Author

While working at the UC Irvine Health Neuropsychiatric Center, Sandy Hoang's mentor suggested working to expand understanding of P50 sensory gating by investigating neural responses in the gamma range. She feels that her results are revolutionary because gamma band responses can be used to diagnose psychiatric patients more accurately and objectively. Sandy says that her favorite part of her research experience was interacting with the test participants, who she found to be very supportive of her work. After graduation, Sandy plans to continue her studies by applying to dental school.

Contribution of Evoked Gamma Oscillations to P50 Sensory Gating in Schizophrenia and Bipolar Disorder

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Abstract

Gamma band responses may account for the deficiency in P50 sensory gating in patients with neuropsychiatric disorders. The intent of this study was to use P50 sensory gating data of patients with schizophrenia or bipolar I disorder to observe the contribution of gamma band power on P50 and examine whether there were any differences in their evoked gamma responses to paired clicks in comparison to controls and each other. It was hypothesized that individuals with schizoaffective, paranoid schizophrenia and bipolar I disorder would have longer latencies, lower peak to peak amplitudes, larger S2/S1 ratios, and smaller S1-S2 differences than controls. In addition, it was hypothesized that these variables would significantly differ between each group. To test this prediction, individuals were recruited from the University of California, Irvine Neuropsychiatric Center and the local community. Electrophysiological information was recorded while a series of paired clicks, stimulus 1 and stimulus 2, were presented. From this data, the P50 sensory gating was filtered between 30 and 50 Hz to analyze gamma oscillations. Consistent with the hypothesis, there were significant differences in latencies, peak to peak amplitudes, and S1 and S2 differences between each group. This suggests that the abnormal sensory gating in P50 is influenced by neural activities in the gamma range.

Key Terms

- Bipolar Disorder
- Electroencephalography
- Gamma Oscillations
- P50 Sensory Gating
- Schizophrenia

Faculty Mentor

Sensory gating is the ability of the brain to inhibit irrelevant or redundant stimuli, preserving needed resources for effectively processing relevant information. It is quantified using the amplitude of evoked brain potentials derived from the EEG (EPs). Neural synchrony of oscillations in the gamma band is thought to relate to the integration of features into a recognizable whole, essential for sensory and cognitive processing. Sandy's findings suggested that the sensory gating EP reflects synchronized gamma activity and thus may provide evidence of intact or impaired neural synchrony in psychiatric disorders. UROP is a valuable opportunity for students to personally experience the research process. My students have consistently reported their very positive benefits from UROP and its significant contribution to their applications for higher education.

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Introduction

Psychiatric disorders are characterized by a variety of unstable mental states that impair normal functioning. In the United States, the prevalence of psychological illnesses is significant, with approximately 4.13% of adults experiencing some type of serious mental disorder in the past year (Lipari et al. 2017). Within this group, approximately 1.1% are diagnosed with schizophrenia and 2.19% are diagnosed with bipolar I disorder (BPI) (Fleischhacker et al. 2014; Hoertel et al. 2013).

Schizophrenia is a type of psychiatric disorder that causes a person to lose touch with reality through a combination of positive and negative symptoms. With the onset of schizophrenia, positive symptoms appear, which include delusions, conceptual disorganization, hallucinations, heightened responsivity to stimuli, grandiosity, suspiciousness, and hostility (American Psychiatric Association 2013). Negative symptoms appear with the onset of schizophrenia and include blunted affect, emotional withdrawal, poor rapport, social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking (American Psychiatric Association 2013).

Schizoaffective (SCZA) and paranoid schizophrenia (SCZP) are two subtypes of schizophrenia. Individuals with SCZA experience a combination of schizophrenic and bipolar symptoms such as psychotic and mood episodes, while individuals with SCZP experience psychotic episodes that cause them to become unreasonably suspicious of things and people around them (Leposavic et al. 2015).

BPI is another type of psychiatric disorder characterized by extreme mood swings alternating between mania and depression. During the manic stage, individuals are energized and restless, making them feel invincible (American Psychiatric Association 2013). However, during the depressive stage, individuals experience anhedonia, tiredness, and suicidal tendencies (American Psychiatric Association 2013). Approximately 65% of BPI patients also experience psychotic symptoms (Harrow et al. 1995).

To deliver proper treatment, it is essential to accurately diagnose patients. Currently, psychiatrists use the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) as a guide to treat patients. However, since many symptoms overlap, it is often difficult to pinpoint the correct disorder. Biomarkers can serve as an alternative method to provide a more accurate and objective way to mark the risk or manifestation of various psychiatric disorders (Strimbu and Tavel 2010).

