Deficits in Attentional Modulation of Sensory Stimuli in First Episode Schizophrenia

by

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Neuroscience, BPhil, University of Pittsburgh, 2018

Submitted to the Graduate Faculty of

University Honors College in partial fulfillment

of the requirements for the degree of

Bachelor of Philosophy

University of Pittsburgh

2018

UNIVERSITY OF PITTSBURGH

UNIVERSITY HONORS COLLEGE

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Individuals with schizophrenia have abnormal EEG-based measures of brain activity to auditory stimuli. However, it is not known whether the deficits are purely sensory in nature or reflect the inability of executive control cognitive centers to modulate sensory processing by selective attention, another cognitive function impaired in schizophrenia. To address this issue, the late perceptual N100 event-related auditory brain potential was examined between attend and ignore conditions. The N100 is increased in healthy individuals when sounds are attended, providing an objective measure of selective attention effects. Eighteen individuals experiencing their first psychotic episode within the schizophrenia-spectrum (FE) and 17 matched healthy controls (HC) were compared on two auditory attention tasks. In the single tone task, participants ignored the tones in one block and pressed a button to every 7^{th} tone in another block. In the two-tone "oddball" task, participants ignored tones in one block and pressed to the oddball tone (infrequent higher frequency tone) in another. FE showed marginally smaller N100 across tasks and conditions ($p=0.053$). Attentional modulation of the N100 was marginally impaired in FE (Group x Attention, $p =0.058$). The increase in N100 was greater for the oddball task ($p =0.04$) and follow up analyses revealed that FE did not modulate N100 during the oddball task with attention to the same extent as HC ($p = 0.051$). This deficit may reflect a long-range functional disconnection between cognitive control cortical areas and sensory cortex early in disease course. This difference in N100 modulation between groups may be useful in learning more

about the neurophysiology of the disease and could be utilized as a potential biomarker for diagnosis among clinically high-risk individuals.

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PREFACE

I would like to thank Dr. Salisbury for his supportive mentorship throughout this process, the other members of the Clinical Neurophysiology Research Laboratory for their ongoing assistance in the lab, and my family for their constant encouragement. I would also like to thank my defense committee for giving me the opportunity to gain experience in the research field and improve my scientific writing skills.

1.0 INTRODUCTION

Schizophrenia is a chronic psychiatric disorder that results in severe social, behavioral, and cognitive impairment. It was originally considered a dementing disorder in the late 19th century, called dementia praecox, hypothesized to reflect a neurodegenerative disease based on the pervasive deficits for most individuals (Kraepelin 1902). The disease was soon renamed schizophrenia, meaning "split mind," based on the cognitive and affective symptoms in disease presentation rather than a possible biological cause, as dispute arose whether the disease had an invariably dementing course (Bleuler 1911). Worldwide, lifetime prevalence of schizophrenia is believed to be around 1%, with a slightly higher rate of incidence in men compared to women (McGrath 2004). Within the age group of 15-44 years old, schizophrenia is listed as number eight in the leading causes of disability-adjusted life years (DALY), often thought of as lost years of "healthy" life (Rössler 2005). In 2013, this significant economic burden cost the United States over $155.7 billion, with $117.3 billion in indirect costs (Cloutier et al 2016).

Earlier clinical intervention may help ease this burden, with studies showing that early treatment can decrease the long-term morbidity of schizophrenia (Wyatt et al 1998). However, schizophrenia and other major psychotic disorders lack the clear-cut biomarkers that aid in identification before psychosis emerges (Kapur 2012). Although there have been great strides in the pathology-based research of schizophrenia, the underlying mechanisms are still poorly understood, making the establishment of routine biomarkers difficult. Overcoming this obstacle

through biomarker design could lead to improved diagnostic decision-making, better identification of high risk individuals, and more effective prodromal treatments.

This study focused on individuals in the first episode schizophrenia spectrum, defined as being within their first psychotic episode and on antipsychotic medication for less than 2 months. Untreated psychosis has been linked to more severe psychopathological symptoms due the natural course of the disease (Cechnicki et al 2014), so timely intervention is important. Preventing the emergence of psychosis would be ideal. Having the ability to predict the development of psychosis and initiating prophylactic treatment would provide these individuals a higher quality of life.

The hunt for biomarkers of incipient psychosis has been an active area of research, with projects that investigate proteomic indicators in the blood, neuroimaging markers, cognitive test abnormalities, pharmacodynamic activity, and electroencephalogram (EEG) measures (Morgan et al 2012, Perez et al 2014, Schwarz et al 2012). Mismatch negativity (MMN) has been favored as a potential biomarker in EEG data. The MMN response describes an event related potential (ERP), or time-locked electrophysiological response to a stimulus, that occurs during auditory tasks. The passive task that elicits this response is a deviant tone presented at a lower probability among other tones. The rare sound causes an auditory processing response in the form of a negative deflection around 100-250 ms after the onset of the deviant stimulus (Sams et al 1985). Individuals with schizophrenia for many years show decreased amplitude of their MMN response when compared to healthy controls (Javitt et al 1998). However, when MMN was studied in young schizophrenia patients recently diagnosed, the marked reductions in amplitude seen in chronic patients were not present (Salisbury et al 2002, 2007, 2017). Since the MMN deficit was not present early in the disease course, this ERP is not a convincing biomarker for

diagnosis. For example, one leading group initially reported reduced MMN in individuals that transitioned to psychosis among a clinical high risk for psychosis group (CHR, Atkinson et al 2012), suggesting MMN might be a biomarker for incipient psychosis. However, the same group recently failed to replicate that finding, showing larger MMN in transitioners among CHR individuals, concluding that MMN was not a viable biomarker for the psychosis prodrome (Atkins et al 2017).

