

Emitted P3a and P3b in Chronic Schizophrenia and in First-Episode Schizophrenia

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EPISODE SCHIZOPHRENIA**

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Neurophysiological biomarkers may be useful for identifying the presence of schizophrenia and the schizophrenia prodrome among at-risk individuals prior to the emergence of psychosis. This study examined the emitted P3 to absent stimuli on a tone counting task in patients with chronic schizophrenia and newly-diagnosed patients. The P3 is biphasic, with the earlier peak (P3a) reflecting automatic orienting and the later peak (P3b) reflecting cognitive processing. Twenty-four individuals with long-term schizophrenia (minimum 5 years diagnosis; SZ) were compared to 24 matched controls (HCSZ), and 23 individuals within 6 months of their first psychotic episode (FE) were compared to 22 matched controls (HCFE). Participants were presented with standard sets of four identical tones (1 kHz, 50 ms, 330 ms SOA, 750 ms ITI). For one in seven sets, the fourth tone was missing. Participants simply counted the number of tones within each set, with no instruction to detect missing tones. The P3a emitted by missing tones was significantly reduced in SZ compared to HCSZ ($p=.044$). The P3b emitted by missing tones was significantly reduced in both SZ and FE compared to their matched control groups ($p=.049$ and $p=.036$ respectively). SZ and FE showed impaired generation of the emitted P3b during selective attention to stimuli. The emitted P3b may be useful to understand cognitive neuropathophysiology early in psychosis, and shows promise as a biomarker to help detect the true schizophrenia prodrome among clinical high risk individuals prior to disease onset.

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PREFACE

I would like to acknowledge and extend a special thank you to all who have supported and guided me through this process: Dr. Dean Salisbury for being a meaningful mentor and encouraging my growth as a researcher, Sarah Haigh, Brian Coffman, Tim Murphy, and Justin Leiter-McBeth for always being accessible for assistance in the lab, and my family for their constant motivation. I would also like to thank my defense committee for providing constructive feedback and helping me grow as a writer.

1.0 INTRODUCTION

Schizophrenia is a chronic psychiatric disorder that impacts a person's thoughts and behaviors through various types of cognitive and physical symptoms. Each individual experiences a varying degree of symptom severity, which can significantly impact their productivity in life and society. The disease is associated with positive, negative, and cognitive symptoms (Liddle, 1987). Disease onset is defined by an individual's first episode of psychosis, and the typical onset of schizophrenia occurs between ages of 16 and 40 (median = 27 for men, 35 for women (Loranger, 1984). Before first psychotic episode, cognition rapidly declines, which is related to grey matter shrinkage and ventricle enlargements. This cognitive decline stays relatively stable after diagnosis (Lewandowski, Cohen, & Öngur, 2011). Cognition rarely returns to pre-psychosis levels of functioning (Insel, 2010). Therefore, there is a need to identify and treat individuals who are at risk of developing schizophrenia before their first psychotic episode in order to avoid the disease-associated cognitive decline.

Identification of biomarkers for specific diseases like schizophrenia may aid in identifying the presence of disease early before the first psychotic episode. Through identifying biomarkers, researchers in the future may work to reduce symptoms of schizophrenia or prevent disease onset to help an individual better function in society. Past researchers have defined biomarkers as "cellular, biochemical or molecular alterations that are measurable in biological media such as human tissues, cells, or fluids" (Mayeux, 2004). This definition includes any

biological events or characteristics than can be objectively evaluated as a measure of normal biological processes. Biomarkers may be used to measure disease progression, symptom severity, or mark the presence of disease. In the current study, we will investigate a potential biomarker that indicates the presence of schizophrenia.

The biomarker must be present in all individuals with the disease, including both patient groups who have the disease for a long time and those who have a recent onset of disease. In the search for a biomarker for schizophrenia, the auditory system has become a key target due to the common presence of auditory hallucinations and deficits in auditory perception. For example, approximately 70% of individuals with schizophrenia show auditory verbal hallucinations (Chaudhury, 2010), even at first break (Salisbury unpublished data), and Addington et al (2015) reported that 74.2% of their clinical high risk for schizophrenia participants experience perceptual aberrations or brief hallucinations. Also, individuals with schizophrenia show deficits in pitch perception (Javitt, 2009), which are associated with reduced auditory event-related potentials (ERP) (O'Donnell, Vohs, Hetrick, Carroll, & Shekhar, 2004; Rosburg, Boutros, & Ford, 2008).

Auditory mismatch negativity (MMN) has been the historical favorite ERP to investigate as a potential biomarker for schizophrenia. The MMN is a negative deflection in the electroencephalography (EEG) data in response to a novel stimulus (Näätänen, 1990). EEG is a non-invasive electrophysiological monitoring method that records electrical activity of the brain. A standard auditory paradigm to elicit an MMN response is termed the 'oddball paradigm.' In this paradigm, identical tones are repeatedly played, and rare deviants that differ in tone pitch or duration are played infrequently. The MMN is a cognitive event responding to the deviant tone, or deviation in a pattern (Todd, Michie, Schall, Ward, & Catts, 2012), thought to serve as the

perceptual trigger for the orienting response. Patients with schizophrenia reliably show reduced MMN (Umbricht & Krljes, 2005), indicating poor deviance detection in the disorder. Using MMN as a biomarker has failed, however, to produce consistent results among people newly diagnosed with schizophrenia. Previous studies have consistently shown large effect sizes for MMN reduction in chronic schizophrenia groups (Umbricht & Krljes, 2005), but medium to small effect sizes in MMN reductions in first-episode patient groups (Erickson, Ruffle, & Gold, 2016; Haigh, Coffman, Murphy, Butera, & Salisbury, 2016). This is important because we know that individuals in their first-episode of schizophrenia have the disease, but are earlier in the disease course. Therefore, a biomarker of disease presence should be abnormal at first-episode, as well as in chronic stages. Instead, this suggests that MMN responses may be affected by duration of disease, which is interesting for measuring changes in pathophysiology of schizophrenia or a biomarker of disease progression. This makes the MMN ERP insufficient for a biomarker of disease presence prior to the onset of actual psychotic symptoms.