The measurement of sensory gating can serve as a biomarker because it shows how well a person can filter irrelevant information (Cheng et al. 2016). A frequently used method to evaluate sensory gating in schizophrenia and BPI patients is to quantify P50 event-related potentials through electroencephalography (EEG) recordings using the paired click paradigm. The P50 waveform is an evoked potential occurring approximately 50 milliseconds after the presentation of an auditory stimulus (Smith et al. 2013). In a paired click task, stimulus 1 (S1) and stimulus 2 (S2), are delivered 500 milliseconds apart with 10 seconds between pairs. The magnitudes of responses are compared to each other using a ratio of their amplitude of S2/S1 or the difference of S1-S2 (Smith et al. 2013). In addition, the latencies are measured to examine the time interval between presentation of stimulus and reaction.

In healthy individuals, the P50 wave is spontaneously suppressed in response to S2. Patients with schizophrenia or BPI frequently display a defect in the P50 sensory gating relative to controls because they cannot suppress S2 well in the paired-click paradigm (Smith et al. 2013).

Many studies have found that BPI patients, with or without a history of psychosis, scored a significantly higher S2/S1 ratio compared to controls (Cheng et al. 2016; Olincy and Martin 2005). Furthermore, studies have reported sensory gating deficits and reduction of gamma band latencies within schizophrenia patients in response to each stimulus (Nagamoto et al. 1990; Clementz el al 1997).

In addition to P50 event-related potentials, deficits in sensory gating can extend to neural oscillations in the gamma range (Smucny et al. 2013). Another method to study sensory gating in schizophrenia and BPI is to use the P50 sensory data to quantify evoked gamma responses from 30 to 50 Hz. Gamma oscillations are coordinated interactions of excitation and inhibition of neurons that are correlated with many cognitive and sensory processes to integrate neural networks (Buzsaki & Wang 2012). Measuring evoked gamma responses and their spectral power could give an indication of the effects they have on P50 sensory gating. Some studies have found abnormal P50 gating within the gamma range for individuals diagnosed with schizophrenia (Clementz et al. 1997, Johannesen et al., 2008). Another study showed deficits in gamma oscillation power in both schizophrenia and BPI patients with psychosis (Carroll et al. 2008). Due to these findings, P50 sensory gating and

evoked gamma oscillations have been identified as possible biomarkers for schizophrenia and BPI.

Although there are many studies on the connection between evoked gamma responses and schizophrenia, there are few studies on their relationship to patients diagnosed with BPI or schizophrenia subtypes. In addition, most research focuses on the channel at the vertex (CZ) because it displays the largest response to the stimuli. However, in this study, channels surrounding CZ such as FCZ, C1, and C2 were also analyzed to observe the magnitude of responses in those channels and whether they contribute to sensory gating. The purpose of this study was to use P50 sensory gating data to quantify and analyze the effects of evoked gamma responses in individuals with SCZA, SCZP or BPI. Quantifying this data will give an indication of whether they affect P50 gating, how they differ between each subject group, and how they relate to various symptoms. It is hypothesized that individuals with schizophrenia, BPI, and their subtypes will have longer latencies, lower peak to peak amplitudes, larger S2/S1 ratios, and smaller S1-S2 differences in relation to controls. In addition, it is hypothesized that these variables will significantly differ between each group.

Materials and Methods

A total of 129 subjects participated in the experiment, with 30 controls, 33 SCZA, 32 SCZP, and 34 BPI patients. Patients were recruited from the inpatient unit of the UCI Neuropsychiatric Center and from the local community, while controls were recruited from the local community. All participants were within the age range of 15–60 years and had normal hearing, no serious illness, no severe head injury, and no alcohol or substance abuse addiction within the last 2 months. All experiments were carried out in accordance with the Institutional Review Board at the University of California, Irvine, and were consistent with Federal guidelines.

Subjects were diagnosed using the DSM-IV criteria by a licensed psychiatrist and given a modified structured clinical interview for the DSM-IV (SCID). In addition, they were assessed using various symptom scales, including the Young Mania Rating Scale (YMRS) to evaluate manic symptoms, the Montgomery-Asberg Depression Rating Scale (MADRS) and Beck Depression Inventory (BDI) to evaluate depressive symptoms, the Hamilton Rating Scale (HAM-d) to evaluate major depressive symptoms, the Clinical Global Inventory (CGI) to evaluate severity of illness, and the Positive and Negative Syndrome Scale (PANSS) to evaluate positive and negative schizophrenic symptoms. Table 1 shows the demographics of each patient within each group as well as mean symptom scores and medications.