Still, other candidate neurophysiological markers may be developed to provide objective and economical biomarkers of disease presence. Selective attention, the ability to focus on one percept among other competing sensations, has long been understood as a fundamental cognitive deficit in psychosis (Everett et al 1989). This symptom is often present in the prodromal phase of schizophrenia disease progression, making it a promising target for a potential biomarker (Cornblatt & Erlenmeyer-Kimling 1985, Mohamed et al 1999). Auditory processing deficits are also reflected in many of the symptoms of schizophrenia, such as verbal hallucinations and impaired auditory perception (Turetsky et al 2009). The study of these attentional and auditory processing deficits can be joined when examining an auditory ERP called the N100 response.

The N100 response is a negative deflection that occurs approximately 100 ms after the onset of a stimulus. The amplitude of the N100 waveform is enhanced when a subject is paying attention to a stimulus that is task-relevant, such as demonstrated in the oddball paradigm (Hillyard et al 1973). This paradigm involves the presentation of rare deviant stimuli among standard stimuli. Individuals with long-term schizophrenia seem to lack the attentional modulation of the N100 response that is seen in healthy subjects (reviewed in Rosburg et al 2008). If present in first episode schizophrenia-spectrum individuals, this brainwave abnormality could serve as an objective measure of system-level selective attention circuit pathophysiology

that could also be utilized as a biomarker of disease presence. A deficit in the size of the N100 was observed during the oddball paradigm in newly hospitalized schizophrenia patients (Salisbury et al 2010), but it is unknown if this deficit was the result of a sensory component of the response or an attentional component. Keeping in mind the failure of MMN to be reduced at first episode despite great impairment in long-term illness, it is important to replicate the N100 reduction in first episode schizophrenia to assess its viability as a potential biomarker of incipient psychosis (i.e. even earlier in the disease course). Further, understanding whether the observed N100 reduction (Salisbury et al 2010) reflects a simple sensory deficit or an essentially cognitive deficit will aid in the design of appropriate tasks to be tested as biomarkers.

This study examined the N100 and its attentional modulation in first episode schizophrenia-spectrum subjects and matched healthy control individuals. A one-tone task and a two-tone oddball tone task were performed by the subjects while paying attention to the stimuli and while ignoring. The attend condition was expected to enhance the N100 response amplitude in both tasks relative to the ignore condition. A deficit in first episode individuals in the ignore condition would reflect a more purely sensory abnormality. A deficit in the enhancement of N100 with attention in first episode individuals would indicate a more cognitive system-level impairment. Either outcome would reveal an auditory processing abnormality in schizophrenia that is present at first break, and the abnormal waveform could be tested as a potential biomarker for disease presence prior to psychosis.

2.0 METHODS

2.1 PARTICIPANTS

Eighteen first episode schizophrenia spectrum individuals (FE) recruited from consecutive admissions to Western Psychiatric Institute and Clinic (WPIC) inpatient and outpatient services were compared with 17 matched healthy controls (HC). Within the FE group, 13 were diagnosed with schizophrenia (paranoid =10, undifferentiated =3), 3 with schizoaffective disorder (depressed type =2, bipolar type =1), and 2 with psychotic disorder not otherwise specified (NOS). FE participated within their first episode of psychosis and had less than two months of lifetime antipsychotic medication exposure (medicated =12, unmedicated =4, unknown =2).

All subjects had normal hearing as assessed by audiometry, at least nine years of schooling, and an estimated IQ over 75. None of the subjects had a history of concussion or head injury with sequelae, history of alcohol or drug addiction, detox in the last five years, or neurological comorbidity. Groups were matched for age, gender, premorbid estimates of intelligence based on the Wechsler Abbreviated Scale of Intelligence (WASI) IQ, and parental socioeconomic status. The 4-factor Hollingshead Scale was used to measure socioeconomic status (SES) in participants and in their parents. Demographic information can be found in Table 1. All participants provided informed consent and were paid for participation. All procedures were approved by the University of Pittsburgh IRB.

Table 1. Subject Demographics. The demographic averages for both groups are included along with the results of statistical analyses. Chi-squared tests were used to compare gender and t-tests were used to compare age, IQ, PSES, and SES.

	FE	HC	Statistics
Number	18	17	
Gender	14M / 4F	12M / 5F	x^2 =0.24, p =0.63
Age	22.06 ± 4.66	21.59 ± 4.90	t(33) =0.29, p =0.78
WASI IQ	106.72 ± 13.99	110.94 ± 9.74	t(33) =-1.04, p =0.31
PSES	43.68 ± 13.09	50.79 ± 13.95	t(32) =-1.53, p =0.14
SES	27.06 ± 11.55	32.91 ± 15.19	t(33) =-1.28, p =0.21
MATRICS	37.06 ± 15.00	49.83 ± 5.71	t(33) =-3.36, p =0.003

2.2 DIAGNOSTIC ASSESSMENTS

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.

2.3 NEUROPSYCHOLOGICAL TESTS

All participants completed the MATRICS Cognitive Consensus Battery and the WASI. Social functioning was assessed with the Global Assessment Scale (GAS), Global Functioning: Social and Role scales (GF:S, GF:R), the brief UCSD Performance-based Skills Assessment (UPSA-B) and the Social Functioning Scales (SFS).

2.4 PROCEDURE

EEG was collected while participants partook in two different auditory tasks. Stimuli were generated with Tone Generator (NCH Software), and presented in Presentation (Neurobehavioral Systems, Inc.). Binaural auditory stimuli were presented at 80 dB using Etymotic 3A insert earphones, with loudness confirmed with a sound meter. Participants watched a silent nature video while tones were played over earphones.

2.5 STIMULI

2.5.1 Auditory Evoked Potential (AEP) Task

Stimuli consisted of repetitious tones (1kHz, 50 ms duration, 5 ms rise/fall) presented with a stimulus onset asynchrony of 1050-1550 ms. A total of 340 tones were presented. Following each tone, a 500 ms duration 40Hz click train was inserted in the inter-tone interval, but the results of this gamma oscillation investigation will not be further discussed in this paper. In one

block, participants were asked to ignore the tones and focus on a silent nature video. In another, participants were asked to pay attention to the tones and press a button to every seventh tone. Blocks were counterbalanced.