This study hypothesizes that the emitted P3 would serve as a biomarker of disease presence. P3 as a general ERP is pathophysiologically relevant to schizophrenia, as it describes a variety of cognitive functions, such as attention, orienting, effort, and memory performance. Past research has replicated decreased amplitude of P3 in response to auditory stimuli in people with schizophrenia, aiding in its use as an efficient biomarker (Pfefferbaum, Ford, White, & Roth, 1989). These reductions in P3 amplitude support the view that disease course in schizophrenia leads to a core deficit of dysfunction in working memory and attention (Van der Stelt, Frye, Lieberman, & Belger, 2004). Deficits in working memory and attention may be characterized by noticing dysfunction in auditory pattern analysis. To serve as a biomarker of disease presence, it is expected to see a P3 abnormality in patients with chronic schizophrenia, as

well as patients newly diagnosed with schizophrenia. For example, in the standard oddball P3 task, where participants count the oddballs, both chronically ill and first episode psychosis participants show P3 reductions (Salisbury, Shenton, & McCarley, 1999).

The P3 ERP is typically the third positive electrical event elicited after stimulus onset, occurring 300 ms after onset (Sutton, Braren, Zubin, & John, 1965). The P3 component can occur in response to an infrequent task-relevant event (Begleiter et al., 1998). P3 can be used to assess cognitive functions in healthy and diseased patients because of P3's properties of a cognitive marker and its reliability in measuring specific time-related events. Since P3 is generated in response to subjects' attending to and discrimination of different stimuli, it is expected that the P3 complex relates to attention allocation, information processing mechanisms, and immediate memory (Polich & Kok, 1995). The measurement of time-locked events provides insight into the functioning of the brain, especially in terms of working memory and stimuli processing. People with schizophrenia consistently show deficits in attention (Green, 1996) and novelty detection (Javitt, Shelley, & Ritter, 2000). These qualities make P3 complex a good candidate to investigate for a potential biomarker in measuring disease presence.

P3 is often constituted of two separate events: P3a and P3b (Squires, Wickens, Squires, & Donchin, 1976). A distinct presence of both P3a and P3b create a bimodal distribution of neuroelectrical activity and generate the entire P3 complex. Past literature finds that the P3a event reflects more automatic processing and orienting to salient stimuli whereas P3b reflects more deep and controlled cognitive processing of task-relevant events (Polich, 2007; Polich & Criado, 2006).

A complex auditory pattern paradigm was chosen to study the presence of P3 complex in schizophrenia. Previous research hypothesizes that complex patterns tend to be more sensitive

to cognitive abnormalities in evaluating auditory patterns (Salisbury & McCathern, 2016). This hypothesis is relevant when testing first-episode patients, because their working memory deficits may not be robustly seen in simple pattern tasks. Additionally, more cognitively demanding tasks tend to elicit larger P3 responses, and larger deficits in diseased individuals (Javitt, Spencer, Thaker, Winterer, & Hajós, 2008). For these reasons, this study examined the use of a complex auditory task to elicit the P3 complex.

In addition to the oddball tasks referenced above, P3 can also be elicited by the absence of an expected stimulus. This is termed the “emitted” P3 (Ruchkin & Sutton, 1978). Results from studies using P3 responses from oddball tasks cannot be assumed to be equivalent in emitted tasks. Since each task requires different mechanisms of processing, the elicited responses will reflect different neural and cognitive activities. Deficits in P3 elicited in response to oddball or infrequent stimuli paradigms in chronic schizophrenia have long been reported (Ford, Pfefferbaum, & Roth, 1992; Levitt, Sutton, & Zubin, 1973; Roth & Cannon, 1972), however, little studies on emitted P3 impairments in chronic or first-episode schizophrenia exist.

This study compared the emitted P3 complex between individuals with chronic schizophrenia, individuals at their first-episode of schizophrenia, and their matched healthy controls. Participants heard groups of 4 tones with infrequent deviant groups only containing 3 tones. Participants counted the number of tones in a group, and it was expected that subjects would develop an expectancy for four tones per group. Hence, the absence of the fourth tone would evoke an emitted P3 response. By examining chronic and first-episode patients, the emitted P3 complex can be validated as abnormal in long-term illness, investigated for abnormalities at first break, and evaluated as a potential biomarker for the disease presence of schizophrenia prior to actual psychosis.