EEG data were recorded as each subject wore a cap containing 64 electrodes. The electrodes were referenced to link mastoids and connected to a headbox linked to Neuroscan

Table 1

Age, gender, education, symptoms, and medication for BPI with and without psychosis, controls, SCZA, and SCZP

Group	BPI Nonpsychotic	BPI Psychotic	Controls	SCZA	SCPT
Age	31.136	37.417	31.767	38.485	35.5
Male I Female	12 1 10	316	9121	16117	2418
Education(years)	11.846	12.85	15.8	12.233	13.174
PANSS positive	10.9444	14.167	7.143	17.636	17
PANSS negative	13.722	13.417	7.81	18.424	19.032
PANSS general	29.889	32.083	17.857	36.393	33.29
CGI	4.167	4.25	1	4.727	4.156
Hamilton	11.778	12.417	2.591	15.333	10.567
MADRS	12.5	13.909	2.857	16.063	10.563
YMRS	5.389	8.333	1.333	6.424	4
Total not medicated	1	2	30	3	1
Typical Antipsychotics	0	1	0	1	15
Atypical Antipsychotics	26	23	0	29	37
Mood Stabilizers	24	21	0	11	2
Anti-Depressants	22	12	0	13	9
Anti-Anxiety	12	5	0	6	12

amplifiers to record brain activity. An electro-oculogram (EOG) containing four electrodes placed above, below, and at the outer edge of each eye was used to record blinks and eye movements. In addition, subjects were given ear inserts in which a series of paired clicks, S1 and S2, were presented 500 milliseconds apart, with each pair of clicks 10 seconds apart.

An eye blink correction procedure in the Cortech Solutions software was used to clean ocular artifacts. From the P50 data, evoked gamma responses were analyzed by using a broadband filter of 30 to 50 Hz. Peak to peak amplitudes and peak latencies (time from stimulus onset) were measured. Averages across trials for S1 and S2 were obtained and grand averages were conducted by averaging S1 and S2 across subjects for each group. A procedure called Fast Fourier Transform (FFT) was used to convert each subject's averages from the time domain to the frequency domain so that major frequencies in each subject waveform could be determined.

Data were analyzed using repeated measures analysis of variance (ANOVA), with p-values less than 0.05 considered significant. Ratios and difference scores were analyzed by group and channel, while amplitudes and latencies were analyzed by group, click, and channel. A Newman-Keuls Multiple-Comparison Test was used to identify which pairs of means were significantly different from each other.

Results

In Figure 1, the P50 waveform for each group shows that controls had the largest peak, while SCZP had the smallest peak. In addition, SCZA had the smallest difference in amplitude between S1 and S2.

Figure 2 shows the evoked gamma responses for S1, with BPI having the greatest power and SCZA having the weakest power. Controls and SCZP had intermediate power, with controls greater than SCZP. All groups displayed the greatest power between 30 to 40 Hz.
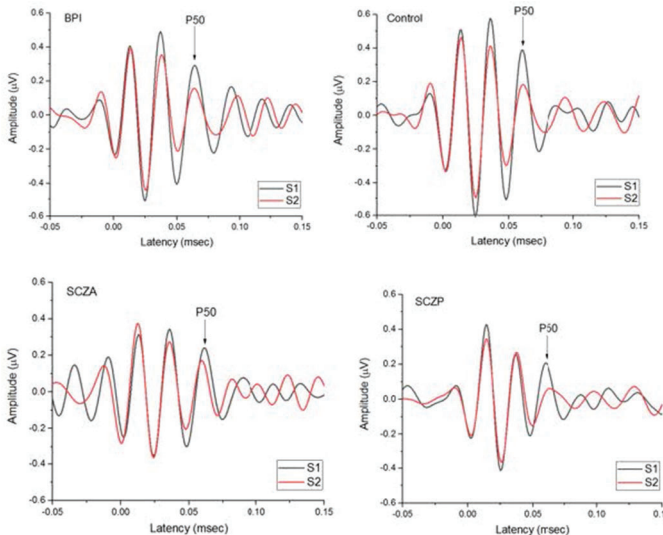

Figure 1

Grand averaged S1 and S2 gamma responses with 30–50 Hz bandpass for each group.