2.5.2 Oddball Tone Task

Stimuli consisted of a standard tone (1000 Hz, 50 ms duration, 5 ms rise/fall) and a deviant tone (1200 Hz, 50 ms duration, 5 ms rise/fall) presented with a stimulus onset asynchrony of 1050-1550 ms. A total of 400 tones were presented, including 340 standard tones (85%) and 60 deviant tones (15%). As for the AEP task, a 500 ms duration 40Hz click train was inserted in the inter-tone interval, but the results of attention of the gammaband oscillation investigation will not be further discussed here. In one block participants were asked to ignore the tones and focus on a silent nature video. In another, participants were asked to pay attention to the tones and press a button to every deviant tone. Blocks were counterbalanced.

2.6 EEG RECORDING

EEG was recorded using a low impedance 60-electrode EEG array based on the 10-10 system. It was part of an MEG Elekta Neuromag system with a sampling rate of 1000 Hz and an online bandpass filter of 0.1 – 330 Hz. EEG recordings were referenced to the left mastoid and the right mastoid was used as ground. Additional bipolar leads placed above and below the left eye (VEOG) as well as lateral to the outer canthi of both eyes (HEOG) were used to monitor blinks

and horizontal eye movements. Bipolar ECG leads were placed just below the left and right clavicle.

2.7 EEG SIGNAL PREPROCESSING

Pre-processing was done off-line with the MATLAB-based EEGLAB Toolbox (Delorme and Makeig, 2004). 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. ICA was then performed to detect and remove eye-blink, eye movement, and ECG components in the EEG data.

2.8 EEG ANALYSIS

Following pre-processing in EEGLAB, event-related potentials were processed using BrainVision Analyzer2 (Brain Products GMBH). ICA-corrected EEG data were rereferenced to the averaged mastoids and low-pass filtered at 20 Hz to remove muscle and other high frequency artifact. EEG data were then segmented into epochs starting 100ms prior to the stimulus and ending 1000ms after. These epochs were baseline-corrected using the 100ms pre-stimulus baseline and epochs in which the voltage exceeded ±50 μV in EEG channels were rejected.

Averages were constructed for the standard tones in the AEP task and oddball task. The N100 response was measured by detection of the peak amplitude between 75 ms and 125 ms at

Fz, where enhancement of the N1 was largest, in each participant, and a 10ms segment centered around this peak was exported.