2.0 METHODS AND MATERIALS

2.1 PARTICIPANTS

Twenty-four participants with chronic schizophrenia (SZ) were compared with 24 matched healthy control (HCSZ) participants. SZ had at least 5 years length of illness or were hospitalized at least three times for psychosis. Sixteen SZ had a diagnosis of schizophrenia (undifferentiated = 4; paranoid = 6; residual = 5; disorganized = 1), and 8 had schizoaffective disorder (depressed type = 1, bipolar type = 1, not specified = 6). Twenty-three participants newly diagnosed with psychosis in the schizophrenia spectrum (FE) were compared with 22 matched healthy control (HCFE) participants. FE had a first episode of psychosis within six months of participation in the study. Nine FE had a diagnosis of paranoid schizophrenia, 2 had a diagnosis of undifferentiated schizophrenia, 3 had a diagnosis of schizophreniform disorder, 7 had a diagnosis of a psychotic disorder not otherwise specified, and 2 had a diagnosis of schizoaffective disorder depressed type. All subjects had normal hearing as assessed by audiometry, at least nine years of schooling, and an estimated IQ over 85 (Wechsler Abbreviated Scale of Intelligence, WASI). None of the participants had a history of concussion or TBI with sequelae, history of alcohol or drug addiction, or detox in the last five years, or neurological comorbidity. Control subjects additionally had no psychiatric illnesses. Groups were matched for age, estimated premorbid IQ, and parental socioeconomic status. The 4-factor Hollingshead

Scale was used to measure socioeconomic status (SES) in participants and in their parents. As expected, SZ had lower SES than HCSZ, and FE had lower SES than HCFE, consistent with social and occupational impairment as a disease consequence (see Table 1 for demographic measures). All participants provided informed consent after receiving a complete description of the study, and were paid for participation. The study was approved by the University of Pittsburgh IRB.

Table 1. Subject Demographics. Demographic data of all four experimental groups. Statistic values for comparisons are shown, either chi-squared test or t-test where appropriate. Significant differences in matched groups are bolded.

	HCFE	FE	Statistics	HCSZ	SZ	Statistics
Number of Subjects	22	23		24	24	
Age	25.6 (9.6)	22.3 (5.5)	t(43)=1.4, p=.16	32.7 (9.3)	35.6 (7.6)	t(46)=-1.2, p=.23
Gender	7 F/15 M	8 F/15 M	$\chi^2=0.44$, p=.83	8 F/16 M	8 F/15 M	$\chi^2=.01$, p=.92
% Right Handed	75%	89.4%	$\chi^2=4.44$, p=.22	95.8%	88%	$\chi^2=4.09$, p=.25
Subject SES	37.8 (13.1)	27.0 (12.1)	t(38)=2.69, p=.01	38.3 (12.2)	30.5 (12.1)	t(44)=2.17, p=.04
Parental SES	49.6 (11.4)	44.7 (12.1)	t(41)=1.35, p=.18	41.8 (9.8)	37.8 (13.3)	t(45)=1.16, p=.25
IQ	106.9 (9.1)	108.3 (14.1)	t(43)=-.39, p=.69	103.01 (9.6)	105.8 (11.5)	t(46)=-.89, p=.38
MATRICES	29.18 (2.3)	28.4 (4.1)	t(43)=.79, p=.44	27.9 (2.4)	27.0 (4.3)	t(46)=.92, p=.36

2.2 DIAGNOSTIC ASSESMENTS

Diagnosis was based on the Structured Clinical Interview for DSM-IV (SCID-P). Symptoms were rated using the Positive and Negative Symptom Scale (PANSS), Scale for Assessment of Positive Symptoms (SAPS), and Scale for Assessment of Negative Symptoms (SANS). All tests were conducted by an expert diagnostician. SZ were medicated and moderately symptomatic. Only 67% of FE subjects were medicated (see Table 1 for clinical measures).

2.3 NEUROPSYCHOLOGICAL TESTS

All participants completed the MATRICS Consensus Cognitive Battery and the WASI. Social functioning was assessed with the brief UCSD Performance-based Skills Assessment (UPSA-B. See Table 1 for neuropsychological test scores).

2.4 PROCEDURE

Stimuli were generated with Tone Generator (NCH Software) and presented in Presentation (Neurobehavioral Systems, Inc.). Binaural auditory stimuli were delivered using Etymotic 3 A insert earphones, with loudness confirmed with a sound meter.

2.5 STIMULI FOR AUDITORY PARADIGM

All tones had identical physical parameters of 1 kHz, 50 ms pips with 5 ms rise/fall times, 80 dB. Temporal proximity was used to form discrete groups, with a SOA within groups of 330 ms. Groups were separated by an ITI of 750 ms. Four tones formed the standard group. The deviant group consisted of three tones, omitting the fourth tone. Deviant groups were presented 14.3% of the time, with a total of 50 deviant groups. Deviant groups never followed one another. Participants were instructed to internally count the number of tones that played within each group. Triggers were embedded in the EEG file for each tone and for missing but expected 4th tones.

2.6 ELECTROENCEPHALOGRAM (EEG) RECORDING AND PROCESSING

EEG was recorded from a custom 72 channel Active2 high impedance system (BioSemi), comprising 70 scalp sites including the mastoids, 1 nose electrode, and 1 electrode below the right eye. The EEG amplifier bandpass was DC to 104 Hz (24 dB/octave roll off) digitized at 512 Hz, referenced to a common mode sense site (near PO1). Processing was done off-line with EEGLAB (Delorme & Makeig, 2004) and BrainVision Analyzer2 (Brain Products GMBH). First, using EEGLAB, EEG was filtered at 0.5 Hz to remove DC drifts and skin potentials. Data were visually examined and any channels with excessive noise were interpolated. Adaptive Mixture ICA (Palmer et al., 2007; Delorme et al., 2012) was used to remove one vertical and one horizontal EOG component. Next, in BrainVision Analyzer2, data were filtered at 20 Hz to remove muscle and other high frequency artifact, and were rereferenced to the mastoids. Epochs

of 650 ms were extracted to include all ERP responses from the deviant missing fourth tone until just prior to the first tone of the next group. Epochs were extracted from the EEG based on stimulus triggers, including a 50 ms prestimulus baseline. Epochs were baseline corrected. Epochs were subsequently rejected if any site contained activity $\pm 50 \mu\text{V}$. Averages were constructed for the “missing” 4th tone.