The time-frequency analysis in Figure 3 displays the power of each frequency in relation to time. The bar below indicates that a darker color relates to weaker power, while a lighter color relates to stronger power. The graph confirms that the frequency with the greatest power at P50 is within the gamma range.
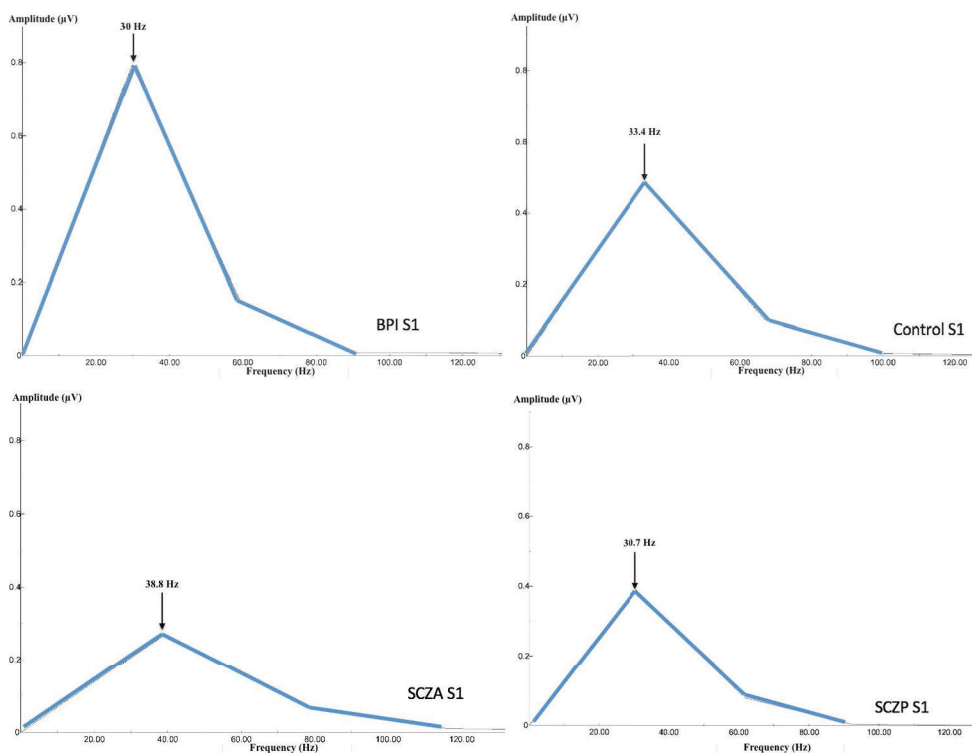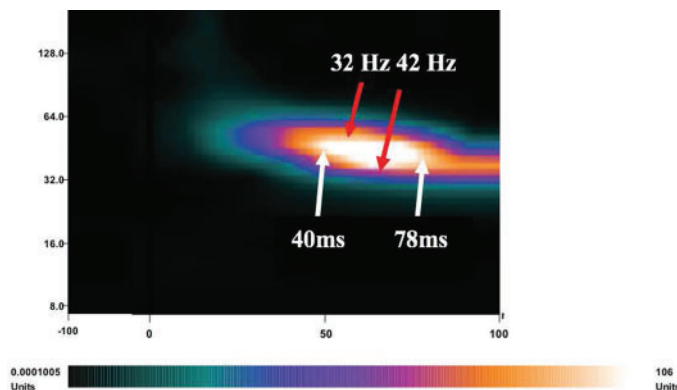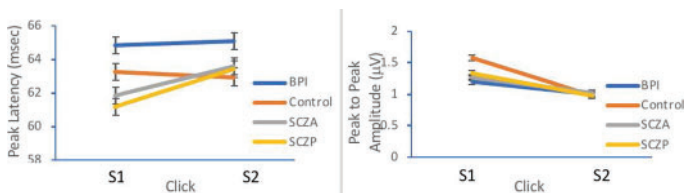

Figure 2

Line plots created by the FFT program showing amplitudes (µV) vs. frequencies (Hz) for S1.

Figure 3

Example of a time-frequency analysis showing frequencies (Hz) vs. time (ms).

Figure 4

Means plot of peak latency and peak to peak amplitude by click and group.

Figure 4 displays the means of peak latency and peak to peak amplitude as a function of clicks for each group. There was a significant interaction for peak latency (F=2.71; p=0.044) as well as peak to peak amplitude (F=8.69; p=0.000011).

A Newman-Keuls test was utilized to further examine the differences between groups. Table 2 shows the post-hoc differences between paired (S1 and S2) clicks for each group, with the direction of the difference indicated by greater than (>) or less than (<) symbols. When examining latencies, S2 latencies were longer than S1 latencies, but only for SCZA and SCZP. In addition, BPI had longer latencies at S1 than SCZA and SCZP and longer latencies at S2 than controls. When examining the amplitude, S1 was greater than S2 for each group. However, when comparing the amplitudes of all the groups, there were only differences at S1, with controls having the largest amplitude.