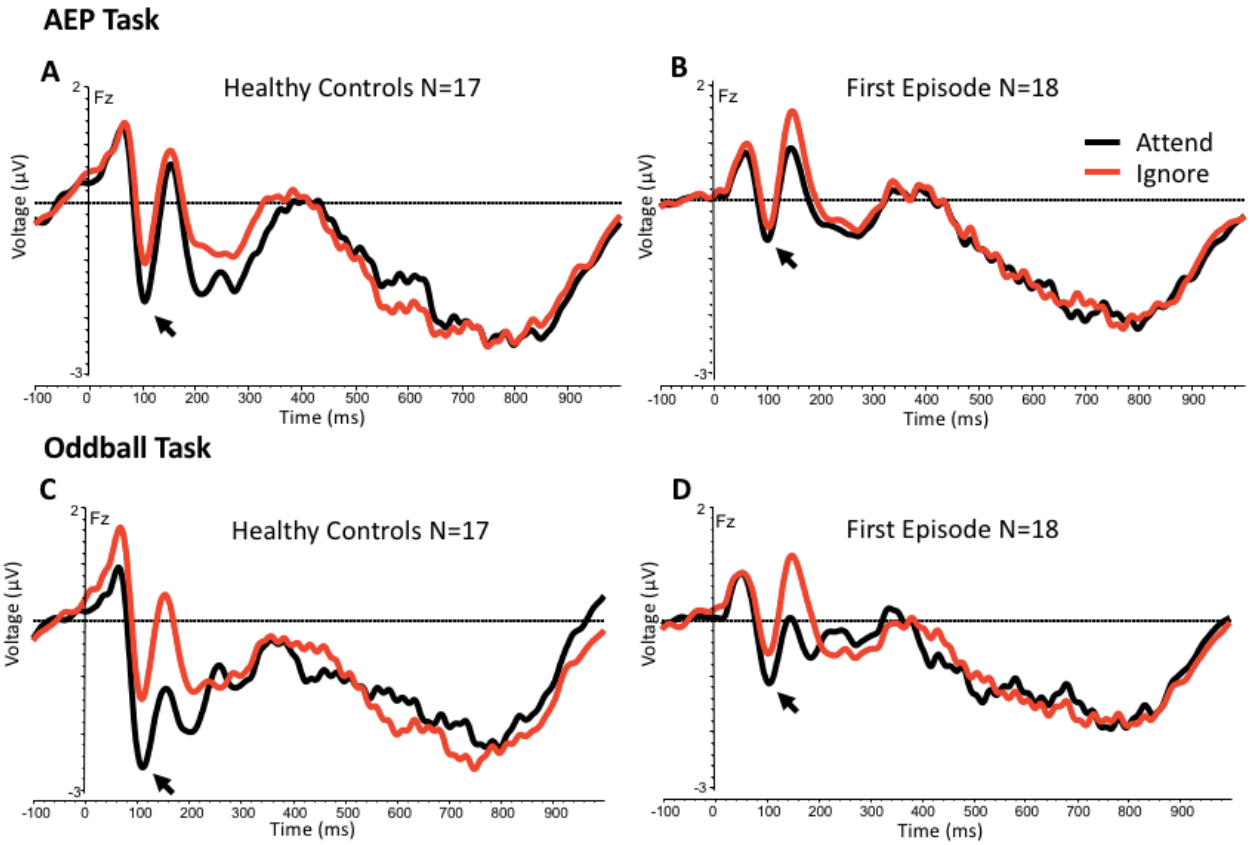
2.9 ANALYSES

Group demographics and neuropsychological scores were compared using t-tests and chi-squared tests where appropriate. N100 analyses utilized repeated-measures ANOVA with group (FE, HC) as the between subjects factor and task (AEP or oddball) and attention condition (attend or ignore) as within subjects factors. Follow-up task analyses utilized repeated-measures ANOVA with group (FE, HC) as the between subjects factor and attention condition (attend or ignore) as the within subjects factor. Subsequent comparisons of specific conditions and tasks between groups utilized t-tests. N100 enhancement was calculated by subtracting the ignore condition N100 voltage from the attend condition N100 voltage for each task. Spearman's correlations were performed between N100 enhancement and neuropsychological, clinical, and social functioning variables for FE participants. Values are reported as Mean ± SD. Significance was attained at $p < 0.05$.

3.0 RESULTS

ERP Waveforms across tasks and conditions are presented in Figure 1. An omnibus ANOVA revealed marginally significant reductions of N100 in FE across tasks and conditions ($F(1,33) = 4.03$, $p = 0.053$). The AEP task N100 responses were significantly smaller than those of the oddball task ($F(1,33) = 10.646$, $p = 0.003$). This effect did not interact between groups. N100 was larger across tasks in the attend condition compared to the ignore condition ($F(1,33) = 19.725$, $p < 0.001$). Of primary importance, however, the effect of attention on N100 was marginally greater in HC than in FE ($F(1,33) = 3.865$, $p = 0.058$). Finally, there was an interaction between task and attention such that the effect of attention on N100 response was significantly greater in the oddball task than in the AEP task ($F(1,33) = 4.512$, $p = 0.041$). To follow up on this interaction, separate ANOVAs were conducted for each task. Statistical means can be found in Table 2.

Figure 1. Event Related Potential Averages. Waveforms for FE and HC groups collected at electrode position Fz. 1a) Attend (black) and ignore (red) ERP events in healthy controls for the AEP task. 1b) Attend and ignore ERP events in first episode schizophrenia participants for the AEP task. 1c) Attend and ignore ERP events in healthy controls for the oddball task. 1d) Attend and ignore ERP events in the first episode schizophrenia participants for the oddball task. Arrows indicate N100 responses.



3.1 AEP TASK

The N100 amplitude in the FE group was not significantly different from the HC group on the AEP task. There was trend-level significance in the effect of attention for this task, with the responses while attending showing larger amplitudes than responses while ignoring ($F(1,33) = 3.375$, $p = 0.075$). This effect of attention did not interact between groups ($F(1,33) = 1.018$, $p = 0.320$).

3.2 ODDBALL TASK

The N100 amplitude in the FE group was significantly smaller than the HC ($F(1,33) = 5.665$, $p = 0.023$) to frequent tones on the two-tone oddball task. N100 responses were significantly larger when paying attention compared to ignoring the stimuli ($F(1,33) = 12.546$, $p < 0.001$). However, the effect of attention on N100 response was marginally larger in HC than FE ($F(1,33) = 4.093$, $p = 0.051$). Separate analyses of attend and ignore N100 in FE revealed a marginal effect of attention ($p = 0.055$), while HC showed a marked effect ($p < 0.001$). As can be observed in Table 2, the effect of attention on N100 in this task was over two times greater in HC than FE.

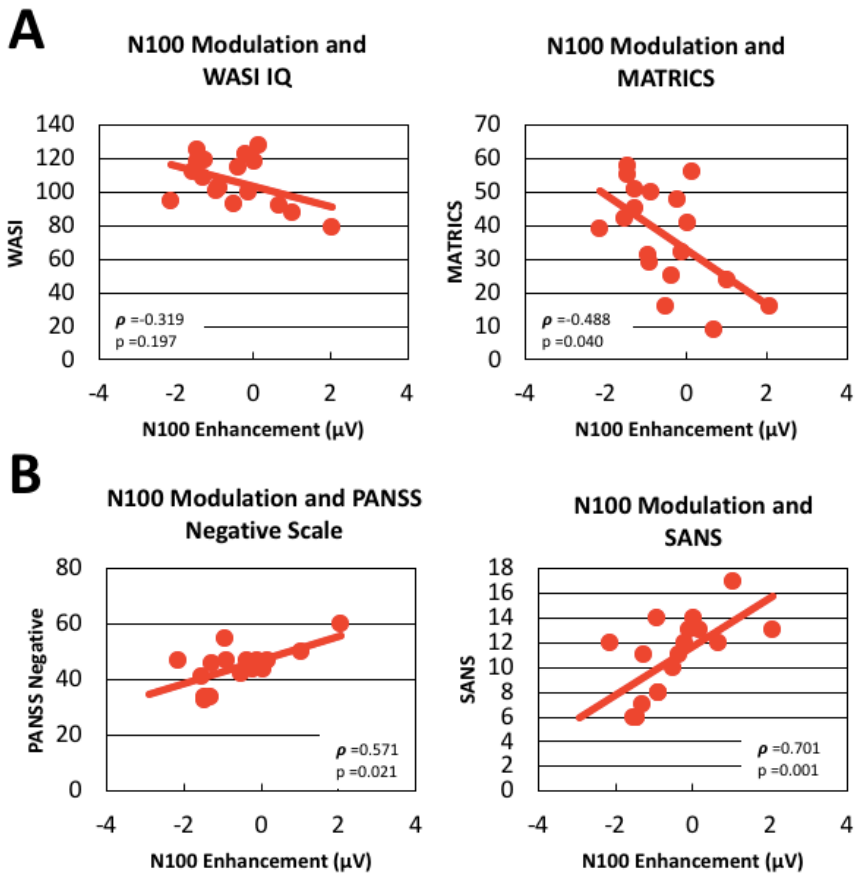
Table 2. Mean N100 Responses. Calculated mean responses at Fz site used in statistical tests.