2.7 DATA ANALYSIS OF EMITTED P3

Emitted P3a to the omitted stimulus was measured from electrode site Fz and P3b from electrode site Pz. The 50 msec window measurement intervals were centered on the P3 peak in healthy control groups. For SZ and HCSZ, P3a was measured between 350 ms and 400 ms after the omitted fourth tone. P3b was measured between 360 ms and 410 ms after the stimulus should have occurred. For FE and HCFE, P3a was measured between 250 ms and 300 ms after the fourth tone should have been played. P3b was measured between 350 ms and 400 ms after the stimulus should have occurred. P3a and P3b ERPs were subjected to current source density (CSD) analysis to infer source-sink topography. Interpolation was done using spherical splines, with the order of splines set to 4, the maximum degree of Legendre polynomials set to 10, and a default lambda of $1\text{e-}5$.

2.8 STATISTICS

Group demographics were compared using t-tests and chi-squared tests where appropriate. Emitted P3a analysis was performed at Fz and emitted P3b analysis was performed at Pz, using independent samples t-tests.

Two-tailed Spearman's correlations were used to examine relationships between P3a and P3b components at Fz and Pz (respectively) and demographic, clinical, and neuropsychological items. Values are reported as Mean \pm SD. Significance was attained at $p < .05$.

3.0 RESULTS

3.1 EMITTED P3 IN PATIENTS WITH CHRONIC SCHIZOPHRENIA

SZ and HCSZ showed a significant difference between their P3a ERP responses. SZ had a significantly smaller P3a response ($0.92 \pm 1.87 \mu\text{V}$) than HCSZ ($2.18 \pm 2.31 \mu\text{V}$; $t(46)=2.07$, $p=.044$). Figure 1a shows the P3a ERP waveforms for SZ and HCSZ, as well as the scalp topography and CSD distribution maps. The voltage topography maps for both SZ and HCSZ show expected frontal-central distribution for a P3a ERP. The CSD for both groups show a likely source of the P3a ERP located in anterior regions.

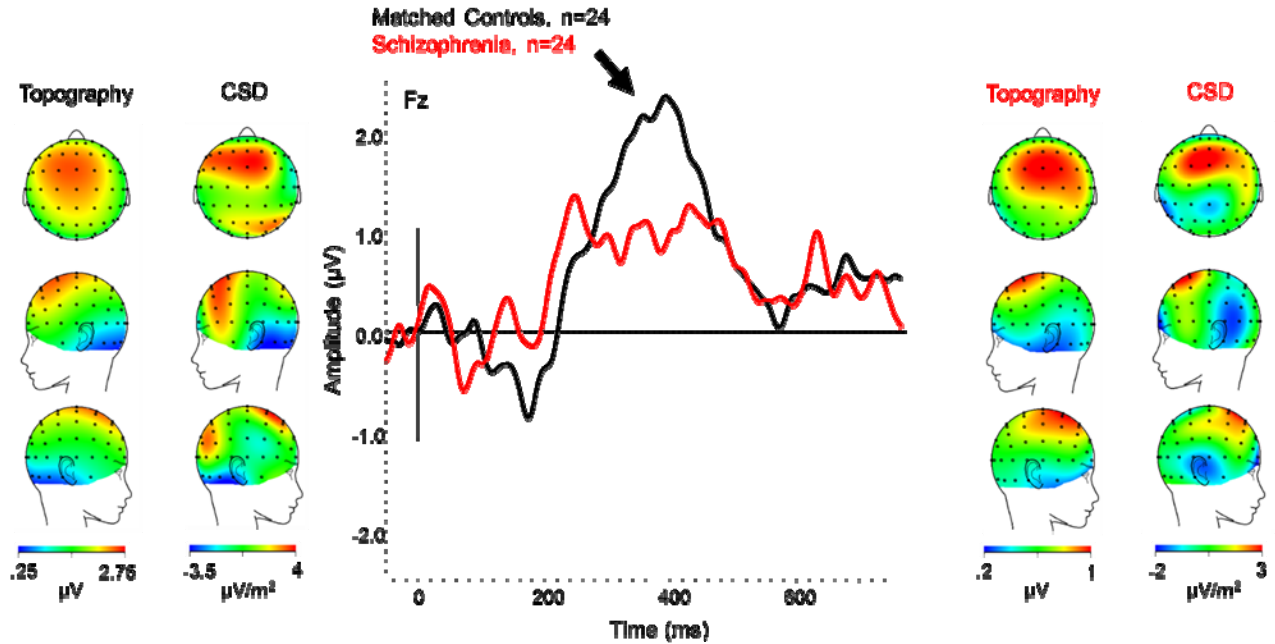


Figure 1a. Emitted P3a for SZ and HCSZ. (From Left to Right) Scalp topography and current source density (CSD) maps of the P3a response to the deviant group in HCSZ; Waveforms of P3a ERP response at Fz (HCSZ in black, SZ in red); Scalp topography and CSD maps of the P3a response to the deviant group in SZ.