When analyzing individual channels C1, C2, CZ, and FCZ for S2/S1 ratios and S1-S2 differences between groups, there were significant differences between groups for CZ and FCZ, but not for C1 or C2. For the CZ channel, a significant main effect for group approached significance for the baseline to peak S2/S1 ratio (F=2.6251, p=0.05341), with BPI having larger ratios than controls. In addition, there was significance for the baseline to peak S1-S2 difference (F=2.8950, p=0.03791), with controls having a larger difference than both BPI and SCZA. For the FCZ channel, the main effect for group approached significance for the baseline to peak S2/S1 ratio (F=2.3527, p=0.07542) and for the peak to peak S2/S1 ratio (F=2.5078, p=0.062), with BPI having larger ratios than the controls. When CZ and FCZ were both used in a group by channel analysis with repeated measures for channel, there was a significant main effect for group (F=2.82, p=0.041792), with BPI having larger S1-S2 differences than controls.

Discussion

In this study, neural activities were quantified by calculating peak latencies, peak to peak amplitudes, S2/S1 ratios, and S1-S2 differences to observe the effect gamma responses have on P50. The results aligned with the hypothesis because there were significant differences for all the variables between groups, clicks, and channels.

From the FFT and time-frequency analysis, the greatest power in the P50 range was found between 30 and 42 Hz, which is the gamma frequency. Consistent with the result, one study also found significant difference in gamma power at S1 (Johannesen et al. 2008). This suggests that evoked gamma responses contribute to P50 and may explain the deficits of sensory gating in patient groups.

The significant differences in latencies of the P50 waveform at S1 and S2 are indicative of varying times between different diagnostic groups in response to each stimulus. Since BPI had longer latencies than controls, SCZA, and SCZP, it shows that BPI had the longest delay in responding when the stimulus was presented. Contrary to this, one

Table 2

Newman-Keuls Multiple-Comparison Test showing differences for group and click

P50 Latency Differences: Group x Click			P50 Amplitude Differences: Group x Click		
BPI	S1	> SCZA S1 > SCZP S1	BPI	S1	(>) BPI S2
BPI	S2	> Control S2	Control	S1	(>) Control S2 (>) BPI S1 (>) SCZA S1 (>) SCZP S1
SCZA	S1	(<) SCZA S2	SCZA	S1	(>) SCZA S2
SCZP	S1	(<) SCZP S2, (<) Control S1	SCZP	S1	(>) SCZP S2

study found no significant latency effects between groups in the gamma band response (Clementz et al., 1997). When comparing clicks, SCZA and SCZP had significantly shorter S1 latencies than S2. This aligns with the results in the previous study because they found that individuals with schizophrenia also had a significant reduction of gamma band latency at S1 (Clementz el al, 1997).

The significant differences of the peak to peak amplitudes were observed between groups at only S1, with controls having the largest peak compared to all other groups. In accordance with our results, one study found a response deficit at S1, but not for the S2 amplitude (Carroll et al. 2008). Differences at the first stimulus suggests that the deficits in sensory gating may be due to S1 registration and not S2 suppression. When comparing within individual groups, the amplitudes of S1 and S2 were significantly different from each other with S1 larger than S2. This indicates that all groups were able to suppress the stimulus when it was presented a second time.

When considering individual channels C1, C2, CZ, and FCZ, significant differences were only observed in CZ and FCZ. While many studies only analyze channel CZ because it generally has the greatest response, this finding shows that FCZ may also be important to analyze. When looking at the CZ channel alone, there were significant differences between groups for S1-S2 differences, with controls having larger differences than BPI and SCZA. One previous study also saw larger S1–S2 differences in controls compared to BPI patients (Carroll et al. 2008). In addition, the S2/S1 ratio approached significance between groups with BPI having larger ratios than controls. Another study found that both S1-S2 difference and S2/S1 ratio were significantly different between BPI patients and controls (Cheng et al. 2016). For the FCZ channel, there were significant differences for the peak to peak S2/S1 ratio, with BPI having larger ratios than controls.

In conclusion, the findings of this study suggest that neural oscillations in the gamma range influence P50 sensory gating, since there were significant sensory gating deficits in the gamma response. These measures may be possible biomarkers to aid in the diagnosis of patients, and further research should be conducted to validate these findings. One limitation of this study was a relatively small sample size; future studies should increase this to achieve greater power. Additionally, groups should be further divided by subdiagnosis, psychosis, and medication to study the precision of these markers. Neural oscillations within other frequency bands such as beta should also be analyzed to examine their contribution to P50 gating.

Acknowledgements

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