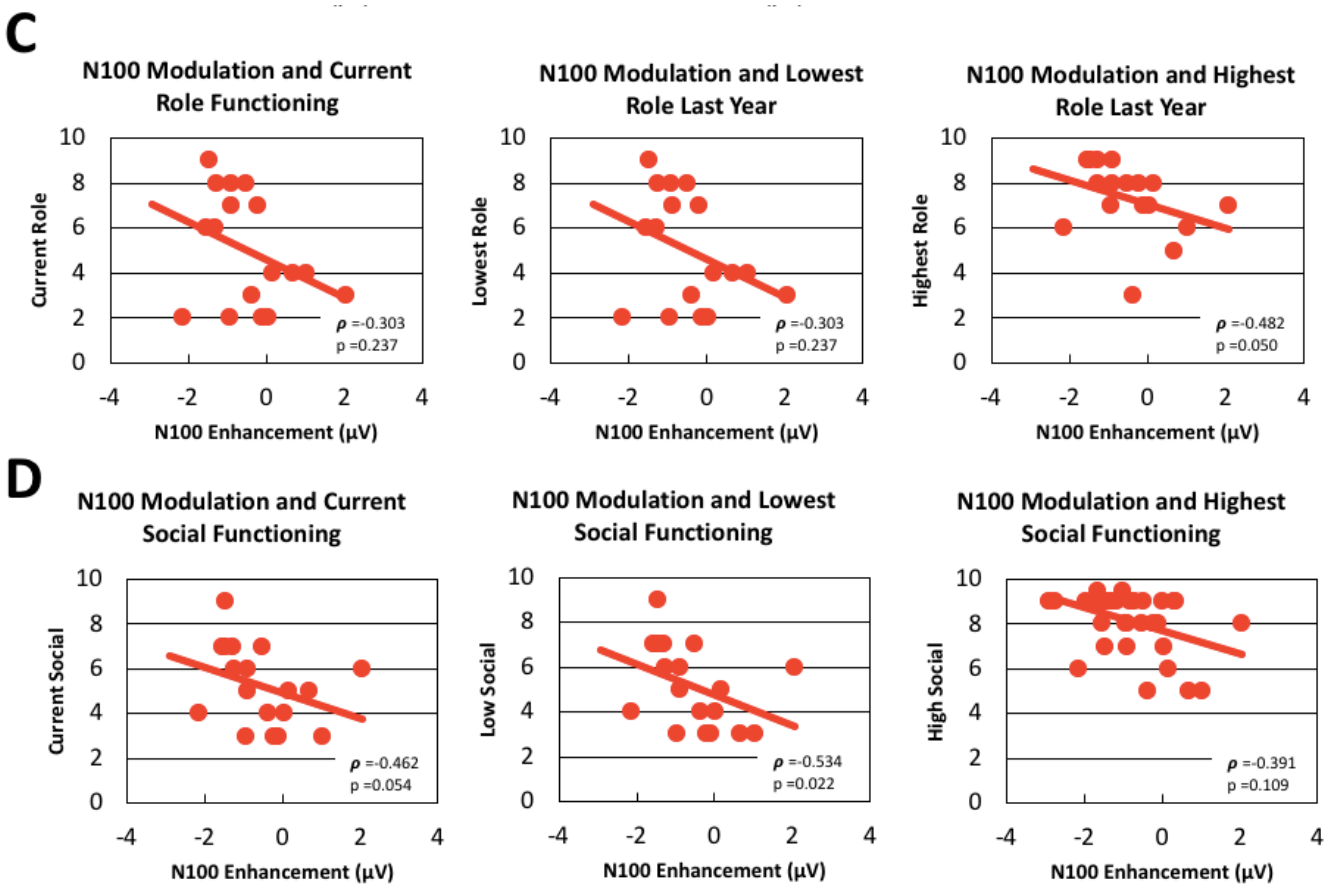
		Mean (μV)	Standard Deviation
Group	FE	-1.20	1.43
	HC	-2.02	1.32
Task	AEP	-1.40	1.41
	Oddball	-1.82	1.35
Group*Task	FE AEP	-1.08	1.48
	FE Oddball	-1.31	1.39
	HC AEP	-1.72	1.34
	HC Oddball	-2.33	1.30
Attention	Attend	-1.91	1.46
	Ignore	-1.31	1.29
Group*Attention	FE Attend	-1.36	1.51
	FE Ignore	-1.03	1.35
	HC Attend	-2.46	1.41
	HC Ignore	-1.59	1.24
Group*Attention*Task	FE AT AEP	-1.16	1.53
	FE AT Oddball	-1.57	1.50
	FE IG AEP	-0.99	1.42
	FE IG Oddball	-1.06	1.28
	HC AT AEP	-1.99	1.44
	HC AT Oddball	-2.92	1.38
	HC IG AEP	-1.45	1.24
	HC IG Oddball	-1.73	1.23

3.3 N100 ENHANCEMENT CORRELATIONS WITH CLINICAL DATA IN ODDBALL TASK

In FE, N100 enhancement on the oddball task was correlated with neuropsychological, clinical, and social functioning measures. (Recall, the oddball but not the AEP task was associated with N100 enhancement deficits in FE). Although not significant, estimates of premorbid functioning based on WASI IQ, tests selected to be resistant to the effects of psychosis, suggested higher premorbid IQ was reflected in a larger N100 enhancement. N100 enhancement was associated with better MATRICS Overall Composite scores (ρ =-0.488, p =0.040), tests selected to be sensitive to the effects of psychosis on cognition. Higher scores on the negative symptom assessments were correlated with smaller N100 enhancement, utilizing the PANNS Negative factor scores (ρ =0.571, p =0.021) and the SANS scores (ρ =0.701, p =.001). Correlations were observed between role and social functioning and attentional modulation, indicating that poorer role and social functioning both currently and in the past year were associated with impaired ability to modulate N100 with attention. Correlation data can be found in Figure 2.