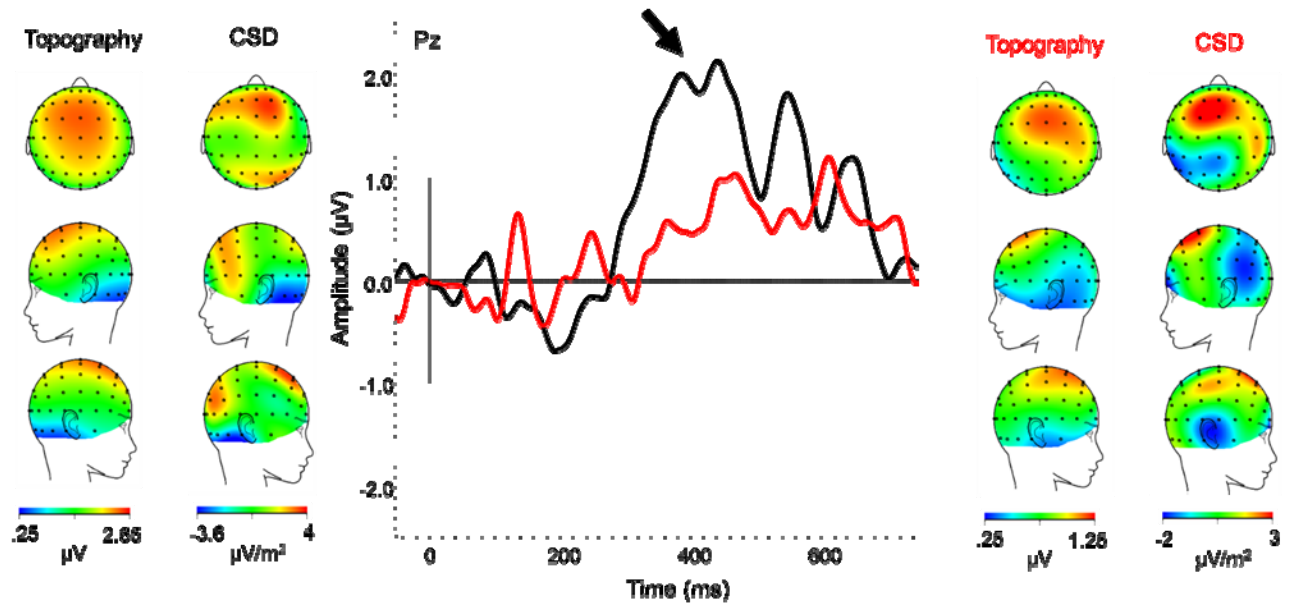


Figure 1b. Emitted P3b for SZ and HCSZ. (From Left to Right) Scalp topography and CSD maps of the P3b response to the deviant group in HCSZ; Waveforms of P3b ERP response at Pz (HCSZ in black, SZ in red); Scalp topography and CSD maps of the P3b response to the deviant group in SZ.

SZ also produced a significantly smaller P3b response ($0.50 \pm 1.87 \mu\text{V}$) than HCSZ ($1.90 \pm 2.81 \mu\text{V}$; $t(46)=2.02$; $p=0.049$). Figure 1b shows the P3b ERP waveforms for SZ and HCSZ, as well as the scalp topography and CSD distribution maps. The voltage topography map for HCSZ shows the expected distribution of P3b, with positivity in a more centro-posterior region. The topography map for SZ, however, shows an abnormally frontal positivity for what is expected for P3b response. The CSD map in HCSZ generally shows an expected source for the P3b response, occurring in a posterior temporo-parietal region. The CSD map in SZ shows an abnormal source for P3b occurring in a more anterior region than what is expected, mostly likely reflecting continued P3a activity with little P3b activity in that group.

3.2 EMITTED P3 IN PATIENTS WITH FIRST-EPISODE SCHIZOPHRENIA

FE ($1.15 \pm 2.30 \mu\text{V}$) and HCFE ($1.58 \pm 1.80 \mu\text{V}$) showed no difference in P3a ERP responses ($t(43)= 0.69$, $p>.49$). Figure 2a shows the P3a ERP waveforms for FE and HCFE, as well as the scalp topography and CSD distribution maps. The voltage distribution maps for both FE and HCFE show expected distributions for a P3a ERP, with positivity over the frontal-central scalp. The CSD for both groups show a likely source of the P3a ERP located in anterior regions.

