer understanding of this phenomenon and of the sensory processing deficits apparent in individuals with schizophrenia.

Tables

Table 1: *Demographic Information.*

	HC (n=24)			Sz (n=25)		
Characteristic	*n*	*M*	*SD*	*n*	*M*	*SD*
Age		29.33	6.592		33.16	9.99
Gender						
Female	16			18		
Male	8			7		
Ethnicity						
Asian	13			9		
Caucasian	10			10		
Hispanic	0			1		
Native American	0			2		
Other	1			3		
Handedness						
Right	22			22		
Left	2			3		

Note. Sz = Schizophrenia group.

Table 2: *Medication Breakdown for Schizophrenia Group*

	n
Anti-psychotics	
Typical	5
Atypical	19
No Antipsychotics	1
Other Meds	
SSRI	3
SNRI	3
Bupropion	3
Benzodiazepine	5
Anticonvulsant	2

Table 3: *Patient Variables for Schizophrenia Group*

	M (*n*=25)	*SD*
Age of Onset	20.24	4.75
Years Since 1st Episode	12.92	9.78
CPZ Equivalency	305.04	294.41
PANSS		
Positive	12.10	4.65
Negative	13.10	4.9
General	26.54	8.80
Total	51.63	15.68

Note. CPZ = chlorpromazine; PANSS = Positive and Negative Syndrome Scale

Table 4: *Behavioural Data for Intensity and Number Conditions*

	Controls (n=24)		Sz (n=25)	
	M	SD	M	SD
Correct Trials (max = 82)				
Intensity	80.29	1.94	79.64	2.91
Number	81.71	0.62	80.80	2.43
Reaction Time (ms)				
Intensity	801.97	273.20	973.60	227.10
Number	923.87	140.58	1013.06	197.42

Note. Sz = Schizophrenia group.

Table 5: *P50 ERP Latencies in ms*

Condition		Controls (n=24)		Sz (n=25)	
		M	*SD*	*M*	*SD*
Baseline					
	S1	59.96	8.65	60.24	7.62
	S2	58.75	11.20	62.00	7.97
Intensity					
	S1	60.92	8.50	62.36	10.04
	S2	60.96	12.57	62.96	8.89
Number					
	S1	59.58	6.09	61.24	8.94
	S2	58.88	9.83	63.76	9.42

Note. Sz = Schizophrenia group.

Table 6: *P50 S1-S2 ERP Difference Scores*

		Controls (n=24)		Sz (n=25)		Cohen's *d*
		M	*SD*	*M*	*SD*	
Baseline						
	S1-S2	0.38	1.06	0.65	0.92	.27
Intensity						
	S1-S2	0.86	0.91	0.67	0.97	-.20
Number						
	S1-S2	0.56	0.69	0.58	1.04	.02

Note. Sz = Schizophrenia group.

Table 7: *P50 S1 and S2 Amplitudes*

	Controls (*n*=24)		SZ (*n*=25)		Cohen's *d*
	M	*SD*	*M*	*SD*	
Baseline					
S1	1.20	0.98	1.51	0.93	.32
S2	0.82	0.65	0.86	0.55	.07
Intensity					
S1	1.54	1.05	1.63	1.09	.08
S2	0.68	0.54	0.95	0.70	.43
Number					
S1	1.33	0.93	1.58	0.95	.26
S2	0.77	0.58	1.00	0.71	.35

Note. Sz = Schizophrenia group.

Table 8: *Wavelet Export Windows*

		Beta-1 (12-20Hz)
Baseline	S1	27-147ms
	S2	527-647ms
Intensity	S1	21-157ms
	S2	521-657ms
Number	S1	33-159ms
	S2	533-659ms

Table 9: *Beta-1 Power Values at S1*

	Controls (n=21)		Sz (n=24)		Cohen's *d*
	M	*SD*	*M*	*SD*	
Baseline					
S1	9.37	8.70	14.99	12.84	.51
Intensity					
S1	12.45	10.93	16.00	11.76	.31
Number					
S1	8.00	6.05	17.40	13.46	.59

Note. Sz = Schizophrenia group.

Table 10: *Beta-1 Power Values at S2*

	Controls (n=21)		Sz (n=22)		Cohen's *d*
	M	*SD*	*M*	*SD*	
Baseline					
S2	3.70	2.49	4.57	5.01	.22
Intensity					
S2	4.16	4.35	5.55	4.28	.32
Number					
S2	5.17	4.02	9.03	9.76	.51

Note. Sz = Schizophrenia group

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