Figure 2. N100 Enhancement and Clinical Data from FE. Results from Spearman's correlation tests for first episode schizophrenia spectrum. 2a) Intelligence measures through the Wechsler Abbreviated Scale of Intelligence and the MATRICS Consensus Cognitive Battery. 2b) Measurements of negative symptoms through Positive and Negative Syndrome Scale (PANSS) negative scale portion and the Scale for the Assessment of Negative Symptoms (SANS). 2c) Assessment of role functioning through the Global Functioning: Role Scales (GF:R) 2d) Assessment of social functioning through the Global Functioning: Social Scales (GF:S).

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N100 Modulation and Current Role Functioning
Current Role
N100 Enhancement (μV)
ρ =-0.303
p =0.237
N100 Modulation and Lowest Role Last Year
Lowest Role
N100 Enhancement (μV)
ρ =-0.303
p =0.237
N100 Modulation and Highest Role Last Year
Highest Role
N100 Enhancement (μV)
ρ =-0.482
p =0.050
D
N100 Modulation and Current Social Functioning
Current Social
N100 Enhancement (μV)
ρ =-0.462
p =0.054
N100 Modulation and Lowest Social Functioning
Low Social
N100 Enhancement (μV)
ρ =-0.534
p =0.022
N100 Modulation and Highest Social Functioning
High Social
N100 Enhancement (μV)
ρ =-0.391
p =0.109

4.0 DISCUSSION

The enhancement of the N100 response with attention in healthy controls matches results found in previous ERP studies and helps validate the tasks and procedure used in this study (Hillyard et al 1973). A deficit in this attentional enhancement of the N100 response has been shown in chronic schizophrenia (Rosburg et al 2008), but our results indicate that it is also impaired in first episode individuals, at least for the oddball task where attention seemed to have a larger effect. The auditory processing events modulated by selective attention that are reflected in the N100 response appear to be abnormal even around the time of an individual's first break.

After analyzing waveform responses for subjects in both tasks independently, it was determined that the oddball task was more effective at demonstrating the deficit in attentional modulation in FE. We speculate that this is due to increased signal representation in perception that may occur on the more complex two-tone task. Follow-up paired t-tests revealed that the AEP task produced only trend-level attentional modulation, while the oddball task elicited robust modulation. It is possible that a single tone task is too simple for perceptual mechanisms, and only with increasing task complexity (as in going to two tone task) does sensory enhancement become necessary. Current work is examining this possibility by measuring increases in N100 enhancement from 1 to 2 to 4 tone tasks.

Another important finding is that when ignoring, the groups do not have significantly different N100 response amplitudes in either the AEP task ($p = 0.322$) or the oddball task (p

=0.121), shown in Figure 1 in red. This indicates that first episode schizophrenia-spectrum individuals have largely intact sensory processing, at least as reflected in the late perceptual N100. A difference between the two groups becomes apparent when adding an attention factor to the task. The dysfunction in N100 response does not seem to be linked exclusively to auditory processing centers in the auditory cortex. It may instead involve communication to the auditory cortex from other brain areas, such as the frontal and parietal lobes that support the executive attentional mechanisms (Petersen & Posner 2012).

Our results suggest a long-range functional disconnection between cognitive control cortical areas and the auditory temporal lobes early in disease course. Further examination of this connection could lead to a better understanding of the attentional circuitry involved in auditory neurophysiology in schizophrenia. More specifically, this project's focus on young patients provides information on the timing of disease progress, allowing researchers to learn more about which areas of functioning deteriorate first. A future direction of this project is to use concurrently recorded EEG and magnetoencephalogram (MEG) data along with structural MRI images to create a more complete picture of the underlying brain circuitry associated with these auditory responses. The combination of MEG and EEG data will reveal brain activity occurring not only at the scalp level, but also at the source level, as we use information from the electromagnetic fields to project activity on to the cortical surface (Huotilainen et al 1998). Structural MRI taken from each participant will allow for more accurate mapping of source activity within each individual's head due to the personalized headspace. This allows us to investigate cortical dynamics of activity in the executive control and auditory nodes of the brain, and to investigate the inter-relationships between nodes.

Correlations in N100 enhancement of FE during the oddball task were also analyzed. There was no significant correlation between modulation of N100 and premorbid intelligence as estimated by the WASI, although the direction of the association suggested better modulation with higher premorbid IQ. However, larger attentional modulation was associated with higher scores on the MATRICS Overall Composite score. Since the MATRICS battery was designed to include tests sensitive to the effects of psychosis on cognition, and is often utilized to track changes in cognitive function during an individual's treatment for psychiatric disorders, it follows that our FE group would show significantly lower scores on this assessment than HC despite being matched for premorbid IQ. The correlation between lower cognitive functioning and impaired ability to modulate the size of the N100 ERP indicates that attentional enhancement is sensitive to the consequences of psychosis. Given that neuropsychological deficits predate overt psychosis (Woodberry et al 2008), this finding suggests failure of N100 enhancement on the oddball task is a candidate pre-psychosis biomarker. The significant association between negative symptoms and impaired attentional modulation suggests that these may be related to similar pathological prefrontal cortex systems. For example, Asami et al (2012) showed persistent negative symptoms were associated with longitudinal reductions of inferior frontal gyrus gray matter in first episode individuals, and the executive control system. Correlations that examined the relationship between N100 enhancement and social functioning showed that reduced modulation of N100 response was also slightly predictive of current and pre-psychosis levels of social role and functioning. This association suggests the current lack of N100 enhancement is related to the degree of prodromal deficit.