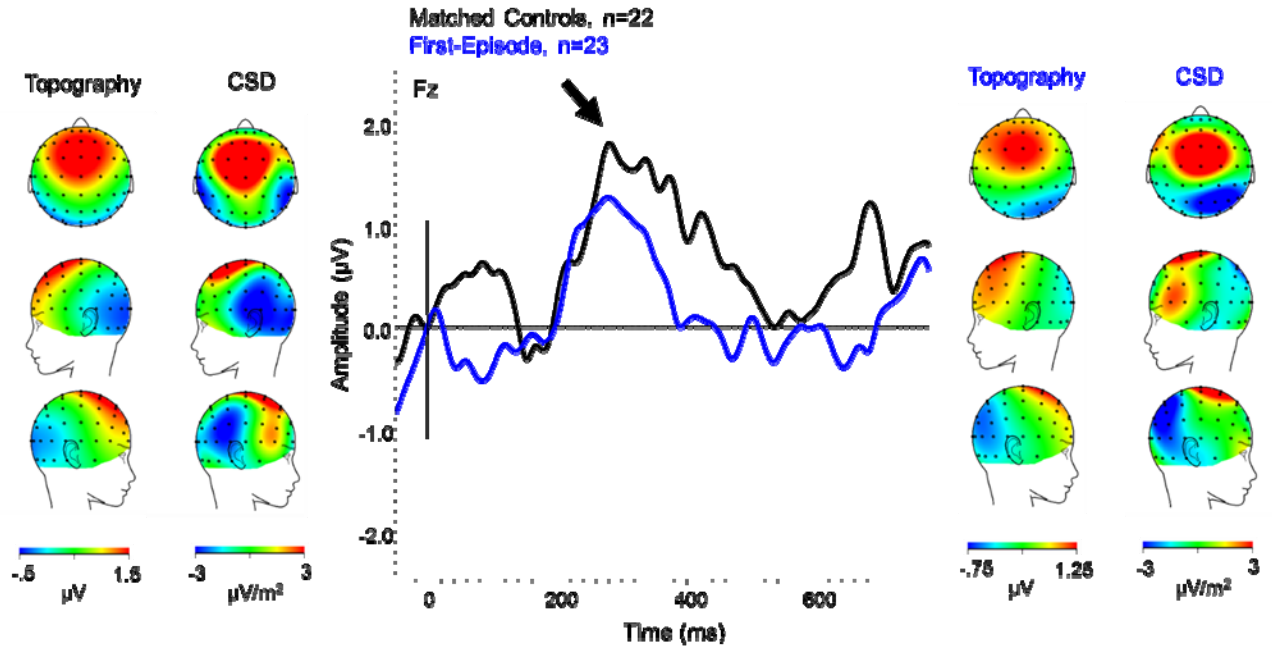


Figure 2a. Emitted P3a for FE and HCFE. (From Left to Right) Scalp topography and CSD maps of the P3a response to the deviant group in HCFE; Waveforms of P3a ERP response at Fz (HCFE in black, FE in blue); Scalp topography and CSD maps of the P3a response to the deviant group in FE.

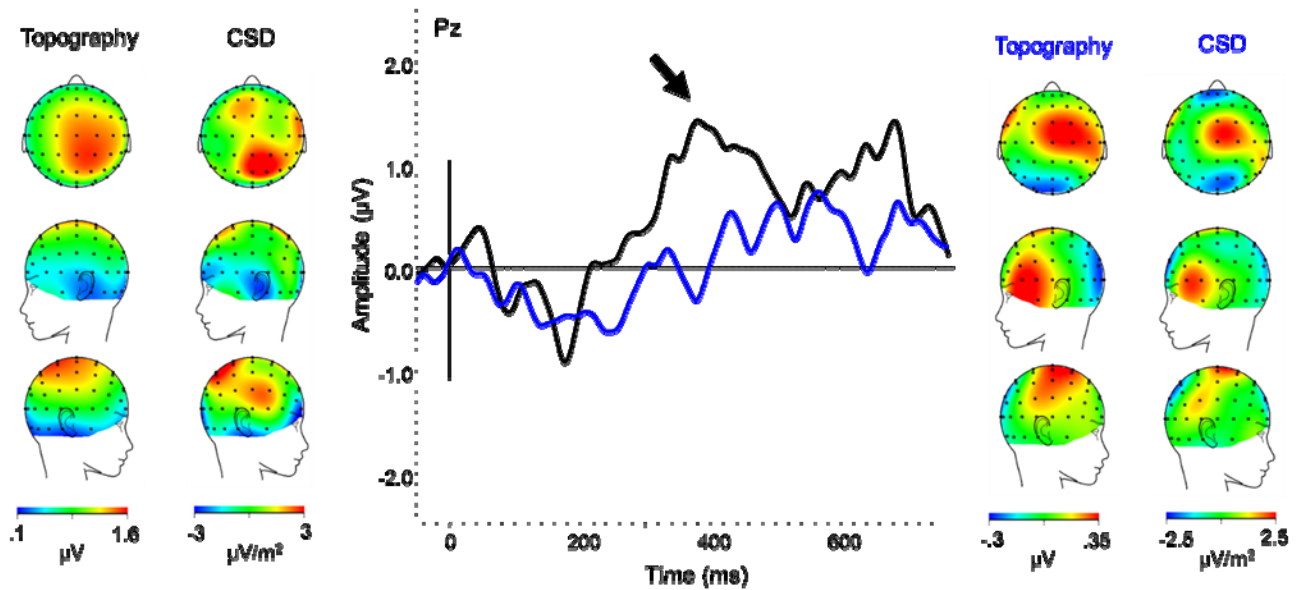


Figure 2b. Emitted P3b for FE and HCFE. (From Left to Right) Scalp topography and CSD maps of the P3b response to the deviant group in HCFE; Waveforms of P3b ERP response at Pz (HCFE in black, FE in blue); Scalp topography and CSD maps of the P3b response to the deviant group in FE.

FE produced a significantly smaller P3b response ($-0.15 \pm 1.99 \mu$) than HCFE ($1.28 \pm 2.46 \mu$ V; $t(43)=2.17$; $p=0.036$). Figure 2b shows the P3b ERP waveforms for FE and HCFE, as well as the scalp topography and CSD distribution maps. The voltage topography map for HCFE shows the expected distribution of P3b, with positivity in a more centro-posterior area. The topography map for FE, however, shows an abnormal positivity for what is expected for P3b, reflecting an asymmetrical positivity occurring in the occipital region. The CSD map in HCFE generally shows an expected source for the P3b response, occurring in temporo-parietal regions. The CSD map in FE shows an abnormal source for P3b occurring in a more frontal region than what is expected.

3.3 CORRELATIONS WITH CLINICAL AND COGNITIVE VARIABLES

3.3.1 HCSZ

The HCSZ group had no demographic or neuropsychological factors that correlated with P3a or P3b ERPs.

3.3.2 SZ

Parental SES positively correlated with P3b ERP response ($r(23)=.544$, $p=.007$), such that higher pSES was reflected in larger P3b.

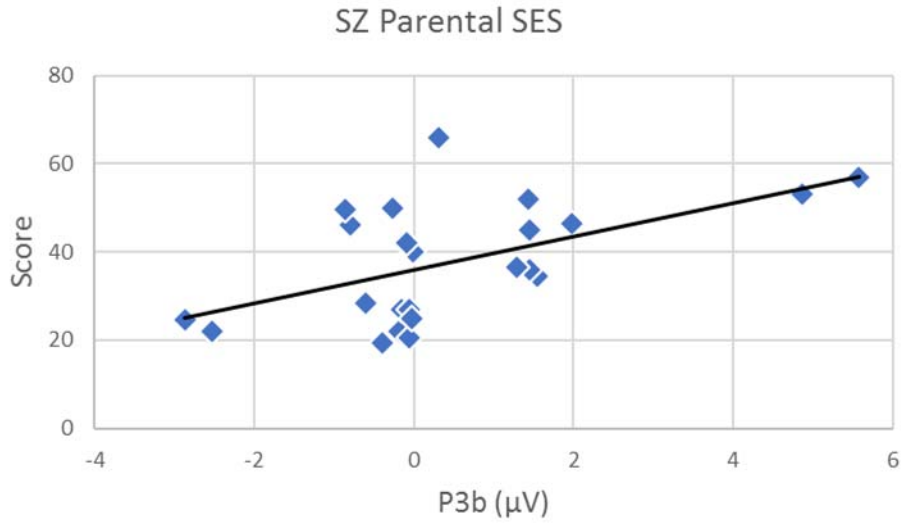


Figure 3. SZ pSES and P3b Correlation. Correlation scatterplot graph of SZ experimental group comparing P3b ERP responses to parental SES scores

3.3.3 HCFE

A positive correlation existed between HCFE's P3a and years of education ($r(21)=.497, p=.028$), such that more years of education was reflected in larger P3a.

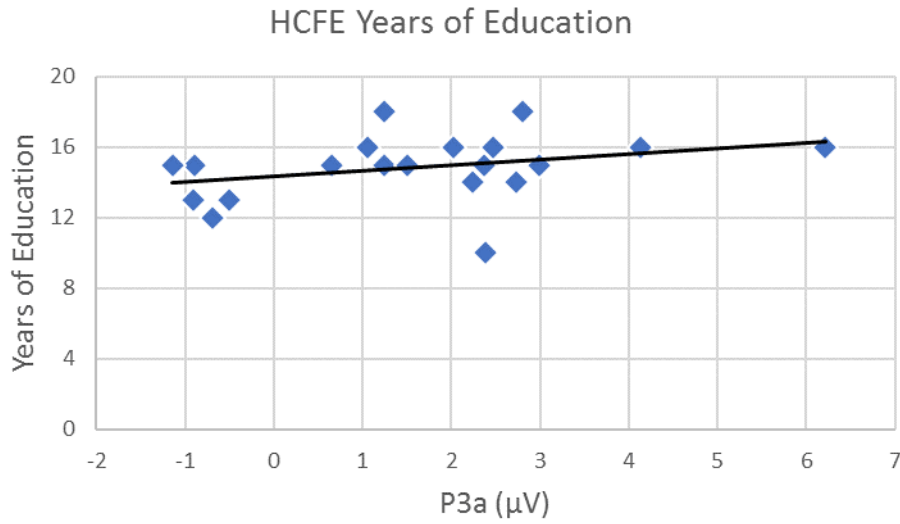


Figure 4. HCFE Education and P3a Correlation. Correlation scatterplot graph of HCFE experimental group comparing P3a ERP responses to years of education

3.3.4 FE

The FE group had no demographic factors or psychiatric symptom scores that correlated with P3a or P3b ERPs.

4.0 DISCUSSION

The novel contribution of this experiment is that we examined P3 in response to an omitted stimulus, which has not been previously examined in FE. FE showed a healthy emitted P3a when compared to their matched healthy controls, while SZ had a significantly impaired emitted P3a compared to their matched healthy controls. Both patient groups also had significantly impaired emitted P3b responses compared to their controls. When referencing the CSD and topography maps, HCSZ appears to have a mix of P3a and P3b distributions. This distribution is not seen in SZ. Since P3b is significantly reduced, any activity reflected in these distributions is likely noise or residual P3a and not true brain activity reflecting P3b. The distribution of P3a and P3b were as expected in healthy comparison individuals. This study supports earlier reports of decreased P3b in chronic schizophrenia patient populations (Kiehl & Liddle, 2001), but expands on the research concerning first-episode patients by concluding that P3b responses are also reduced in first-episode patient groups (Salisbury et al., 1999).