From a clinical perspective, the results of this study support reduction of attentional modulation of the N100 response as a promising biomarker for the development of a diagnostic

tool for clinically high-risk individuals. This group would include individuals that have family members with schizophrenia or are exhibiting abnormal behavior, such as reduced psychosocial functioning or mild psychotic symptoms (Fusar-Poli et al 2013). These individuals are generally believed to be in the prodromal phase of the disease, but the criteria for this group only results in a maximum of 4 in 10 individuals receiving a schizophrenia diagnosis (Yung et al 2004), and is likely to be closer to 2 in 10 (Nelson et al 2013). This low rate of conversion makes it difficult to predict individuals that would benefit from early treatment and often prevents clinicians from intervening before the first episode.

A possible next step for this study would be to bring the oddball task to the clinical high-risk group and determine if their N100 modulation is impaired like the first episode individuals, or if it more closely matches the modulation of healthy controls. Collecting data on conversion rates and ability to modulate the N100 response would test the effectiveness of this biomarker as a predictor of disease onset. Successful testing in this group could lead to improved prodromal treatments that help with the transition phase and even mitigate symptoms before they reach a critical level (McGorry et al 2002, Morrison et al 2004). The simple oddball task utilized in this study would be a relatively easy and inexpensive procedure and has the potential to improve the predictive power of conversion to a schizophrenia diagnosis.

We focused on the enhancement of N100 specifically, based on our group's previous demonstration of a narrow temporal window of N100 enhancement with attention (O'Donnell et al 1995). However, inspection of Figure 1 indicates a broader negativity spanning the N100, P200, and N200 time windows. This broad negativity more closely resembles the Nd (negative difference) response originally reported by Hillyard and colleagues (e.g., Hansen & Hillyard 1980), and which may reflect separate components (e.g., Giard et al 1988). Currently

we are examining the broader Nd observed on this task and conducting several studies to differentiate increases in specific ERPs (e.g., N100, P200) versus a broad negativity (the Nd).

Several caveats must be discussed. The number of subjects on this task is relatively small, and the marginal and trend-level findings may attain significance with larger samples. Currently we are testing additional participants on this task to that end. The insertion of click trains between tones leads to a broad negativity between 300 and 800 ms as shown in Figure 1. It is unclear to what extent this task parameter may affect the N100 enhancement. Currently we are testing participants without the click trains inserted. Another potential limitation is that the majority of patients were on antipsychotic medication at the time of participation. However, no participant had a long course of treatment. We did not observe an effect of medication on ability to modulate N100 response with attention.

In summary, individuals in the first-episode schizophrenia spectrum exhibit impaired attentional modulation of their N100 ERP on the oddball task, indicating abnormal attentional processing can be objectively measured from neurophysiological sensory responses at the start of psychosis. This finding suggests that the impairment in selective attention is present at the onset of psychotic symptoms. The results of this study therefore support the use of N100 modulation in the oddball task as a potential diagnostic tool in clinical settings. Future work will collect data from more subjects, further investigate the hypothesized functional disconnection present in diseased auditory processing, and test the effectiveness of this impairment as a predictor of disease presence.

BIBLIOGRAPHY

Atkinson, R. J., Fulham, W. R., Michie, P. T., Ward, P. B., Todd, J., Stain, H., Langdon, R., Thienel, R., Paulik, G., Cooper, G. (2017). Electrophysiological, cognitive and clinical profiles of at-risk mental state: The longitudinal minds in transition (MinT) study. *Public Library of Science*. 12(2):e0171657

Atkinson, R. J., Michie, P. T., Schall, U. (2012). Duration mismatch negativity and P3a in first-episode psychosis and individuals at ultra-high risk of psychosis. *Biological Psychiatry Journal*. 71(2):98-104

Asami, T., Bouix, S., Whitford, T. J., Shenton, M. E., Salisbury, D. F., McCarley, R. W. (2012). Longitudinal loss of gray matter volume in patients with first-episode schizophrenia: DARTEL automated analysis and ROI validation. *NeuroImage*. 59(2):986-996

Bleuler, E. (1911). *Dementia Praecox: Or the Group of Schizophrenias*. New York: International Universities Press

Cechnicki, A., Cichocki, Ł., Kalisz, A., Bładziński, P., Adamczyk, P., Franczyk-Glita, J. (2014). Duration of untreated psychosis (DUP) and the course of schizophrenia in a 20-year follow-up study. *Psychiatry Research*. 219(3):420-5

Cloutier, M., Aigbogun, M. S., Guerin, A., et al. (2016). The economic burden of schizophrenia in the United States in 2013. *Journal of Clinical Psychiatry*. 77(6):764-771

Cornblatt, B. A., Erlenmeyer-Kimling, L. (1985). Global attentional deviance as a marker of risk for schizophrenia: specificity and predictive validity. *Journal of Abnormal Psychology*. 94(4):470-86

Everett, J., Laplante, L., Thomas, J. (1989) The selective attention deficit in schizophrenia: limited resources or cognitive fatigue? *The Journal of Nervous and Mental Illness*. 177(12):735-738

Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J. et al (2013). The psychosis high-risk state: A comprehensive state-of-the-art review. *Journal of the American Medical Association Psychiatry*. 70(1):107-120

Giard, M. H., Perrin, F., Pernier, J., Peronnet, F. (1988). Several attention-related wave forms in auditory areas: a topographic study. *Electroencephalography and Clinical Neurophysiology*. 69(4)371-84

Hillyard, S. A., Hink, R. F., Schwent, V. L., Picton, T. W. (1973) Electrical signs of selective attention in the human brain. *Science*. 182(4108):177-80

Huotilainen, M., Winkler, I., Alho, K., Escera, C., Virtanen, J., Ilmoniemi, R. J., Jääskeläinen, I. P., Pekkonen, E., Näätänen, R. (1998). Combined mapping of human auditory EEG and MEG responses. *Electroencephalography and Clinical Neurophysiology*. 108(4):370-9

Javitt, D. C., Grochowski, S., Shelley, A. M., Ritter, W. (1998). Impaired mismatch negativity (MMN) generation in schizophrenia as a function of stimulus deviance, probability, and interstimulus/interdeviant interval. *Electroencephalography and Clinical Neurophysiology*. 108(2): 145-53

Kapur, S., Philips A. G., Insel, T. R. (2012). Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? *Molecular Psychiatry*. 17(12), 1174-1179

Kraepelin, E. (1902). *Textbook of Psychiatry*. Abstracted and adapted from the 6th German edition of *Lehrbuch der Psychiatrie* [1899] by Defendorf (New York: A. R. Macmillan and Co.)