A general decrease of the emitted P3 is thought to reflect inappropriate attention resource allocations during tasks (Demiralp et al., 2002). P3a deficits, specifically, reflect problems in the automatic orienting to salient stimuli. Healthy P3a responses in the first-episode patient group validates the saliency of the stimulus task, meaning that FE have the ability to attend to the stimuli. SZ impairments in P3a indicate that development of chronic disease in schizophrenia creates deficits in orienting to salient or deviant stimuli. A reduction in P3b is more directly

related to deep, controlled processing of task-relevant information deficits. The distribution of P3b in this study is consistent with an expected distribution around the temporo-parietal region, and this brain region is implicated in attention, working memory, and other memory-related processes. Impaired neural activity in these brain regions in patients with schizophrenia may be related to dysfunction in cognitive tasks related to memory processing (Kiehl & Liddle, 2001). FE deficits in P3b may be related to poor resource allocation for cognitive tasks. A healthy P3a but impaired P3b in FE suggests that first-episode schizophrenia is associated with the automatic detection of the missing stimulus, yet the information does not appear to receive further higher order cognitive processing. SZ exhibit both P3a and P3b impairments, indicating deficits in attention orienting and impairments in controlled deep processing of stimuli. In the case of an expected but missing stimulus, this suggests that in chronic schizophrenia, deficits in both the automatic detection and higher order cognitive processing exist.

The results of this study support the conclusion that aspects of attention or working memory may be impaired in people with schizophrenia rather than a component of the sensory system being impaired. Since P3a, the more automatic orienting to sensory stimuli component of the emitted P3, is not significantly reduced in FE group, sensory orienting of the FE patient group does not seem to be impaired. Both P3a and P3b are impaired in SZ, however. This indicates that deficits in P3b are not related to abnormalities in hearing the tones or structural abnormalities in the auditory cortex, but abnormalities in the top-down processing and control of sensory information. While top-down processing and resource allocation is impaired before the disease is diagnosed, sensory responses may degrade with the progress of disease.

Correlational analysis between emitted P3 and cognitive and neurological assessment scores showed no association between symptoms and emitted P3 impairments. When doing

correlational analysis, we looked at PANSS total, negative, and positive scores. If one factor appeared significant, we analyzed the subcategories to see what dimension was driving the correlation with the larger factor. Analysis in this method showed no association between symptom severity and ERP responses. Several demographic factors were correlated with emitted P3 responses. A positive correlation between SZ emitted P3b and parental SES indicate that healthier ERP responses are associated with a more affluent background. A positive correlation between HCFE emitted P3a and years of education indicate that healthier ERP responses are associated with higher education. Both correlations insinuate that healthier ERP responses indicate a higher quality of life, which may be expected in patient groups. These correlations are highly exploratory, and further research in this direction should be pursued to extract meaningful conclusions from this data.

P3b deficits may relate to impairments in general functioning that is seen in patients with schizophrenia. A disturbance of top-down control and cognitive processing of stimuli is linked to clinical disturbances in motivation, attention, and reality testing (Turetsky, Bilker, Siegel, Kohler, & Gur, 2009). Deficits in P3b during emotional categorization tasks hypothesize that P3 may be involved in encoding and deep processing of salient information, like emotion (Johnston, Stojanov, Devir, & Schall, 2005). These clinical disturbances could relate to some of the hallmark symptoms seen in patients with schizophrenia.

In terms of practical clinical application, the results of this study show that emitted P3b is a promising physiological event to use as a biomarker of disease presence. Emitted P3a was not significantly reduced in the first episode patient group compared to the first-episode patients or healthy controls, so it is an insufficient event to use as a biomarker to determine which among the clinical high risk individuals might covert to psychosis. Emitted P3b,

however, was significantly reduced in both chronic and first episode groups, showing it is affected early in the disease course in those known to have schizophrenia. Past research as sought to use oddball P3b, rather than emitted P3b, as a biomarker for schizophrenia. Although oddball P3b is reduced in true prodromal cases (van Tricht et al., 2010), it is also somewhat reduced in a large percentage of ultra-high risk non-converters (Bramon et al., 2008; Özgürdal et al., 2008; Van der Stelt et al., 2004). This may indicate general cognitive impairment common to the at risk individuals rather than the specific presence of the psychosis prodrome. Emitted P3b, however, may be a specific biomarker for schizophrenia prodromal phase, rather than identifying high risk individuals. If emitted P3b is unique to psychosis prodrome, specific diagnostic techniques and therapies may be used effectively and efficiently to target patients before they enter first episode psychosis.

One limitation of this study is that some of the chronic and first-episode patients were on medications. However, no significant effect of antipsychotic medications on P3 have been reported (An et al., 2003; Condray, Steinhauer, Cohen, van Kammen, & Kasparek, 1999; Ford et al., 1994; Pfefferbaum et al., 1989). We are, however, ethically obligated to treat patients, so this is an intractable issue for most work in schizophrenia.

Future directions include conducting this experiment in individuals in the prodromal phase of schizophrenia. If this task is to be used to identify biomarkers that show disease presence, an impaired emitted P3b should be elicited in prodromal individuals. Several other biomarkers of disease presence have been identified. If the emitted P3b adds unique predictive power to the slate of measures, it may prove a valuable addition to the screening battery. Overall, the emitted P3 response to omitted stimuli showed abnormalities in long-term and in first episode schizophrenia, specifically in the emitted P3b in both groups and the

emitted P3a in long-term illness. Hence, the emitted P3b shows promise as serving as a biomarker due to its significant reduction even at first-episode, and may be useful for detecting disease presence in schizophrenia, prior to the emergence of overt psychosis.

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