Marcus, S. C., Olfson, M. (2008). Outpatient antipsychotic treatment and inpatient costs of schizophrenia. *Schizophrenia Bulletin.* 34(1):173-180

McGrath, J., Sukanta, S., Welham, J., El Saadi, O., MacCauley, C., Chant, D. (2004). A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status, and methodology. *BMC Medicine*. 2:13

McGorry, P. D., Yung, A. R., Philips, L. J., Yuen, H. P., Francey, S., Cosgrave, E. M., Germano, D., Bravin, J., McDonald, T., Blair, A., Adlard, S., Jackson, H. (2002) Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. *Archives of General Psychiatry*. 59(10):921-8

Mohamed, S., Paulsen, J. S., O'Leary, D., Arndt, S., Andreasen, N. (1999) Generalized cognitive deficits in schizophrenia: a study of first-episode patients. *Arch Gen Psychiatry*. 56(8):749-754

Morgan, P., Van Der Graaf, P. H., Arrowsmith, J., Feltner, D. E., Drummond, K. S., Wegner, C. D., Street, S. D. A. (2012). Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival. *Drug Discovery Today*. 117(9-10), 419-424

Morrison, A. P., French, P., Walford, L., Lewis, S. W., Kilcommons, A., Green, J., Parker, S., Bentall, R. P. (2004) Cognitive therapy for the prevention of psychosis in people at ultra-high risk: randomized controlled trial. *The British Journal of Psychiatry*. 185:291-7

Nelson, B., Yuen, H. P., Wood, S. J., Lin, A., Spiliotacopoulos, D., Bruxner, A., Broussard, C., Simmons, M., Foley, D. L., Brewer, W. J., Francey, S. M., Amminger, G. P., Thompson, A., McGorry, P. D., Yung A. R. (2013). Long-term follow-up of a group at ultra high risk ("prodromal") for psychosis: the PACE 400 study. *JAMA Psychiatry*. 70(8):793-802

O'Donnell, B. F., Faux, S. F., McCarley, R. W., Kimble, M. O., Salisbury, D. F., Nestor, P. G., Kikinis, R., Jolesz, F. A., Shenton, M. E. (1995). Increased rate of P300 latency prolongation with age in schizophrenia. Electrophysiological evidence for a neurodegenerative process. *Archives of General Psychiatry*. 52(7):544-9

Perez, V. B., Swerdlow, N. R., Braff, D. L., Näätänen, R., Light, G. A. (2014). Using biomarkers to inform diagnosis, guide treatment and track response to interventions in psychotic illnesses. *Biomarkers Medicine*. 8(1), 9-14

Petersen, S. E., Posner, M. I. (2012). The attention system of the human brain: 20 years after. *Annual Review of Neuroscience*. 35:73-89

Rosburg, T., Boutros, N. N., Ford, J. M. (2008). Reduced auditory evoked potential component N100 in schizophrenia – A critical review. *Psychiatry Research*. 161(3):259-274

Rössler, W., Salize, H. J., van Os, J., Riecher-Rössler, A. (2005). Size burden of schizophrenia and psychotic disorders. *European Neuropsychopharmacology*. 15:399-409

Salisbury, D. F., Collins, K. C., McCarley, R. W. (2010) Reductions in the N1 and P2 auditory event-related potentials in first-hospitalized and chronic schizophrenia. *Schizophrenia Bulletin.* 36(5): 991-10000

Salisbury, D. F., Shenton, M. E., Griggs, C. B., Bonner-Jackson, A., McCarley, R. W. (2002). Mismatch negativity in chronic schizophrenia and first-episode schizophrenia. *Archives of General Psychiatry*. 59(8):686-94

Sams, M., Paavilainen, P., Alho, K., Näätäen, R. (1985). Auditory frequency discrimination and event-related potentials. *Electroencephalography Clinical Neurophysiology*. 62:437-448

Schwarz, E., Guest, P. C., Rahmoune, H., Harris, L. W., Wang, L., Leweke, F. M., Rothermundt, M., Bogerts, B., Koethe, D., Kranaster, L., Ohrmann, P., Suslow, T., McAllister, G., Spain, M., Barnes, A., van Beveren, N. J. M., Baron-Cohen, S., Steiner, J., Torrey, F. E., Yolken, R. H., Bahn, S. (2012). Identification of a biological signature for schizophrenia in serum. *Molecular Psychiatry*. 17, 494-502

Turetsky, B. I., Bilker, W. B., Siegel, S. J., Kohler, C. G., Gur, R. E. (2009). Profile of auditory information-processing deficits in schizophrenia. *Psychiatry Research*. 165(1-2):27-37

Woodberry, K. A., Giuliano, A. J., Seidman, L. J. (2008) Premorbid IQ in schizophrenia: A meta-analytic review. *The American Journal of Psychiatry*. 165(5):579-587

Wyatt, R. J., Damiani, L. M., Henter, I. D. (1998). First-episode schizophrenia: Early intervention and medication discontinuation in the context of course and treatment. *The British Journal of Psychiatry*. 172(33):17-83

Yung, A. R., Philips, L. J., Yuen, H. P., McGorry, P. D. Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. *Schizophrenia Research*. 67(2-3):131-142